Chapter 9

Pharmacological actions of indolealkylamines and precursor aminoacids on the central nervous system*

By

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With 2 Figures

A. Effects on behaviour

I. 5-Hydroxytryptamine

1. Mouse

Simple behavioural observation showed that 5-HT had sedative or depressive effects on mice. The doses used were the following: 20 mg/kg i.p. (SHORE et al. 1955), 1—20 mg/kg i.v. (CHESSIN et al. 1956, 1957), 86—172 mg/kg i.p. (ASTON and CULLUMBINE 1960).

Behavioural examination with quantitative methods yielded results in agreement with those furnished by direct observation. BROWN (1957) and KOBINGER (1958a) investigated the effects of amine on the motility. BROWN observed reduction in the spontaneous motor activity of grouped mice with 5—320 mg/kg i.p. and KOBINGER obtained the same result in grouped or single mice with 4.55 mg/kg i.p. KOBINGER also reported that 5-HT (4.55 mg/kg) injected intraperitoneally together with D-methylamphetamine (3.3 mg/kg) or with cocaine (20 mg/kg) prevented the hyperactivity induced by these two drugs.

YEN et al. (1959) tried out the effect of the amine on the aggressivity. It is well known that prolonged isolation induces in the male mouse aggressive behaviour towards another mouse of the same sex temporarily placed in the same cage. Mice, after three weeks' isolation, were injected with 5-HT (50 mg/kg i.p.) and caged for five minutes with a mouse not previously isolated. Whereas before the injection all the mice attacked their cage-mates, after the injection only 10% of the animals maintained aggressive attitudes. The same results were obtained by prolonging the treatment with 5-HT for 14 days (50 mg/kg/day i.p.). MANTEGAZZINI and PEGRASSI (unpublished observations) observed extinction of the aggressive behaviour after intraperitoneal injection of 5 mg/kg of 5-HT. The body temperature of the injected animals was 3—4 °C lower than that of control animals.

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* The coverage in this chapter extends, with a few later additions, to june 1963, when the manuscript was completed.

The doses of 5-HT are expressed in term of base, except when otherwise indicated.

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HALEY (1957a, b) injected 5-HT into the cerebral ventricles, with the aim of by-passing the blood-brain barrier. After injection of 0.4 and 1.2 μg of 5-HT (volume of the injection = 0.05 ml), the author observed together with autonomic symptoms (micturition, defaecation and bristling) central depression, stupor and bouts of scratching. Normal activity resumed in 15—60 minutes.

According to the author, no motor disturbance appeared after 5-HT and control injection of saline had no effect. The size of the brain made it difficult to direct the tip of the needle without the aid of a stereotaxic instrument, and the mechanical trauma of the injection could have greatly interferred with the effects of the drug.

2. Rat

In rats, as in mice, 5-HT induces symptoms considered as expression of sedation (reduction of motor activity and aggressivity) and moreover blocks the conditioned-reflexes and self-stimulation behaviour.

Depression of spontaneous motor activity and sedation (or prostration) have been observed by ERSPAMER since 1952 and subsequently by COOK and WEIDLEY (1957) (0.5—40 mg/kg s.c.), by HOFFMAN (1958b) (5 mg/kg s.c.) and by KÄRKI and PAASONEN (1959) (4.3 mg/kg i.v.).

BRUNAUD and SIOU (1959) reported that 5-HT reduced aggressivity in rats. In these experiments two male rats caged together were electrically stimulated at regular intervals through the floor. The painful stimulation evoked the fighting behaviour. 5-HT at a dose of 20 mg/kg blocked it. Lower doses were inactive. 5 mg/kg of chlorpromazine had the same effect as 20 mg/kg of 5-HT.

WINTER and FLATAKER (1956) administered 5-HT to rats trained to climb a vertical rope under the double incentive of food at the top and noxious stimuli at the bottom. 5-HT (0.9 mg/kg i.p.) did not reduce the animal performance; LSD-25 (0.5 mg/kg i.p.) markedly prolonged climbing time; 5-HT (0.9 mg/kg i.p.) injected 30 minutes before LSD-25 strongly antagonised the effect of the latter.

The action of 5-HT on the conditioned avoidance responses was examined by COOK and WEIDLEY (1957), by GRANDJEAN and BÄTTIG (1957), by PLETSCHER et al. (1959) and by GESSNER et al. (1961). COOK and WEIDLEY reported that 5-HT (0.5—40 mg/kg s.c.) blocked the pole-climbing responses to a conditioned stimulus (a buzzer). 0.5 and 2 mg/kg knocked out the conditioning in 10% of the animals. The maximum effect observed (after 10 mg/kg or more) was a block of responses in 50% of the animals only and occurred 1 and 2 hours after treatement. The deconditioning was accompained by falling off in spontaneous motor activity; the unconditioned responses were unaffected. The effects of the 5-HT were antagonized by 0.5 mg/kg of LSD-25. The well-known blocking actions of chlorpromazine and reserpine were also antagonized by the LSD-25; a fact supporting the idea that the LSD-25—5-HT antagonism is not specific. GRANDJEAN and BÄTTING (1957) reported that 5-HT (0.5—5 mg/kg i.p.) prolonged the reaction time and partly abolished the conditioned avoidance responses. The deconditioning effect increased linearly with the logarithm of the dose; 0.25 mg/kg were ineffective. According to the authors, neither hypothermia nor gross behavioural changes occurred after deconditioning doses. PLETSCHER et al. (1959) obtained a 25% block of conditioned pole climbing responses with 4 mg/kg i.p. of 5-HT (unconditioned responses were unaffected). Adrenaline, noradrenaline and dopamine had qualitatively the same effect as 5-HT. GESSNER et al. (1961) observed a partial block of the conditioned responses together with paresis of the hind legs in rats injected with 17.6 mg/kg of 5-HT. The research workers did

not report if the unconditioned responses were blocked or not when the neurological disturbances appeared.

The above results allow us to think that 5-HT blocks the conditioned avoidance responses and that the block is specific, i.e. it does not involve the unconditioned responses. This means that the deconditioning does not depend on an obstacle in the execution of the motor task.

The intracerebral injection route was used by OLDS and OLDS (1958). Electrodes and pipette were chronically implanted to stimulate the ventral posterior hypothalamus just in front of the mamillary body. The rats were at first trained to self stimulate by pressing a lever. When the animals had attained high rates of self stimulation, the electrical stimulus was replaced by a chemical one (self injection through the pipette of 0.6 μg of 5-HT base in 1/700 ml). The rate of self-injection quickly fell off and the animals lost muscular tone and apparently went to sleep. According to the authors, 5-HT had no rewarding effect. Acetylcholine behaved like the 5-HT; noradrenaline and saline did not show any effect.

Rats with electrodes implanted in the posterior hypothalamus and midbrain tegmentum were trained by STEIN (1960) to regulate the intensity of self-stimulation (reward threshold). 5-HT (4 mg/kg s.c.) increased the reward threshold or knocked out self stimulation behaviour. Chlorpromazine (1.5 mg/kg s.c.) had the same effect as 5-HT.

From the above data, it is clear that 5-HT, peripherally administered, produces marked behavioural changes in the mouse and in the rat: reduction of spontaneous motility and hostility and extinction of the conditioned reflexes and self-stimulation behaviour. The problem is now to find out if the behavioural effects depend on the direct action of 5-HT on the CNS or if they depend on the multiple effects of the amine on the extracerebral regions wich, in turn, act on the CNS.

Let us consider the facts:

I. In the unanaesthetised rat 5-HT (0.4 mg/kg or more s.c.) induces hypotension and marked cutaneous vasodilatation (ERSPAMER 1952; CORREALE 1954). After 2 mg/kg (the highest dose tried) the blood pressure falls to 60—70 mm Hg, recovery occurring only after 120—160 minutes. In the anaesthetised rat, the amine intravenously injected, induces, even at the dose of 0.8 μg/kg, marked hypotension lasting 3—4 minutes (SALMOIRAGHI et al. 1956a). The extent of hypotension induced by the amine in quantities as high as those generally used in behavioural studies is unknown, but it will probably be much higher than that induced by the relatively small doses quoted above, and therefore such as to interfere greatly with animal behaviour.

II. In rats and mice 5-HT induces marked hypothermia at doses within the range of those active on behaviour. It has been reported (LESSIN and PARKES 1957) that chlorpromazine and reserpine, two drugs which definitely act on the CNS, do not induce sedation in the mouse if the fall in body temperature is prevented by keeping the animals at a room temperature of 31° C. This means that the hypothermia largely contributes to produce sedation after chlorpromazine and reserpine. We may justly suspect that in the case of 5-HT hypothermia also plays an important part in inducing sedation, at least in the mouse.

To sum up: 5-HT peripherally administered markedly affects the behaviour; it is strongly to be suspected that the peripheral effects elicited by 5-HT are the determining factors in the behavioural responses to the drug. This suspicion is strengthened by the fact that up to now there is no evidence to show that 5-HT can cross the blood-brain barrier.

3. Rabbit

Reduction of spontaneous motility and of reactivity to acoustic and painful stimuli, together with a tendency to maintain forced positions were observed by BARUCCI (1956) in rabbits intravenously injected with 1 mg/kg of 5-HT. Recovery occurred within 20 to 40 minutes. Substantially the same symptoms, but preceded by transitory restlessness immediately after injection, were also observed by GANGLIOFF and MONNIER (1957) after i.v. injection of 0.1—1 mg/kg of amine.

The observations reported above would lead us to think that 5-HT has a sedative or depressive action on the rabbit, but it is wise to wait for quantitative results before accepting the conclusions drawn from visual observations.

4. Cat

The greater part of the observations reported in the literature refer to the injection of 5-HT into the lateral ventricle. This route has been proposed in order to bypass the blood-brain barrier and to avoid the peripheral effects of the amine. The injection was made through a permanently implanted canula and the animal was allowed freedom of movement during the observation period.

FELDBERG and SHERWOOD (1954) first described the pattern of behavioural effects of 5-HT intraventricularly injected. After 75—500 μg the cat lay down not asleep but with its eyes wide open and when compelled to walk, it did so unsteadily, as if it had muscular weakness. Tachypnea, bursts of profuse salivation, licking movements, tremors of the head and neck muscles and twitching of the eyelids appeared after large doses. These effects began to appear within ten minutes and lasted up to 1 hour and a half. A dose of 10 μg was ineffective.

FELDBERG and SHERWOOD'S observations were confirmed by GADDUM and VOGT (1956), by SCHWARZ et al. (1956), by BRADLEY and HANCE (1956) and by SCHAIN (1961). GADDUM and VOGT moreover reported that LSD-25 (0.8 mg) and ergometrine (1.5 mg), injected into the lateral ventricle at the same time with of after 5-HT, delayed the appearance or interrupted the lethargy induced by the amine. LSD-25 and ergometrine, at the doses used, produced sham rage. Morphine (1 mg into the ventricle) methadone (10 mg s.c.) and amphetamine (15 mg s.c.) shared the antagonistic action of LSD-25 and ergometrine in spite of the fact that they have no anti-5-HT action on the peripheral organs. Bromo LSD (1 mg into the ventricle) and 5-benzyloxygramine (2.1 mg into the ventricle) did not prevent the appearance of the usual 5-HT effects although they had an anti-5-HT action on the peripheral organs. These results suggested that there was no relation between the antagonism observed on the behaviour and that observed on the peripheral organs.

No antagonism between 5-HT and LSD-25 intraventricularly injected was observed by SCHWARZ et al. (1956) with doses of LSD-25 (15 μg) much lower than those tried by GADDUM and VOGT. BRADLEY (1958) briefly reported that 5-HT had the same behavioural effects when it was injected in the ventricle as when it was injected peripherally.

DOMER and FELDBERG (1960a and b) examined the tremor produced by the intraventricular injection of 5-HT. The tremor started 1—2 minutes after injection of 110—215 μg of amine and lasted from 20 minutes to 2 hours. It appeared first in the ears, then in the hind legs and finally spread all over the body. Also in this set of experiments the animals were less alert after 5-HT injection than before. They sat or lay down in their cages.

In complete contrast with the results given till now are those reported by JOHN et al. (1958). These authors administered 5-HT intraventricularly to cats

trained to avoid shock on the presentation of either an auditory or visual stimulus (conditioned avoidance response). Neither lethargy nor attenuation of the conditioned responses occurred after doses of amine as high as 270 μg even when iproniazid (135 μg) was simultaneously injected to block the amine metabolism. The authors reported that KILLAM and JOHN (unpublished data) had previously observed changes in drug action after avoidance conditioning. According to the authors this could account for the ineffectiveness of 5-HT in inducing lethargy and apathy in their experiments.

Administration into the ventricle has the double advantage of avoiding the blood-brain barrier and reducing the interference of the amine's peripheral effects on the central effects. It must however be remembered that as yet there is no direct evidence as to whether 5-HT can get into the brain tissue from the ventricles. Also admitting that 5-HT penetrates the brain, it remains to be seen to what extent the drug's action on the blood vessels in the region near the ventricle walls interferes with the direct action on the neurons. In our opinion the results obtained after intraventricular injection of 5-HT do not clarify the physiological meaning of the amine normally present in the CNS more than those obtained after peripheral administration.

5. Dog

Intravenous injection (0.6—2.5 mg/kg) (SACCHI et al. 1955b; BONAMINI and GARELLO 1956) or intravenous infusion of 5-HT (1.7 μg/kg/min, for three hours) (CRONHEIM and GOURZIS 1960) had no gross effects on the behaviour of the dog. On the other hand, in dogs treated with reserpine, intravenous administration of 5-HT changed the slight sedation into a very marked comatose state and at the same time caused a fall in blood pressure to about 40 mm Hg (CRONHEIM and GOURZIS 1960). Such a fall in blood pressure might well account for the deep sedation and the coma!

According to FLORU et al. (1959), salivary conditioned reflexes and conditioned behaviour were inhibited by 5-HT (0.5—2.5 mg/kg i.v.). The authors did not report data which clarify the part played on the genesis of the deconditioning by the peripheral effects of 5-HT.

SACCHI et al. (1955b) and BONAMINI and GARELLO (1956) reported that 5-HT directly injected into the Cisterna Magna produced marked behavioural and neurological changes; on the contrary it had no effect when intravenously injected. Catatonia occurred 10—15 minutes (rarely more) after the injection of 80—120 μg/kg. The symptomatology gradually increased until complete block of the motility; muscular tone was reduced and responsiveness to visual, acoustic and olfactory stimuli was abolished. Slight salivation and micturition were the only apparent vegetative symptoms. Adrenaline (0.1—2.5 mg) did not produce catatonia; a fact which led the authors to claim that vasoconstrinction was not responsible for catatonia. LSD-25 and methedrine prevented or abolished the 5-HT catatonia (SACCHI et al. 1955a).

With the aim of localising the regions responsible for catatonia, SACCHI et al. (1956) injected the amine through an outside loop of a canula permanently implanted along the Aqueduct of Sylvius in such a way that one tip was in III. ventricle and the other one in the Cisterna magna; 5-HT was administered into III. ventricle or into Cisterna magna, the passage of the drug from one place to the other being prevented by clamping the loop of the canula during the injection. The injection into the III. ventricle produced catatonia, whereas injection into the Cisterna magna had no effect whatsoever. This led to the claim that the structures responsible for the 5-HT catatonia were located near

the walls of III. ventricle or lateral ventricles. No more can be said about the position of these structures nor about the mechanism of 5-HT action. What has been said about this technique when applied in the cat is valid also in the dog.

6. Pigeon

APRISON and FERSTER (1961c) trained hungry pigeons to get food after pecking a disk for a fixed number of times or for a fixed period of time depending from the color of the disk. 5-HT (1.75 and 4.3 mg/kg i.m.) lowered the rate of pecking. It must be pointed out that the highest dose was sometimes lethal and that a dose of 0.86 mg/kg did not significantly interfere with the animal's performance.

7. Fish

5-HT (40—200 mg/kg i.m.) markedly reduced the motility of the *Carassius auratus*. The fish assumed abnormal positions: it stayed with its head up or down or it lay on one side, but resumed the normal behaviour after strong stimulation. The mortality was high (about 25%) (SACCHI and GIANNIOTTI 1956a). LSD-25 prevented the effect of 5-HT (SACCHI and GIANNIOTTI 1956b). In *Betta splendens* in a stress situation (hypoxia), 5-HT (13 mg/l) increased the motor activity (TROUT 1957).

8. Frog

High doses of 5-HT injected into the linphatic sack (54—182 mg/kg) or the peritoneal cavity (54—108 mg/kg) or intramuscularly (43—108 mg/kg) did not impair the motor functions of *Rana esculenta*. The animal lost muscular tone when the amine (43 mg/kg) was put in direct contact with the brain through a breach in the frontal bones (DOLCE and GARELLO 1956).

II. 5-Hydroxytryptophan

After the demonstration that the cerebral 5-HT increases following injection of its precursor, 5-hydroxytryptophan (5-HTP) (UDENFRIEND et al. 1956, 1957a), the latter has been used as a tool for investigating the physiological significance of cerebral 5-HT, in the hope that the effects of an excess of 5-HT might throw some light on the functions of the amine normally present in the brain.

1. Mouse and rat

BOGDANSKI et al. (1956, 1958) did not observe any marked behavioural change in animals intraperitoneally injected with doses of 5-HTP as high as 120 mg/kg (mice) and 300 mg/kg (rats). In rats, three hours after an intraperitoneal injection of 75 and 150 mg/kg of 5-HTP, the brain 5-HT level increased about 2 and 6 times respectively (UDENFRIEND et al. 1957a). Pretreatment with iproniazid increased the sensivity of the animals to the 5-HTP: 30—60 mg/kg i.p. in mice and 50—100 mg/kg in rats (i.e. doses inactive in normal animals) produced excitement, trembling, increase in motor activity, brief clonic convulsions, peripheral vaso-dilatation and mydriasis. The increased sensitivity was associated with an increased brain 5-HT level. According to the authors the 5-HTP grossly resembled LSD-25 in its effects. CHESSIN et al. (1957) confirmed 5-HTP (25 mg/kg i.v.) produced stimulation in mice pretreated with iproniazid; that in absence of iproniazid the amino acid produced slight sedation only, even at a very large dose (200 mg/kg i.v.). The neurological pattern after 5-HTP plus iproniazid was characterised by muscle tremors, preconvulsive twitches and loss

of placing reactions; nor motor hyperactivity of a purposeful nature occurred. TEDESCHI et al. (1959a) observed hypotonia, decrease of motor activity and peripheral vaso-dilatation in rats after 100—400 mg/kg of 5-HTP i.v. Lower doses produced no overt effect.

HESS and DOEPFNER (1961) reported that 5-HTP (8 and 16 mg/kg i.p.) provoked headshake and aimless hypermotility in rats pretreated with JB 516 (5 mg/kg i.p.) (a MAO inhibitor). The amino acid alone (160 and 320 mg/kg i.p.) did not provoke any behavioural change in normal rats, in spite of the fact that in these animals it (320 mg/kg) increased the cerebral 5-HT more than it did at lower doses (8 and 16 mg/kg) in JB 516 pretreated rats. Furthermore the rats treated with JB 516 alone (5 mg/kg) showed a normal behaviour but had cerebral 5-HT level as high as that of rats treated with JB 516 + 5-HTP. From such a result it seems that the cerebral 5-HT increase is not the determining factor of the behavioural changes induced in rats by 5-HTP plus MAO inhibitors.

BROWN (1960) studied the effect of 5-HTP on the motility of grouped mice (photocell counter technique): doses between 0.1 and 100 mg/kg i.p. reduced spontaneous motility; 20 mg/kg i.p. prevented hyperactivity induced by cocaine and amphetamine.

PLETSCHER et al. (1959) and STEINER et al. (1959) briefly reported that 5-HTP (100 mg/kg i.p.) partially blocked the conditioned avoidance responses (pole climbing response) in rats.

ERSPAMER et al. (1960a) reported that 5-HTP reduced the aggressiveness induced in the male mouse by prolonged isolation: 100 mg/kg i.p. abolished the aggressive behaviour in 50% of the couples of males caged together following an isolation period.

WINTER and FLATAKER (1956) and MAHLER and HUMOLLER (1959) injected with 2 and 5 mg/kg and 100 mg/kg of 5-HTP respectively, rats trained to climb a vertical rope to reach food at the top. The animal performance was unaffected. Rats trained to cross a maze were given 100 mg/kg of 5-HTP intraperitoneally. After dosing, the animals made mistakes and took longer to reach the goal box (MANTEGAZZINI and PEGRASSI, unpublished data).

To sum up: 5-HTP, even at very high doses (200 mg/kg i.v. in mice and 400 mg/kg i.v. in rats) induces sedation, reduces motility and aggressiveness (in mice) and blocks the conditioned reflexes and worsens the performance of animals trained to cross a maze (in rats). After pretreatment with MAO inhibitors, 5-HTP, at much lower doses, produces excitement, motor hyperactivity, muscular trembling and preconvulsive twitches. It is doubtful if the differences in the 5-HTP behavioural effects in normal and in the MAO inhibitors pretreated rats may be ascribed to differences in the 5-HT cerebral level.

2. Rabbit

BOGDANSKI et al. (1956, 1958) observed motor excitement, muscular tremors, twitches and, occasionally, brief clonic convulsions together with symptoms of sympathetic stimulation after intravenous injection of doses of 5-HTP ranging from 40 to 100 mg/kg i.v. COSTA and RINALDI (1958) observed alertness, muscular tremors, chewing movements, uncoordinated movements of the legs, bristling, panting and unresponsiveness to auditory and tactile stimuli in rabbits intravenously injected with 75 mg/kg of 5-HTP. The effects appeared about 30 minutes after the injection and lasted about two hours. After such a dose of 5-HTP, the 5-HT concentration increased in the telencephalon, in the hippocampus, in the medulla-pons and in the midbrain and returned to normal within three hours in all structures but the mid-brain where the increase lasted longer than the

behavioural effects. Chlorpromazine premedication prevented the behavioural effects of the 5-HTP but facilitated the increase of 5-HT concentration in brain tissue. MONNIER and TISSOT (1958) and MONNIER (1960) observed slight sedation in the rabbit after intravenous injection of 10—20 mg/kg of 5-HTP, and muscular tremors, motor excitement, mydriasis and transitory tachypnea after 30 mg/kg or more.

To sum up: in the rabbit 5-HTP produces different effects according to the dose. Low doses produce only slight sedation, high doses (generally more than 30 mg/kg i.v.) produce motor excitement, muscular trembling and twitches, uncoordinated movements of the limbs, chewing movements and some time brief clonic convulsions. Mydriasis, bristling and panting are the overt vegetative symptoms induced by high doses.

3. Cat

BOGDANSKI et al. (1956, 1958) first described the neurological and behavioural effects of 5-HTP in the cat. The neurological effects consisted in ataxia and other abnormalities in walking (for doses higher than 50 mg/kg i.v.) and in generalised tremors, extensory twitches, abolition of the patellar reflex and rigidity (for doses higher than 100 mg/kg i.v.). The behavioural effects consisted in sedation (for doses lower than 100 mg/kg i.v.) and in excitement, sham rage reaction, reduced responsiveness to painful stimuli and unresponsiveness to visual and auditory stimuli (for doses higher than 120 mg/kg i.v.). The vegetative symptoms were myosis that at the highest doses turned into mydriasis, nasal, lacrimal and salivary secretions, diarrhea and dispnea. Two hours after injection of 120 mg/kg i.v. the amine content increased two-threefold in the hypothalamus, in the midbrain, in the medulla, in the pons, in the thalamus and in the white matter (corpus callosum and internal capsule) and 4—6 times in the cerebellum, in the cortical grey matter and in the caudate nucleus. LEWIS (1958) reported that normal or iproniazidized cats injected with 30 mg/kg of 5-HTP showed no sign of excitement but lay slightly drowsy.

To produce an unilateral increase of the brain 5-HT level, ANTONELLI, BERTACCINI and MANTEGAZZINI (unpublished results) infused 5-HTP (20 mg in 20 min) into one of the carotid arteries of conscious cats through a canula tied in the lingual artery. No behavioural change nor neurological asymmetry occurred after the infusion, the only effects being a marked myosis on the infused side, salivation and some times vomiting. Two cats were killed ten minutes after dosing: the amine concentration of the caudate nucleus of the infused side was twofold that of the caudate nucleus of the opposite side and of the caudate nucleus of untreated animals.

From the above data it is clear that, in the cat, low doses of 5-HTP, which induce marked increases in the brain amine content and marked peripheral effects, do not affect the behaviour, or, at the most, produce a slight drowsiness; on the other hand, high doses produce excitement and sham rage.

4. Dog

BOGDANSKI et al. (1958) observed ataxia and other abnormalities in walking after 20 mg/kg or more of 5-HTP i.v. and trembling, extensory twitches, plastic rigidity, abolition of the patellar reflex and of the responsiveness to painful stimuli after 40 mg/kg or more. Doses between 40 and 60 mg/kg i.v. were often lethal. The animals seemed to be drowsy after 5—30 mg/kg and excited after 40—60 mg/kg i.v. During the excitement phase, the animals walked hesitatingly

and although they had the eyes open, they did not avoid obstacles as blind. They did not show aggressive attitude, on the contrary they seemed to be terrified. Even after the lowest dose there was mydriasis that was not reduced by light. Other vegetative effects were dyspnea, increased nasal, salivary and lacrimal secretions and intestinal hyper-motility. Two hours after the injection of 60 mg/kg i.v. of 5-HTP the content of 5-HT increased about 4 times in the medulla, 7 to 10 times in the cortical grey matter, in the thalamus, in the hypothalamus, in the mid-brain, in the cerebellum and in the pons, and 15 times in the caudate nucleus. CRONHEIM and GOURZIS (1960) injected dogs with 30 mg/kg i.v. of 5-HTP. During the first 15—30 minutes after injection, the animals appeared to be subdued; during the next two hours they still lay quietly without showing any interest in their surroundings, but reacted hostilely to the approach of persons or objects. There were no signs of blindness or of motor incoordination, but there was marked salivation and mydriasis and pupillary light reflex was depressed. Later on the animals frequently assumed a peculiar posture, hunching on their hindquarters, with their snouts touching the floor. Recovery took place within 4—6 hours. In dogs pretreated with reserpine (1 mg/kg i.v.) the 5-HTP (30 mg/kg i.v.) accentuated the reserpine induced sedation and transformed it into a comatose state.

HIMWICH and COSTA (1960) injected 5-HTP into a vein or cranially into a common carotid or vertebral artery without interrupting the arterial blood flow, and compared the increase in the 5-HT content in certain brain structures with the severity of the symptomatology. The dogs were pretreated with tranylcypromine (a MAO inhibitor). 10—15 min after intravenous injection of 5-HTP (3—7 mg/kg) the animals appeared to be drowsy and showed no interest in their surroundings; after 20—30 min hypertonic extension of the legs occurred; after 40—50 min the animals showed motor hyperactivity and were more alert; there was motor incoordination accompanied by a hunched back and, then, by steppage gate. The syndrome developed gradually into a state so called as "obstinate progression": the animals walked constantly and aimlessly until they found an obstacle to push against obstinately. During this phase they were insensitive to light, sound and touch. Hostility and aggressiveness sometimes appeared before "obstinate progression". Salivation, hyperthermia and panting occurred inconstantly. Recovery started 3—4 hrs after the injection. Intrarterial injections gave the same symptomatology, but for the same dose of 5-HTP the severest symptoms occurred after intravertebral injection or after intracarotid injection in dogs with the basilar artery clipped at mid-medullary level. In the latter case the carotid blood reached all the regions placed cranially to the arterial block. These results suggested to the A.A. that the structures more involved in the 5-HTP syndrome are placed between the mid-medullary level and the area of the brain normally irrigated by carotid blood. Dogs injected with tranylcypromine and 5-HTP (5—7 mg/kg i.v.) were killed at definite stages of the syndrome. The contents of 5-HT in the pons, the extralaminar nuclei of the thalamus, the corpora quadrigemina and the hippocampus significantly increased when the dogs exhibited "ostinate progression"; the 5-HT content in the extralaminar nuclei of the thalamus, the piriform cortex and the amygdalae significantly increased when the dogs showed agressive behaviour; the 5-HT content in the caudate nucleus and the septum increased in all the stages of the syndrome so that no correlation could be made between the concentration of 5-HT in these structures and behaviour; no significant increase was observed in the frontal cortex, the midbrain, the hypothalamus and in the medulla oblongata at any stage of the 5-HTP syndrome.

From the data given above it appears that 5-HTP gives different effects according to the dose; at low doses (between about 5 and 20 mg/kg i.v.) induces only sedation; at higher doses (above 40 mg/kg i.v.) it chiefly induces excitement and affects postural aptitude, motility and responsiveness to stimuli; at intermediate doses it induces sedation at first and excitement later. Tranylcypromine, a MAO inhibitor, increases sensitivity to 5-HTP.

5. Pigeon

APRISON and FERSTER (1960, 1961a) administered 5-HTP to pigeons trained to peck a key in order to gain access to food. Depending on the colour of the key the 50th peck (fixed ratio) or the first peck after 10 min (fixed interval) operated the food magazine. After 25, 50 and 75 mg/kg i.m. of 5-HTP the rate of pecking fell off proportionally to the dose. Lower doses had little or no effect. The treated pigeons showed tremors, head-shaking and continuous shifting from one leg to the other. Iproniazid potentiated the behavioural effects of 5-HTP (APRISON and FERSTER 1961b).

III. Bufotenine

1. Rat

MAHLER et al. (1958) and MAHLER and HUMOLLER (1959) injected bufotenine (8—27 mg/kg i.p.) into rats trained to climb a pole under the double incentive of food at the top and noxious stimuli at the bottom. After the injection, the animals seemed confused, often climbed only part way up and returned to the stimulating grid instead of making a systematic ascent to the food platform. The effect started 5—10 min after the injection and lasted 90—120 min. LSD-25 (0.3—0.7 mg/kg i.p.) produced the same effects. GESSNER et al. (1961) observed a partial block of the conditioned avoidance responses after 20.5 mg/kg of bufotenine.

2. Dog

FABING and HAWKINS (1956) reported that dogs intravenously injected with bufotenine (4 mg/kg) splayed out their hind legs, howled violently and exhibited indifference to noxious stimuli as well as to attacks from other dogs. The vegetative symptoms were salivation and piloerection.

HIMWICH and coll. (HIMWICH et al. 1959; COSTA et al. 1959; HIMWICH and COSTA 1960) injected bufotenine (1 mg/kg) into the vertebral artery, the internal carotid artery, the descending aorta or intravenously and compared the effects produced by the different routes. In some of the experiments the basilar artery was tied in order to separate the vertebral circulation from the carotid one. The carotid receptors were denerved. After the injection there was always marked muscular weakness, often unresponsiveness to visual or auditory stimulation and hypersensitivity to touch and, in the dogs most severely affected, inhability to stand up. The animals frequently responded to prodding by howling or crying and did not attempt to defend themselves. Later they howled even when they were not stimulated. A few animals responded by circling or by convulsing to the injection into the carotid artery. Salivation and mydriasis were the vegetative symptoms. The effects produced by the bufotenine appeared a few minutes after the injection and lasted up to 4 hrs. They were more pronounced after the injection into the vertebral artery than after the injection into a vein or into the descending aorta; the intracarotid route was the least effective. These results allow us to exclude the peripheral effects as the determining factor of the be-

havioural response to bufotenine and support the claim that the behavioural effects depend on the amine action on structures located in the regions irrigated by the vertebral artery.

3. Monkey

For about 20 min after intravenous administration of bufotenine (5 mg/kg) the monkeys *(Macaca mulatta)* maintained a prone position; afterwards they assumed a sitting posture and made attempts to move around. The movements were ataxic but within 1 hr ataxia faded out. Muscular power was unaffected by the bufotenine, while the reactions to visual and painful stimuli were abolished. The animals were unusually tame. Once ataxia had gone, the animals moved around, bumping headlong into any objects interposed in their path and showed no reactions to moving objects or lights. The bufotenine effects lasted from one and a half to two hours. Doses below 5 mg/kg produced weaker effects. LSD-25 behaved like bufotenine (EVARTS 1956).

To sum up: In the rat, bufotenine partially blocks the conditioned responses and impairs the performance of trained animals; in the dog and the monkey it reduces reactions to visual and auditory stimuli, defensive and aggressive reactions and affects motility and posture. It is proved that, in the dog, the behavioural effects are not dependent on the peripheral actions of the amine.

IV. Psilocybin

1. Mouse

10 and 50 mg/kg s.c. of psilocybin reduced spontaneous motor activity (light beam interruption method) and produced piloerection and mydriasis. Lower doses were ineffective. 50 mg/kg s.c. significantly reduced the reaction time to noxious stimulation in normal mice as well as in mice previously injected with morphine (WEIDMANN et al. 1958; CERLETTI 1959). Reduced motor activity after psilocybin was also observed by DELAY et al. (1959). The authors registered by actographic method the spontaneous motor activity and that induced by noxious stimuli both in normal mice and in mice pretreated with imino-$\beta\beta'$-dipropionitrile (IDPN) (souris tournante). In normal mice, 0.5 mg/kg of psilocybin i.p. had no effect, 5—50 mg/kg slightly reduced the spontaneous motility only, and 100 mg/kg markedly reduced spontaneous motility as well as that induced by noxious stimulation. The effect was more evident in the IDPN mice and lasted from 15 min to more than 1 hr according to the dose. LSD-25 had the same action as psilocybin on motility, but, at variance with the amine, produced bristling, salivation and tremors.

2. Rabbit

WEIDMANN et al. (1958) and CERLETTI (1959) briefly reported that psilocybin (1—3 mg/kg i.v.) produced slight sedation together with pupillary dilatation, increase in heart rate and hyperthermia. The hyperthermia appeared with doses as low as 0.02 mg/kg and increased rather slowly with the dose. Doses lower than 1 mg/kg i.v. did not modify the behaviour. Tameness or sedation, associated to slight hyper-excitability to stimuli, was also observed by MONNIER (1959) in rabbits intravenously injected with psilocybin (1.5—5 mg/kg). The vegetative effects were mydriasis, slight hypertension, long lasting hyperpnea and transitory bradycardia.

3. Monkey

In the monkey, psilocybin gives effects similar to those observed in the mouse and in the rabbit i.e. slight tranquillization after large doses (CERLETTI 1959).

4. Spider

Psilocybin (0.3—6 g/kg) given orally to *Araneus diadematus* stopped their web-building activity for 24 hrs in more than 90% of the animals (WITT 1960, CHRISTIANSEN et al. 1962). 150 mg/kg of amine given on 4 different days caused a delay in web-building. From the changes of the webstructure the AA. concluded that the treated spiders behaved as if they were heavier.

V. Tryptamine and tryptophan

In rats, intravenous tryptamine produced clonic convulsions localised in the forepaws or generalized, depending on the dose. 5 mg/kg gave convulsions in 4% and 40 mg/kg in 98% of the animals. The convulsive phase lasted, after the highest doses, 30—40 seconds. In rabbits (i.v. infusion for 5—10 min of 2—3 mg/kg/min) and in monkeys (10 mg/kg or more i.v.) tryptamine produced the same effects. Iproniazid enhanced the convulsant action of the amine (TEDESCHI et al. 1959a, 1959b). Tranylcypromine, another MAO inhibitor, behaved as iproniazid in the rat. Both inhibitors facilitated the accumulation in the brain of the amine injected i.v.; there was some relationship between brain tryptamine level and occurrence, duration and intensity of the convulsions (GREEN and SAWYER 1960).

In cats tryptamine caused convulsions, tonic extension of the limbs, hissing and snarling, piloerection, salivation and mydriasis. The animals behaved as angry or afraid. These effects lasted for about 5 min, but the animals remained subdued for some hours afterwards. Iproniazid premedication prolonged the phase of excitement (VANE et al. 1961).

HESS et al. (1959) reported that in rabbits pretreated with iproniazid, L-tryptophan (800 mg/kg i.p.) produced marked central effects, including convulsions, and marked increase in brain tryptamine level (more than 10 times the normal).

HESS and DOEPFNER (1961) described the behavioural effects of tryptophan in normal rats pretreated with iproniazid (150 mg/kg i.p.) or with nialamide (20 mg/kg) or with JB 516 (5 mg/kg i.p.), three MAO inhibitors. In normal rats and in rats pretreated with nialamide (1 or 16 hrs.) or with iproniazid (1 hr.) tryptophan (200 mg/kg i.p.) did not produce any behavioural change. In rats pretreated with JB 516 (1 or 16 hrs.) or with iproniazid (16 hrs.) the aminoacid at the same dose produced headshake and aimless, continuous motor hyperactivity. Larger doses of tryptophan (800 mg/kg i.p.) administered after iproniazid or JB 516 produced more striking behavioural effects: the rats exhibited a backward circling motion, generalized tremors and then convulsions, paralysis and death occurring within about 2 hours. In animals pretreated with MAO-inhibitors, the tryptophan (200 mg/kg i.p.) induced marked increase in brain concentrations of 5-HT and tryptamine, but there was no direct relationship between brain amine levels and behavioural changes.

According to CRONHEIM and GOURZIS (1960) i.v. infusion of L-tryptophan (0.1 mg/kg/min for 3 hrs.) in the dog did not induce any behavioural change. Tryptamine, when injected into lateral ventricles, produced in the dog (800 μg/kg) a catatonic-like state similar to that observed after injection of 5-HT into the third ventricle (EDERY and SCHATZBERG-PORATH 1960), and in the cat (200 μg) ataxia, tremor, loss of spontaneous motor activity and tachypnea, i.e. symptoms similar to those observed after 5-HT (SCHAIN 1961).

L-Tryptophan and tryptamine (as 5-HTP and 5-HT) markedly depressed motor activity of grouped mice (photocell counter technique) (BROWN 1960). The effect was already evident after 0.07 mg/kg i.p. of tryptophan, but it did not

increase with the dose (up to 150 mg/kg i.p.). L-Tryptophan (0.018 mg/kg i.p.) also prevented the motor stimulation induced by cocaine, amphetamine and caffeine, but not that induced by pipradol. Depression of spontaneous locomotion in mice injected with tryptamine (50 mg/kg i.p.) was also observed by VANE et al. (1961) (photocell counter technique).

VI. Other indolealkylamines

GREIG et al. (1959) observed excitement and irritability in mice and rats treated with α-methyltryptamine and α-ethyltryptamine, two MAO inhibitors. They also observed that 5-hydroxy-α-methyltryptamine which is deprived of MAO blocking effect, did not change behaviour. Locomotor excitement was also observed by VAN METER et al. (1960) in rats after α-methyltryptamine (10 to 20 mg/kg i.p.), by GREIG et al. (1961) in mice after α-ethyltryptamine and by VANE et al. (1961) in mice injected with α-methyltryptamine (12.5 mg/kg i.p.), α-ethyltryptamine (12.5 mg/kg i.p.) or 5-methoxy-α-methyltryptamine (50 mg/kg i.p.). In cats, motor activity appeared to be reduced after α-ethyltryptamine (10 mg/kg i.p.; 5 mg/kg were ineffective); the animals walked without ataxia when prodded and exhibited a tipical defensive response when stimulated. The pupil was dilated and nictitating membrane contracted (MATTHEWS et al. 1961).

SAI-HALÁSZ and ENDRÖCZY (1959) administered N,N-dimethyltryptamine and N,N-diethyltryptamine (two tryptamine derivatives with psychotic effects on humans) to dogs trained to recognize the bell sound announcing a reward (access to food). The two amines (2 mg/kg and 1.5 mg/kg i.m. respectively) first impaired the discriminating ability and later knocked out the responsiveness to the stimuli. Furthermore animals injected with N,N-diethyltryptamine exhibited hallucinatory behaviour. Recovery occurred after 2 hrs or more.

N,N-diethyltryptamine affected the behavioural responses evoked in dogs by electrical stimulation of the reticular formation and of the amygdalae. Before the drug, stimulation of the reticular formation evoked a fear reaction; after the drug it evoked a reaction of rage and hostility. The stimulation of the amygdalae gave rise to a fear reaction which was enhanced by the N,N-diethyltryptamine (SAI-HALÂSZ and ENDRÖCZY 1959).

GESSNER et al. (1961) reported that 5-methoxygramine (17.5 mg/kg), 5 methoxytryptamine (19 mg/kg) and 5-methoxy-N,N-dimethyltryptamine (11 mg/kg) blocked the conditioned avoidance responses in the rat. The first two amines were just as active as the bufotenine (20.5 mg/kg), whereas the 5-methoxy-N,N-dimethyltryptamine was much more active. Melatonin (46 mg/kg) and gramine (14.5 mg/kg) were inactive.

EDERY and SCHATZBERG-PORATH (1960) injected 5-fluorotryptamine (1 mg/kg), 4-fluoro-7-methyltryptamine (2 mg/kg) and tryptamine (0.8 mg/kg) into the lateral ventricle of dogs. After the injection the animals fell into a catatonic-like state similar to that observed by SACCHI et al. (1956) after 5-HT injection.

CRONHEIM and GOURZIS (1960) infused intravenously 1-benzyl-2,5-dimethylserotonine (BAS), a 5-HT-antagonist, (100 μg/kg/min for 3 hrs.) into normal dogs and dogs treated with reserpine. In the normal dogs the BAS infusion produced mydriasis, skeletal muscle disturbance and apparent depression, without modifying the blood pressure or the heart rate; in the dogs treated with reserpine the BAS infusion (as with the 5-HT infusion) transformed the slight reserpine-induced sedation into a comatose state and made the blood pressure collapse to about 65 mm Hg (low enough to explain the deep sedation!).

GADDUM and VOGT (1956) injected 5-benzyloxygramine (2.1 mg), a 5-HT-antagonist, into the lateral ventricle of cats and did not observe any behavioural change or prevention of the lethargic action of 5-HT administered by the same route.

B. Passage of 5-HT through the blood-brain barrier

In the mouse WOOLLEY and SHAW (1954) did not observe any detectable increase of the brain 5-HT level after intraperitoneal injection of 5 mg of 5-HT (chemical assay) and SHORE et al. (1957) found a small increase (about 25%) 15 min after intraperitoneal injection of a large dose of amine (100 mg/kg).

In the rat KÄRKI and PAASONEN (1959) found a conspicuous rise of the brain 5-HT concentration (from 0.5 μg/g to about 1.2 μg/g) 10 min after intravenous injection of 4.3 mg/kg of amine (biological assay). Similar percentage increase was also observed in animals preinjected with iproniazid. From these results it seems that in the rat the blood-brain barrier is largely permeable to 5-HT, but BERTACCINI, MANTEGAZZINI and PEGRASSI (unpublished data) were not able to confirm the KÄRKI and PAASONEN's data. They did not found any increase of the brain 5-HT level 10—15 min after intravenous injection of 10 mg/kg of amine in normal and iproniazidised rats (biological assay).

MCISAAC and PAGE (1959) found significant amounts of radioactivity in the brains of rats i.p. injected with about 15 mg/kg of 5-hydroxytryptamine-C^{14}. They also observed the same fact in one rabbit 4 days after intraperitoneal administration of 8 mg/kg of amine. According to the AA. the significance of these data is doubtful because the radioactivity might depend on the extracerebral metabolites of the amine rather than on the intracerebral ones or on the amine itself. No detectable increase in 5-HT brain level was observed by UDENFRIEND et al. (1957 b) in rabbits and dogs after 60 mg/kg and by ERSPAMER (1961) in rabbits after 10—20 mg/kg i.v. of 5-HT.

COSTA and APRISON (1957, 1958), in the course of cross circulation experiments in rabbits, injected 2—4 mg of 5-HT into a common or internal carotid artery of the recipient animal. They observed that the amine level in some areas of the brain of the recipient animal was higher than that in the corresponding areas of the donor animal. The significance of this result cannot be generalized because some factors related to the experimental conditions (heparin or interruption of the blood circulation during the insertion of the canulas or reduction of arterial cerebral inflow and of the venous outflow caused by the ligature of some vessels) may have modified the capillary wall, facilitating the passage of the 5-HT into the brain.

To sum up: the proof that 5-HT can get through the blood-brain barrier is lacking. The data backing this suggestion have not been confirmed or are not convincing due to the possibility that the permeability of the capillary wall was modified by the experimental conditions.

C. Effects on body temperature

It has been frequently reported that 5-HT produces hypothermia and 5-HTP hyperthermia, but there is no evidence at all indicating the central origin of these effects.

In mice 5-HT (43 mg/kg i.p.) caused a fall in rectal temperature from 38° C to 33° C in 30 min (room temperature 22° C) (LESSIN and PARKES 1957), and enhanced (20 mg/kg s.c.) (from 3° C to 10° C) the hypothermic response of animals exposed to a cold environment (FASTIER et al. 1957).

In rats injected with 5-HT (5 mg/kg s.c.) the rectal temperature dropped about 2° C below normal in the 1st hr and gradually returned toward normal in the subsequent 3 hrs. A secondary hypothermia occurred 6 and 24 hrs after injection (HOFFMAN 1958b). Adrenalectomy markedly potentiated the effect of 5-HT in rats. Replacement therapy with adrenal cortical extracts prevented the potentiating effect of adrenalectomy and abolished the secondary hypothermia. Treatment with epinephrine prevented the primary hypothermia, not the secondary one, induced by 5-HT in adrenalectomized rats (HOFFMAN 1959). The meaning of these data is not clear. FÖLDES and KOMLÓS (1959) reported that 5-HT (2.1 to 4.3 mg/kg s.c.) induced hypothermia in rats kept at room temperature of 20° C, but not in animals kept at 30° C.

5-HT (5 mg/kg s.c.) lowered also the body temperature of pigeons. Maximal depression (1.6° C) occurred 0.5—1 hr after the injection and recovery was attained 24 hrs later (HOFFMAN 1958a).

5-HTP has an opposite effect to 5-HT, causing hyperthermia. HORITA and GOGERTY (1958) studied the pyretogenic effect of 5-HTP in rabbits kept at room temperature (24° C). 25 mg/kg i.v. had a slight effect; 50 mg/kg i.v. induced hyperthermia (1—1.5° C) lasting 3—4 hrs. 75—100 mg/kg i.v. caused an increase up to 43—44° C within 30—60 min, frequently followed by death. Iproniazid premedication potentiated the pyretogenic effect of 5-HTP. Doses of 5—10 mg/kg i.v. were large enough to give hyperthermia and 20 mg/kg i.v. caused death. Death occurred at the apex of the hyperthermia.

D. Interferences with central acting drugs

This section deals with the interferences at central level between indolealkylamines (and precursors) and central acting drugs. Drugs which antagonize or release the amines, or block the enzymes responsible for their metabolism are not considered here but in the chapters 10, 11 and 12 of this review.

I. Hypnotics and anesthetics

1. 5-Hydroxytryptamine

FORNAROLI and KOLLER (1954, 1955) first reported that 5-HT prolonged the hypnosis induced by barbiturates and ether, and that it induced hypnosis when injected after an ineffective dose of barbiturate. In these experiments, and in followings, the hypnosis was defined as absence of the righting reflexes. Many other AA. confirmed FORNAROLI and KOLLER's observations. The results will be found in Table 1.

Summarizing we may say: I. 5-HT enhances the blocking action on the righting reflexes of many drugs with different chemical structure and different metabolism (barbiturates, ether, chloral hydrate, ethanol, mephenesin and meprobamate). II. 5-HT enhances the hypnotic action of barbiturates even when they are injected intravenously. III. Amine injected i.v. in animals just recovering from barbiturate hypnosis quickly re-induces the hypnosis; injected i.v. after a non-hypnotic dose of thiopental induces hypnosis. These data lead to the conclusion that the potentiating effect of 5-HT does not depend on interferences with the speed of adsorption and the rate of detoxication of the hypnotics. However its implication cannot be completely rouled out.

Hypothermia prolongs the duration of the hypnosis induced in mice by pentobarbital and allylbarbituric acid (FUHRMAN 1947); 5-HT produces hypothermia in mice and rats. FASTIER et al. (1957) and DANDIYA and SELLERS (1961)

Table 1

5-HT		Drugs tested			
Dose (mg/kg) and routes	Time (in min) before or after drugs	Dose (mg/kg) and route	Effects[1]	Animal	Authors
0.43—4.3 i.v.	after	kemithal 100 i.v. thiopental 40 i.v.	+	mouse	Fornaroli and Koller (1954, 1955)
		thiopental 2.5; 5; 10; 15 i.v.	+	rat	
1.3—20	before	ether	+	rat	
0.86 i.p.	same time	urethan 700			
0.86; 8.6 i.p. 0.86 i.v.	10 before or same time	pentobarbital 15; 30	0	rat	
0.86 s.c.	10 before	kemithal 100			
8.6 i.p.	10 before	ether			Pierre and Cahn (1955)
0.86; 8.6 s.c. 2.15 i.v.	5—10 before	thiopental 40	+		
5.4	2 after	thiopental 42 i.v.	0	rabbit	
0.54; 5.4	2 after or 10 before	pentobarbital 59; 65 i.v. kemithal 96; 106 i.v.	+		
20 i.p. 20 i.v.	10 before after recovery	hexobarbital 100 i.p.	+	mouse	Shore et al. (1955)
20 i.p. 20 s.c.	before	cyclobarbital 100 i.p. chloral hydrate 250 i.p.	+	mouse	Fastier (1956)
8.6 i.p.	10 before	hexobarbital 100 i.p.	+	mouse	Salmoiraghi et al. (1956 b)
		hexobarbital 150 i.p.	+	rat	
10; 15 s.c.	30 before	pentobarbital i.v. infusion	+	rabbit	Mantegazzini (1956)
8.6 i.p.	10 before	hexobarbital 70 i.p.	+	mouse	Salmoiraghi and Page (1957)
5—360 i.p. 5 i.v.	60 before after recovery	hexobarbital 100 i.p.	+	mouse	Brown (1957)
4.5 i.v.	10 before	thiopental 20 i.v.	+	mouse	Taeschler and Cerletti (1957)
8.6 i.p.	10 before	hexobarbital 100 i.p. butabarbital 56 i.p. mephenesin 320; 435 i.p. meprobamate 240; 280 i.p.	+	mouse	Zanowiak and Rodman (1959)
10 i.p.	before	chloral hydrate 325 i.p.	+	mouse	Lévy and Michel-Ber (1960)
2.15—8.6 i.p.	10 before	hexobarbital 100 i.p.	+	mouse	Aston and Cullumbine (1960)
8.6 i.p.	10 before	ethanol 5 i.p.			
9 i.p.	10 before	hexobarbital 105 i.p.	+	rat	Gessner et al. (1960)
3.44 i.p.	10 before	pentobarbital 50 i.p.	+	mouse	Dandiya and Sellers (1961)
12.9	60 before	hexobarbital 90—100 i.p.	+	mouse	Pennefather and Thorp (1958)
4.3; 8.6 i.p.	3—5 before	hexobarbital 75 i.p.	+	mouse	Holtz et al. (1957)

[1] + = potentiating effect; 0 = no effect.

put in evidence the contribution of 5-HT hypothermia on the prolongation of the hypnosis. FASTIER et al. reported that amine (20 mg/kg s.c. in mice) prolonged the chloral hydrate sleeping time (200 mg/kg i.p. 10 min after 5-HT) and at the same time enhanced the fall in body temperature induced by the hypnotic. If the fall in body temperature was prevented by keeping the mice in a room at 38° C, the chloral hydrate sleeping time (about 15 min) did not change, while the chloral hydrate + 5-HT sleeping time was markedly reduced (from 82 to about 37 min). DANDIYA and SELLERS (1961) observed that 5-HT (3.44 mg/kg i.p.) prolonged the pentobarbital sleeping time (from about 25 to 64 min) and accentuated the fall in body temperature (11° C instead of 6.7° C) of mice kept at room temperature of 22° C. Keeping the mice at 38° C partly counteracted the potentiating effect of 5-HT on the pentobarbital sleeping time (from 64 to about 37.5 min), but did not modify the effect of pentobarbital alone. We may conclude that hypothermia largely, but not solely, contributes to the hypnosis-prolonging activity of 5-HT.

The speed of re-induction of hypnosis after 5-HT injection in animals recovering from barbiturates, or of induction in animals treated with an ineffective dose of barbiturates is another factor which leads us to think that the lowering of body temperature may not be the only factor responsible for the potentiating effect of 5-HT. In fact, hypothermia takes some time to set in, whereas hypnosis, in the conditions quoted above, almost immediately follows the 5-HT injection. In rabbits, 10 and 15 mg/kg s.c. of 5-HT, i.e. doses large enough to potentiate a non-hypnotic dose of pentobarbital caused a conspicuous fall in blood pressure (from about 110 mm Hg to 70—80 mm Hg) (MANTEGAZZINI 1956). In the rat 5-HT (2—3 mg/kg i.p.) injected immediately after recovery from a thiopental hypnosis, quickly re-induced the hypnosis and brought about a fall of 40—60 mm Hg in blood pressure. Hypotension was long lasting (MANTEGAZZINI and PEGRASSI, unpublished data). Not 5-HT only but many other vaso-active drugs (histamine, dopamine, epinephrine and norepinephrine) enhanced the barbiturates and chloral hydrate hypnotic activity in mice (FASTIER 1956; FASTIER et al. 1957; LÉVY and MICHEL-BER 1960; DANDIYA and SELLERS 1961). The suspect arises that vascular changes, apart from hypothermia, may play some role in prolonging the hypnosis.

To sum up: 5-HT potentiates blocking effects on the righting reflexes of hypnotic and anesthetic drugs. It is certain that hypothermia largely contributes to the production of the potentiating effect; it is also likely that the vascular effects of 5-HT (systemic hypotension or/and cerebral blood flow changes) may contribute to it. There is no proof that the potentiating activity depends on a direct action of 5-HT on the CNS.

2. 5-Hydroxytryptophan

HOLTZ et al. (1957) observed that 5-HTP prolonged, as 5-HT, the hexobarbital sleeping time in mice (15 mg/kg of 5-HTP i.v. 5—8 min before 75 mg/kg i.p. of barbiturate). In the same species, 5-HTP (50 and 40 mg/kg i.p.) also prolonged the hypnosis produced by pentobarbital (50 mg/kg i.p.) (KATO 1959) and chloral hydrate (325 mg/kg i.p.) (LÉVY and MICHEL-BER 1960). After iproniazid, 5-HTP showed an opposite effect, i.e. antagonized the hypnotic effect of hexobarbital (HOLTZ et al. 1957) and chloral hydrate (LÉVY and MICHEL-BER 1960).

3. Bufotenine and psilocybin

Prolongation of the chloral hydrate and hexobarbital sleeping time after bufotenine was observed by FASTIER (1956) (20 mg/kg of amine i.p. 10 min before 250 mg/kg of chloral hydrate i.p. in mice) and by GESSNER et al. (1960) (10.5 mg/kg

of amine i.p. 10 min before 105 mg/kg of barbiturate i.p. in rats). According to SALMOIRAGHI and PAGE (1957) bufotenine in large doses (5 mg/kg i.p. in mice) blocked, and in small doses (2—100 μg/kg i.p.) enhanced the potentiating effect of 5-HT (8.3 mg/kg i.p.) on hexobarbital hypnosis. Psilocybin (11 mg/kg i.p.), like bufotenine, prolonged hexobarbital hypnosis in rats (GESSNER et al. 1960).

4. Tryptamine and tryptophan

Prolongation of the chloral hydrate sleeping time after tryptamine was observed by FASTIER (1956) (20 mg/kg of amine i.p. 10 min before 250 mg/kg of chloral hydrate i.p. in mice) and LÉVY and MICHEL-BER (1960) (50 mg/kg of amine i.p. before 325 mg/kg of chloral hydrate i.p. in mice). The latter AA. reported that tryptophan (600 mg/kg i.p.) behaved as tryptamine. Tryptamine (20 mg/kg i.p.) and tryptophan (20 mg/kg i.v.) also prolonged the hexobarbital sleeping time in mice (75 mg/kg i.p. 3—5 min after dosing); iproniazid potentiated the effect of the amine but inverted that of the aminoacid (HOLTZ et al. 1957).

II. Convulsants

5-HT (8.6 and 215 mg/kg s.c. 15 or 120 min before the convulsants) did not modify the clonic convulsive pattern of camphor (70 and 205 mg/kg i.p.) and leptazol (66 mg/kg i.p.) (BIANCHI 1957) nor (up to 300 mg/kg s.c.) did it afford any protection against the convulsant action of leptazol (40 mg/kg i.v.) in mice, whereas it protected rats from epileptic seizures induced by acoustic stimuli (DE 50 = 7 mg/kg s.c.) (TRIPOD et al. 1957).

5-HTP, even at doses (100 mg/kg i.p.) which induced marked increase in the 5-HT brain content, afforded little protection against the convulsant action of leptazol in rats (BONNYCASTLE et al. 1957) and mice (KOBINGER 1958) or against the lethal action of leptazol in mice (LESSIN and PARKES 1959) and did not modify the supramaximal electroshock seizure pattern in rats (PROCKOP et al. 1959). After iproniazid, 5-HTP (at doses between 25 and 50 mg/kg i.p.) raised the convulsant dose (KOBINGER 1958) and the lethal dose (LESSIN and PARKES 1959) of leptazol i.v. in mice, and prevented the tonic convulsions by electroshock in rats (PROCKOP et al. 1959).

III. Other central acting drugs

5-HT (5—10 mg/kg s.c.), 5-HTP (30—400 mg/kg s.c.) and tryptamine (100 mg/kg s.c.) but not tryptophan (100 mg/kg s.c.) enhaced and prolonged the analgesic effect of morphine in mice (reaction time to painful heat stimulation of the tail). 5-HT by itself (20 mg/kg s.c.) prolonged the reaction time to painful stimulation, whereas 5-HTP was ineffective even in very large doses (400 mg/kg s.c.) (SIGG et al. 1958). 5-HTP (15 mg/kg s.c.) potentiated the analgesic effect of morphine also in mice pretreated with iproniazid (reaction time to painful stimulation of the tail) (SCHAUMANN 1958).

5-HT, at a dose of 4.55 mg/kg i.p., partially blocked the motor hyperactivity induced by d-methylamphetamine (3.3 mg/kg i.p.) and by cocaine (20 mg/kg i.p.) (KOBINGER 1958a). At the dose of 10 mg/kg s.c. it completely prevented the hyperactivity produced by d-amphetamine (4 mg/kg s.c. in mice) (photocell counter technique), but even at high doses (up to 300 mg/kg s.c.) it did not protect grouped mice from the toxic effects of d-amphetamine (MAXWELL 1959). In mice, 5-HTP (20 mg/kg i.p.) and tryptophan (0.018 mg/kg i.p.) reduced

spontaneous motor activity and antagonized the hypermotility induced by cocaine (2.5—10 mg/kg s.c.), by d-amphetamine (2—10 mg/kg s.c.) and by caffeine (20 mg/kg s.c.) (photocell counter technique) (BROWN 1960).

E. Drugs and treatments affecting the brain 5-HT content

Some drugs or treatments affecting the brain functions also affects the 5-HT content. The study of the relationships between changes in brain 5-HT level and pharmacological effects induced by these treatments or drugs may throw some light on the physiological role played by 5-HT normally present in the brain. Drugs which antagonize or release 5-HT or block the enzymes responsible for its metabolism are excluded from this section as they are dealt with in chapters 10, 11 and 12 respectively of this review.

I. Electroshock and convulsants

GARATTINI and co-workers (GARATTINI et al. 1957, GARATTINI and VALZELLI 1957, JORI et al. 1957) reported that after electroshock or leptazol shock (80 mg/kg i.p.) in rats there was a conspicuous increase in brain 5-HT level (spectrophotometric and biological methods). The increase reached the maximum (3.5 times the normal level in spectrophotometric assay and 27—40 times in biological assay) 10 min after electro- or chemo-shock; it gradually fell off and was no longer detectable after 24 hrs. A second increase was detectable between 36 and 72 hrs. after the electroshock. The first increase in brain 5-HT, but not the second one, was associated with a decrease in intestinal 5-HT.

Electroshock also induced an increase in brain 5-HT level (10 min and 40 hrs. after electroshock) in guinea-pigs, rabbits and dogs, but not in mice (FRESIA et al. 1957). Significant increases in the amine level after electroshock in dogs were observed in the motor area of the cerebral cortex (51%), in the hypothalamus (38%) and in the mid-brain (60%) but not in the visual cortex, in the cerebellum and in the thalamus (spectrofluorimetric method) (FRESIA et al. 1958) and in rats in the diencephalic (58%) and mesencephalic portions (93%) and in the cerebral hemispheres (43%) but not in the cerebellum (spectrofluorimetric method) (GARATTINI et al. 1960).

According to GARATTINI et al. (1960) there was no relationship between the increase in brain 5-HT and the intensity of the epileptic seizures after electroshock. In fact when the convulsions have been reduced or abolished pretreating the animals with barbiturates (phenobarbital 120 mg/kg i.p.; pentobarbital 35 mg/kg i.p.; hexobarbital 80 mg/kg i.p.) or with diphenylhydantoin (100 mg/kg i.p.) or using an intensity of current insufficient to induce typical convulsions, there was all the same an increase in brain 5-HT level as that observed after typical convulsions. Note, however, that the three barbiturates used and diphenylhydantoin induce by themselves an increase in the brain amine content (BONNYCASTLE et al. 1957).

Three reports have challenged the findings of GARATTINI and co-workers described above. BONNYCASTLE et al. (1957) briefly reported that convulsant procedures such as electroshock or the administration of leptazol, picrotoxin or CO_2 did not modify the brain 5-HT level in rats (biological method). BERTACCINI (1959) repeated GARATTINI'S experiments but did not find any significant increase in brain 5-HT level in rats 10, 30, 60 and 120 min after electroshock and 10 and 60 min after injection of a convulsant dose of leptazol (60 mg/kg i.p.) (biological method). GAL and DREWES (1961) dosed the brain 5-HT content of

rats injected 1 hr. previously with a convulsant dose of leptazol (60 mg/kg i.p.) or of fluoroacetate (8 mg/kg i.p.). Even these AA. observed no deviations from normal values of the brain 5-HT level (spectrofluorimetric method).

The conclusion is that in rats leptazol and electroshock convulsions do not induce changes in brain 5-HT level.

II. Anticonvulsant drugs

BONNYCASTLE et al. (1957) (see also: BONNYCASTLE et al. 1956) observed that treatment of rats with various anticonvulsant drugs led to a significant increase in 5-HT level of the brain (from 0.34 to 0.5—0.6 μg/g) but not of the small intestine, spleen and venous blood. The drugs (injected i.p.) and the dosage regimens employed were as follows: diphenylhydantoin (100 mg/kg injected 16 times over 2 days), mesantoin (200 mg/kg injected once or 4 times over 2 days), trimethadione (150 mg/kg injected 4 times over 2 days), paramethadione (200 mg/kg injected once or 4 times over 2 days), epidon (400 mg/kg injected 4 times over 2 days), methylphenylsuccinimide (450 mg/kg injected once or 4 times over 2 days), phenacemide (500 mg/kg injected once or 4 times over 2 days), primidone (500 mg/kg injected once or 4 times over 2 days), phenobarbital (125 mg/kg), mephobarbital (125 mg/kg), and sodium bromide (1 g/kg injected 5 times over 2 days). Brain 5-HT levels were checked (biological method) 12 hrs. after the last dose, except in the case of sodium bromide (4 hrs. after the last dose) and of barbiturates (2.5 hrs after the injection). In a subsequent paper ANDERSON et al. (1962) reported that an increase in brain 5-HT level was evident even 30 min after 12.5 (biological method) and 50 mg/kg i.p. (spectrofluorimetric method) of diphenylhydantoin. PROCKOP et al. (1959) did not observe, in contrast with BONNYCASTLE and co-workers, any increase in cerebral 5-HT after doses of diphenylhydantoin (25 to 75 mg/kg) high enough to block the tonic extension component of electroshock in rats.

To sum up: it seems established that anticonvulsant drugs increase the brain 5-HT content in rats, but it has not yet been established whether there is correlation between the increase and the protection against convulsions. It is improbable that such increase may account for the protective action of the anticonvulsant, as 5-HTP which causes marked increase in brain 5-HT affords little protection against leptazol or electroshock convulsions (see D, II of this chapter).

III. Barbiturates and other central depressant drugs

BONNYCASTLE et al. (1957) reported that the treatment of rats with phenobarbital (125 mg/kg i.p.), mephobarbital (125 mg/kg i.p.), hexobarbital (100 mg/kg i.p.) or pentobarbital (50 mg/kg i.p.) resulted in increased 5-HT brain concentration (from 0.34 to about 0.52 μg/g) (biological method). BONNYCASTLE et al. (1962) reported also that many compounds whose common property is to depress the CNS shared in the ability to increase cerebral 5-HT (biological method): chloralose (100 mg/kg i.p.), ethyl urethan (1800 mg/kg i.p.), diethyl ether (administered by inhalation), chloral hydrate (300 mg/kg i.p.) and meperidine (25 mg/kg i.p.). The increase after pentobarbital or chloral hydrate was checked by both the biological and fluorimetric methods.

ANDERSON and BONNYCASTLE (1960) investigated the relationships between the increase in brain 5-HT (biological method) induced by pentobarbital, phenobarbital or ether in rats and the effects of these substances on the righting reflexes and spontaneous motility (photocell counter technique). 2.5 min after i.p. in-

jection of 50 mg/kg of pentobarbital the brain 5-HT level slightly increased (from 0.33 to 0.36 μg/g), and the righting reflexes were blocked. The level reached the peak (0.754 μg/g) 5 min after the injection and then declined slowly. When the righting reflexes reappeared the level was lower than 0.5 μg/g. After i.p. injection of 25 mg/kg of pentobarbital the 5-HT level approached 0.5 μg/g when the righting reflexes disappeared and fell below 0.5 μg/g when they reappeared; there was a good co-relation between the elevation of brain 5-HT and depression of motor activity. After i.p. injection of 100 mg/kg of phenobarbital there was a slow increase in the brain amine content (up to a maximum of 0.572 μg/g 2 hrs. after the injection) accompanied by a slow falling-off in motor activity; the brain 5-HT level was about 0.5 μg/g when the righting reflexes disappeared, and fell below this value when they reappeared. Three min after the beginning of ethyl-ether inhalation the 5-HT content was still normal but the righting reflexes were blocked; the content started to increase only after 10 min inhalation and reached 0.611 μg/g after 20 min inhalation. From these results it seems that the rise in brain 5-HT is not related to the onset of central depression. The AA. suggest that "it is well to keep in mind that the rise in brain 5-HT that is associated with central-acting compounds may be a fortuitous event and no bearing on the mechanism by which these compounds act". SCHANBERG and GIARMAN (1962) observed that the increase in brain 5-HT concentration induced by phenobarbital (100 mg/kg) in rats was associated with an increase in the percentage of "free" 5-HT. Increase in the amount of "free" 5-HT was observed by the AA. after other CNS depressants (chlorpromazine, reserpine, α-methyl-DOPA) irrespective of the change of total 5-HT.

It was also reported that in rabbits i.v. injected with phenobarbital (100 mg/kg) or barbital (200 mg/kg) and killed 4 hrs after dosing (BRODIE et al. 1956) (spectrofluorimetric method) and in rats i.p. injected with phenobarbital (100 mg/kg) or pentobarbital (50 mg/kg) (EFRON and GESSA 1963) (spectrofluorimetric and biological methods) no significant change in brain 5-HT level was detected.

GURSEY and OLSON (1960) reported that ethanol (2 g/kg i.v. infused) reduced the 5-HT content in the brain stem of rabbits. The amine concentration declined to about 40% of control value 30 min after dosing, then increased slowly, reaching normal value in about 6 days. Brain stem noradrenaline concentration declined correspondingly. Alcohol disappeared from the blood in 6 hrs. HÄGGENDAL and LINDQVIST (1961) did not observe any modification of brain 5-HT level after ethanol in rabbits (1 and 12 hrs. after i.v. infusion of 2 g/kg) and in mice (2 hrs. after 2.5 g/kg i.p.). In mice only after 5 g/kg, i.e. after a dose very near the lethal one, there was a slight reduction in 5-HT concentration (spectrofluorimetric method). Cerebral noradrenaline behaved like 5-HT. EFRON and GESSA (1963) confirmed the results of HÄGGENDAL and LINDQVIST, but BONNYCASTLE et al. (1962) reported that in rats ethanol (4.5 g/kg i.p.) increased brain 5-HT level.

It is wise to wait further experimental results before concluding about the effects of barbiturates and ethanol on cerebral 5-HT.

IV. Cortisone

BRODIE et al. (1956) reported that in rabbits the brain 5-HT concentration was normal 4 hrs. after i.v. injection of 26 mg/kg of cortisone (spectrofluorimetric method). WEST (1958) reported that in rats cortisone (50 mg/kg i.m. per day over 14 days) lowered the 5-TH content of the skin and did not affect that of the brain (biological method). The animals were killed 24 hrs. after the last injection. KATO and VALZELLI (1958) obtained different results. They reported that in rats

cortisone (50 mg/kg i.m. per day over 15 days) induced a slight but significant increase in brain 5-HT (from 0.48 to 0.57 μg/g). The increase was restricted to the cerebral hemispheres and to the mid-brain and pons. The content of the cerebellum and the diencephalic-hypothalamic region did not vary (spectrofluorimetric method). The animals were killed 6 hrs. after the last cortisone injection.

V. Central nervous system lesions

Toh (1960) checked the cerebral 5-HT content of rats 3 days after placing bilateral electrolytic lesions in the hypothalamus (biological method). The amine content did not significantly differ from that of control rats. Heller et al. (1962) checked the brain 5-HT content (spectrofluorimetric method) in rats 35 days after placing bilateral electrolytic lesions in the lateral hypothalamus, medial hypothalamus, septal region, hippocampus, ventral midbrain tegmentum, dorsomedial midbrain tegmentum, habenula, lateral pontine tegmentum, caudate nucleus or cortex of the dorsomedial aspect of the cerebral hemispheres. Reduction of the brain 5-HT level ranging from 12 to 15% was observed in rats with lesions in the septal region, the dorsomedial midbrain tegmentum and the ventral midbrain tegmentum. An higher reduction (36%) was observed in rats with lesions in the lateral hypothalamus. The lesions in the septal region, in the hypothalamus or in the hippocampus induced a short-lasting irritability to handling; the lesions in the dorsomedial midbrain tegmentum provoked a persistent aggressive behaviour towards an other rat caged together. There was no relationship between changes in the brain 5-HT content and behavioural changes. According to the AA. the fall in brain 5-HT level may be a result of a central denervation secondary to the section of fibres of the medial forebrain bundle within the lateral hypothalamus. In a subsequent paper the same AA. (Harvey et al. 1963) reported that a unilateral lesion in the lateral hypothalamus destroying the medial forebrain bundle, produced a 5-HT fall restricted to the lesioned hemi-brain. The effect of medial forebrain bundle lesion appeared 2—3 days after operation, reached its maximum 12 days after, remaining constant afterwards.

Antonelli et al. (1961) dosed the brain 5-HT content in cats with brain-stem acutely transected at midpontine level just in front of the trigeminal rootlets, or at mesencephalic level 1—2 mm in front of the superior border of the pons. The pontine section induced an EEG and ocular pattern typical of the waking state, whereas the mesencephalic transection resulted in a sleeping pattern. 5-HT content (biological method) of the midbrain-hypothalamus did not differ in the two opposite states.

To sum up: there is no relationship between the concentration of brain 5-HT and behavioural changes induced by cerebral lesions in rats. In cats the concentration of 5-HT in the midbrain-hypothalamus does not differ in the two opposed states of sleeping and waking induced by brain-stem transections.

F. Effects on the electroencephalogram

I. 5-Hydroxytryptamine

1. Rabbit

Ferro Milone and Gomirato (1956) observed EEG activation and marked reduction of the frequency of the convulsive spikes induced by application of strychnine on motor area after 5-HT (43—215 μg/kg i.v.). The effect began immediately after the injection and lasted 1—3 min. Mantegazzini (1956)

observed no change whatsoever in the synchronised EEG record, typical of the resting animal, after subcutaneous injection of 5-HT up to 10 mg/kg. Only after 15 mg/kg there were long periods of spontaneous activation. Such a dose of 5-HT resulted in severe hypotension which cast some doubt on the significance of EEG data. MONNIER and co-workers (GANGLOFF and MONNIER 1957; MONNIER and TISSOT 1958) observed after intravenous injection of 5-HT (0.1—1 mg/kg), a brief arousal reaction (lasting about 1 min) followed by a longer period of synchronisation (irregular highvoltage, slow waves in the cortex and subcortex with 12—14 c/sec spindle activity in sensory-motor cortex). 30—60 min after injection a "mixed arousal and relaxation pattern" appeared (low voltage fast activity in the sensory-motor cortex and a permanent, regular synchronised 3—5 c/sec rythm in the thalamus, rhinencephalon and parieto-occipital cortex). During this phase paroxysmal spike discharges spontaneously occurred in the hippocampus, and the arousal reaction to the stimulation of the midbrain reticular formation was reduced or abolished. DOMER and LONGO (1962) reported that 5-HT had no detectable effect on the electrical activity of the cerebral cortex, the hippocampus and the midbrain reticular formation up to 100 μg/kg i.v. Higher doses (up to 30 mg/kg i.v.) produced an overall diminution in the voltage of brain waves. According to the AA. the effect of the higher doses was doubtful as a severe and long-lasting hypotension was concomitant.

2. Cat

ROTHBALLER (1957) administered 5-HT (2.15—13 μg/kg i.v.) to curarized cats with intact nervous system and to cats with electrolytic lesions in the midbrain tegmentum. He observed a brief arousal reaction, followed by longer period of deactivation sometimes with abnormal slow waves. A second period of activation occurred only after high doses. There was a brief rise in blood pressure followed by long-lasting fall.

CREPAX and INFANTELLINA (1957) studied the effects of an intracarotid injection of 5-HT on the EEG of cats with intact nervous system. No change in the synchronised record occurred after doses up to 170 μg; after higher doses (up to 860 μg) it appeared a pattern attributed by the AA. to local vasomotor changes: periods of slow waves of simplified shape and low voltage, alternating with periods of electrical silence. The latency and duration of the effect depended on the dose: at 860 μg the effect appeared 10 sec after the injection and lasted up to 45 min. There was no relation between EEG changes and systemic blood pressure changes. MANTEGAZZINI (1957a, 1957b) injected 5-HT directly into the cerebral circulation (vertebral artery or bicarotid trunk) of the "encephale isolé" preparation. Vagi and in some of the experiments trigeminal nerves too, were bilaterally sectioned. 5-HT at 0.5—2 μg did not modify the desynchronized EEG pattern prevalent in the "encephale isolé" with trigeminal nerves intact, while at 0.25—1 μg it desynchronized the enduring sleeping pattern induced by trigeminal deafferentation. The arousal reaction began 3—12 sec after the end of the injection and lasted from tens of seconds to minutes; it was not accompaniep by changes in the systemic blood pressure. Carotid sinus denervation did not prevent the arousal effect, while brain stem transection at ponto-mesencephalic border did it. 5-HT ineffectiveness in arousing the sleeping pattern induced by a mesencephalic transection was confirmed by CREPAX and INFANTELLINA (1957). They observed a reduction in the amplitude of the cortical waves, but not arousal, after intracarotid injection of large doses of 5-HT (86—215 μg) in "cerveau isolé" preparations. Lower doses (8.3—43 μg) were totally ineffective.

Brain stem transection at midpontine level just in front of the trigeminal rootlets ("midpontine pretrigeminal preparation") brings about a persistent EEG activation (BATINI et al. 1959a); hemi-mesencephalic transection in "midpontine pretrigeminal preparation" results in a symmetrically or asymmetrically synchronized EEG record (CORDEAU and MANCIA 1958); combined olfactory and visual deafferentation changes the waking pattern of the "midpontine preparation" into that typical of sleep (BATINI et al. 1959b). GLÄSSER and MANTEGAZZINI (1960a, 1960b) described the effects of 5-HT on the EEG of the "midpontine pretrigeminal preparation". In some of their experiments mesencephalic hemisection or sensory deafferentation was performed. The amine was injected into a carotid artery (through the lingual artery), the other one being occluded. At doses of between 2 and 80 μg it did not change the activated pattern of the "midpontine pretrigeminal preparation". At lower doses (1—4 μg) it frequently activated the EEG synchronized by mesencephalic hemisection or by sensory deafferentation. The changes in blood flow in the common carotid artery of the injected side (REIN's Thermostromuhr method) and the changes in systemic blood pressure induced by 5-HT were often negligeable and in any case had nothing to do with the electroencephalographic changes.

Intraventricular injections of 5-HT (200—500 μg) in conscious cats (BRADLEY and HANCE 1956; SCHWARZ et al. 1956; BRADLEY 1958) or subcutaneous injection of a huge dose of amine (15 mg/kg) in "encephale isolé" preparation (MANTEGAZZINI 1956) had slight or no effects on the electrical activity of the cerebral cortex.

In the writer's opinion, the main effect of the 5-HT injected into the blood stream of the cat is an arousing one. Complete sensory deafferentation does not prevent it. This does not exclude that stimulation of the peripheral receptors may largely contribute to producing the EEG arousal in preparations not deafferented and with nervous system intact. Midbrain transection prevents the 5-HT arousal, a fact which indicates that the arousing action is mediated or conditioned by brain structures located below the midbrain. The arousal reaction occurs even in absence of detectable changes in carotid blood flow.

II. 5-Hydroxytryptophan

1. Rabbit

MONNIER and TISSOT (1958), COSTA and RINALDI (1958) and DOMER and LONGO (1962) studied the effects of intravenously injected 5-HTP on the electrocortical activity of rabbits. According to MONNIER and TISSOT low doses (10 to 20 mg/kg) produced EEG synchronization while higher doses (30 mg/kg or more) gave, within 10—20 min, EEG desynchronization, lasting about 2 hrs, together with spontaneous discharges in rhinencephalic leads. Mesencephalic transection did not prevent the 5-HTP arousal. According to COSTA and RINALDI 5-HTP (75 mg/kg i.v.) at first induced a pattern of slow waves of a very simplified shape; within the second half-hour after injection, an over-all diminution of the voltage of the cortical leads occurred with disappearance of hippocampal 5—7 c/sec waves (theta rhythm). Recovery occurred within the second hour after injection. According to DOMER and LONGO 20—30 mg/kg of 5-HTP produced a marked diminution in the voltage of the spindles and of the slow waves typical of the resting state. Reduction of electrical activity occurred even in the ventromedial nucleus of the thalamus and in the mesencephalic reticular formation, while in the dorsal hippocampus there was a disruption of the theta rhythm. Increasing the dose of 5-HTP (up to 50—100 mg/kg) cortical and subcortical records flattened

until the isoelectric line, while bursts of spikes at 30—40 c/sec appeared in the hippocampus. Hyperpnea, tremors, struggling and hyperthermia accompanied the development of EEG changes. When a total dose of 150 mg/kg was reached the animals died. The same changes occurred when 5-HTP was intravenously infused (5 mg/min).

COSTA et al. (1960) injected 5-HTP into a common carotid artery and tried to relate EEG changes to changes in 5-HT concentration in the mesencephalon-diencephalon, in the hippocampus and in the telencephalon. Both vagi were severed and carotid bodies inactivated. After 22 mg of 5-HTP the EEG synchronization typical of resting state was accentuated for about 30 min and then returned to normal level. After 44 mg some of the animals showed the same changes as those treated with lower doses but some developed, after an initial augmentation of synchronization, a persistent desynchronized pattern which lasted for 1 hr or more. There was no correlation between increases in 5-HT concentrations in the telencephalon and the hippocampus and EEG changes. The 5-HT content of the mesencephalon-diencephalon was higher in animals with an alerting pattern than in animals with a sleeping pattern, reaching values of more than 3 times above the control ones.

To sum up: some results indicate that 5-HTP in rabbits at low doses induces synchronization and at high doses desynchronization of the electrical activity of the cerebral cortex. Other results lead us to conclude that the main effect of 5-HTP is a flattening of EEG and the appearance of bursts of spikes in the hippocampus.

2. Cat

GLÄSSER and MANTEGAZZINI (1960a, 1960b) described the effects of 5-HTP on the EEG of the "midpontine pretrigeminal preparation". 5-HTP was infused through the lingual artery into the external carotid artery on one side, the common carotid artery on the opposite one being occluded during the infusion. The aminoacid (8—20 mg) changed the desynchronized pattern typical of this preparation to a pattern of marked synchronization similar to that produced by thiopental (Fig. 1). Higher doses (40—60 mg) also prevented the arousing effect of visual and olfactory stimulation. The synchronizing effect began within a few minutes after the infusion and lasted for more than 30—45 min. When the contralateral carotid artery was left open during the intracarotid infusion in order to obtain a difference in 5-HTP concentration in the areas irrorated by the two arteries, the hemisphere on the infusion side showed a greater synchronization than that of the other side. This means that the synchronization was not due to by-products of the extracerebral metabolism of the aminoacid nor to its peripheral effects, as these ought to have symmetrically affected the EEG. The electroencephalographic changes were wholly independent of the changes in the systemic blood pressure and in the carotid blood flow (REIN'S Thermostromuhr method). Mesencephalic hemisection in the "midpontine pretrigeminal preparation" resulted in EEG synchronization which was sometimes confined to the hemisphere above the mesencephalic lesion. 5-HTP (5—20 mg) increased the synchronization induced by the lesion and blocked the arousal reaction to olfactory and visual stimulation, but never, even at lower doses (2—5 mg), it desynchronized the EEG. ANTONELLI et al. (1961) dosed the 5-HT content of the midbrain-hypothalamus in "midpontine pretrigeminal preparation" of cats after intracarotid infusion of the minimum synchronizing dose of 5-HTP (5 to 10 mg). The infusion brought about an EEG sleeping pattern in the hemisphere on the side of the infusion and left the activated pattern of the opposite hemisphere

unchanged. When the EEG syndrome developped 5-HT concentration in the midbrain-hypothalamus on the side of the infusion was 50% higher than that on the opposite side and of non-injected preparations.

To sum up: 5-HTP induces in the "midpontine pretrigeminal preparation" of cat an EEG pattern resembling that of barbiturate sleep. The synchronizing

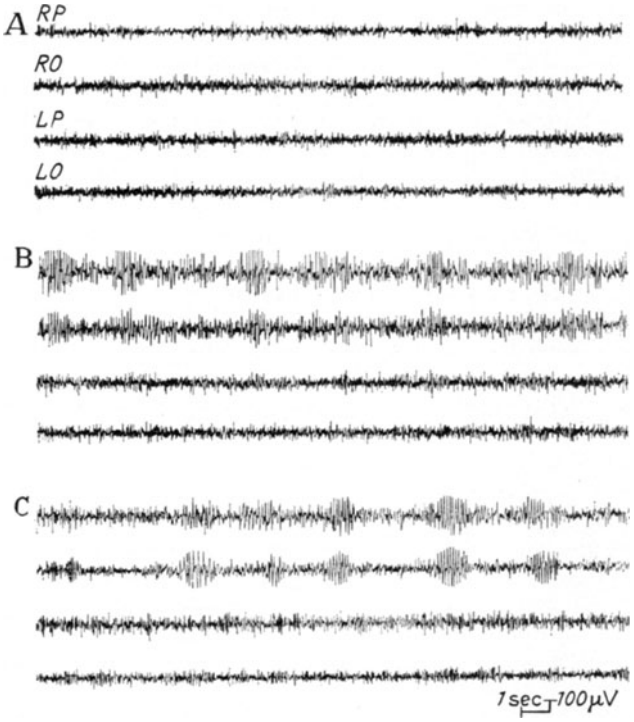

Fig. 1 A—C. Effects of 5-HTP on the EEG of the midpontine-pretrigeminal cat. A EEG pattern symmetrically activated, 2 hr after midpontine transection. B Clear EEG asymmetry produced by 1 mg of thiopental injected into the right carotid artery, the controlateral artery being open: only the hemisphere on the side of the injection shows synchronization. C The same EEG pattern produced by 20 mg of 5-HTP injected as in (B).
(From GLÄSSER and MANTEGAZZINI 1960b)

effect is not due to the peripheral actions of 5-HTP nor to any gross alteration in cerebral circulation. The 5-HT content of the midbrain-hypothalamus increases by 50% after a minimum synchronizing dose of aminoacid.

III. Other indolealkylamines and precursor aminoacids

MONNIER (1959) reported that in rabbits psilocybin (1.5—5 mg/kg i.v.) induced, within a few minutes after injection, activation of the electrical activity in cortical leads, and deactivation in subcortical leads (hippocampus, caudate nucleus, thalamus and mesencephalic reticular formation). Mesencephalic transection partially blocked the amine arousing effect (2 mg/kg i.v.). CERLETTI (1959) also observed an arousal reaction after intravenous injection of 1—2 mg/kg of psilocybin in curarized rabbits. Bufotenine behaved as psilocybin (MONNIER and KRUPP 1960).

BRODEY et al. (1963) reported that in rabbits psilocybin (4—6 mg/kg), psilocin (0.5—2 mg/kg), 4-methyl-α-methyltryptamine (1—2 mg/kg), 4-hydroxy-α-methyltryptamine (5—7 mg/kg) and 1-methylpsilocybin (6.8—12.6 mg/kg) i.v. injected, produced EEG alert patterns lasting 45 min or more. Brain stem

transection at precollicular level prevented the arousing effect of 4-methyl-α-methyltryptamine and psilocin. Pontine transection passing dorsally at retrocollicular level and ventrally at the posterior border of the pons raised the activating dose of the former drug (7 mg/kg) while prevented the arousing action of the latter one (3 mg/kg). In the AA. opinion these results demonstrate that 4-methyl-α-methyltryptamine act at midbrain level while psilocin does not.

VAN METER et al. (1960) reported that in rabbits α-methyltryptamine (2 mg/kg i.v.), an inhibitor of the MAO and 5-HTP decarboxylase, induced EEG desynchronization for more than 2 hrs. When the basilar artery was occluded, injection into a vertebral artery induced an arousal reaction, whereas injection of the same quantity of amine into a carotid artery was ineffective. I.v. injection did not affect the synchronized pattern of the "cerveau isolé". From this data the AA. inferred that the arousing effect was due to an action of the amine on the caudal portion of the brain stem reticular formation. MATTHEWS et al. (1961) (see also MATTHEWS 1963) studied the effects of DL-α-ethyltryptamine, a MAO inhibitor, on the cat EEG. In conscious animals and in "encéphale isolé" preparations, intravenous injection of 10 mg/kg of amine resulted in an EEG activation pattern. The behaviour revealed signs of alertness. The effects began within 60—90 min after the injection and lasted many hours. Rostropontine transection or mesencephalic transection at intercollicular level prevented the DL-α-ethyltryptamine arousal.

DOMER and LONGO (1962) reported that tryptamine (15—20 mg/kg i.v.) in rabbits produced a flattening of the cortical activity and a short-lasting spiking discharge in the hippocampus. The effect lasted only a few minutes. Subsequent injections were less active. Tryptamine was ineffective when slowly i.v. infused (1 mg/min for 90 min).

According to VANE et al. (1961) DL-α-methyltryptamine, DL-α-ethyltryptamine, DL-5-methoxy-α-methyltryptamine and N,N-dimethyltryptamine (2 mg/kg i.p.) did not produce EEG arousal in unrestrained conscious cats. Bursts of 6—10 c/sec high-voltage activity appeared within few min after injection and lasted for more than 6 hrs. In "encéphale isolé" preparation DL-α-methyltryptamine (0.5—2 mg/kg i.v.) produced a brief arousal reaction followed by a longer period of bursts of high-voltage cortical activity.

ERSPAMER et al. (1960a) described the effect of 4-HTP on the "midpontine pretrigeminal preparation" of the cat. 4-HTP penetrates into the brain and is there decarboxylated to 4-HT (ERSPAMER et al. 1960b). The aminoacid injected slowly into a carotid artery (25—40 mg) transformed the activated EEG pattern into a sleeping pattern. 5-HTP had the same effect, but at lower doses. COSTA et al. (1960) injected rabbits intracarotidly with 44 mg of DL-5-methyltryptophan, an aminoacid not attacked "in vitro" by mammalian decarboxylase (ERSPAMER et al. 1961). No EEG change was detectable after the injection.

G. Effects on action potentials evoked in cerebral cortex and in subcortical structures

I. 5-Hydroxytryptamine

1. Responses of the cerebral cortex to direct electrical or chemical stimulation

DI STEFANO et al. (1956) studied the effect of 5-HT on the action potentials evoked, by electrical stimulation, in neuronally isolated slab of cerebral cortex of cats. 5-HT (2.15—4.3 μg i.v.) gave transitory depression of the evoked potentials and caused a fall in cortical oxygen tension (polarographic technique), and

in systemic blood pressure. Depression of cortical potentials occurred 1—3 min after the injection, when both the blood pressure and cortical oxygen tension had returned to normal, and persisted for 4—8 min. Cortical oxygen tension was not measured in the isolated slab but in the intact cortex; diminution in blood flow and hypoxia, probably more marked and long-lasting here than in the intact cortex, could account for the depression of the electrical response of the slab.

Crepax and Infantellina (1957) found that 5-HT applied on the isolated cerebral cortex of cats enhanced at low concentrations ($1:10^4$—$1:10^3$) and depressed at higher concentrations the spontaneous electrical activity of the slab. The amine differently affected the two components of the response set up by electrical stimulation (single shock). Surface-negative wave (superficial response) was unaffected by any concentration whatsoever of the amine between $1:10^4$ and $2:10^2$, whereas surface-positive wave (deep response) was enhanced by low concentrations ($1:10^4$—$5:10^4$) and was reduced both in amplitude and duration by higher concentrations ($1:10^3$—$1:10^2$) (5-HT concentrations expressed in terms of creatinine sulfate salt). 5-HT intracarotidly injected enhanced at doses of 2.15—4.3 μg, and depressed at higher doses (6.45—10.75 μg) the spontaneous electrical activity of the slab and the surface positive component of response to electrical stimulation (single shock). Even at the highest dose tested (10.75 μg) the amine did not affect the surface negative component of the response. Electrical responses to repetitive stimulation were blocked by amounts of 5-HT (locally applied or intracarotidly injected) lower than those depressing the response to single shock. In the AA. opinion 5-HT effects could be attributed to hypoxia affecting the postsynaptic potentials of deep-lying neurones (positive wave) more than that of apical dendrites of pyramidal cells (negative wave) and affecting repetitively stimulated neurones more than those submitted to a single shock. Ochs et al. (1960) reported that 5-HT ($5:10^3$—$1:10^2$) topically applied on the intact cerebral cortex of cats or rabbits diminished or eliminated the surface negative response to direct electrical stimulation. A fact which would indicate that the amine also affects the postsynaptic potential of the apical dendrites of pyramidal cells.

Rech and Domino (1960) explored the effects of 5-HT on the electrical activity induced by local application of strychnine or d-tubocurarine on the neuronally isolated cerebral cortex of dogs. 5-HT (20—60 μg/kg) intravenously or intracarotidly injected lowered the frequency of strychnine or d-tubocurarine spiking but the effect was variable and not significant. It did not depend on changes in blood pressure.

Crossland and Mitchell (1956) briefly reported that 5-HT (0.1—0.4 μg) injected into the internal carotid artery of decerebrated rabbits did not modify the electrical activity of the cerebellar cortex.

From the above data it appears that 5-HT mainly depresses the cortical response set up by direct electrical stimulation; there is no agreement between the authors as to the sensitivity of the single components of the response. It appears that the amine hardly affects the electrical activity induced in the isolated cortex by strychnine. The cortical origin of the effects observed is beyond dispute, as all the experiments were performed in neuronally isolated cortex or applying the amine directly on the cortex. The mechanism whereby 5-HT depresses cortical responses remains open to investigation. It may be thought that the amine acts directly on the nerve cells, but it can't be ruled out that it acts indirectly for instance through local blood flow changes in turn acting on the neurones. It must be stressed that the amine has the same effects either when it is

locally applied or when it reaches the cortex through the blood. In the latter case the direct action on the neurones can be upheld only admitting that 5-HT passes the blood-brain barrier, that is to say accepting a fact not yet proved.

2. Cortical and subcortical responses evoked by afferent impulses

a) Transcallosal stimulation

MARAZZI and HART (1955) (see also: HART et al. 1956 and MARAZZI 1957) studied the effects of 5-HT on the response of the visual cortex to stimulation of the symmetrical point in the contralateral cortex, in cats lightly pentobarbitalized. 5-HT (1 μg) injected into the carotid artery of the recording side reduced the amplitude of the surface negative component of the response, and left the initial positive component unaffected. The effect began 30—40 sec after injection, reached the maximum after 1 min and disappeared after about 3 min. No pressure change occurred after such a dose of amine. The participation of the discharges of the carotid receptors to the inhibition of the transcallosal response which followed the intracarotid injection of 5-HT was ruled out in experiments in which glomus carotideus was by-passed (RODRIGUEZ et al. 1961). GUTH and SPIRTES (1959) confirmed MARAZZI'S results. On the basis that the initial positive wave is the action potential of impulses propagating up to the afferent terminals in the cerebral cortex and that the secondary surface negative wave is the post-synaptic response of cortical neurones, MARAZZI stated that 5-HT acts as an inhibitory synaptic neurohumor.

KOELLA et al. (1960) studied the effects of the amine on the transcallosal response of the cortex of the suprasylvian gyrus in cats anaesthetized with dial-urethan. 5-HT (4.3 μg) was injected into the common or into the external carotid artery (that is to say above or below the carotid sinus) of the recording or of the contralateral side (stimulating side). When the drug was injected into the external carotid artery it reached the brain, avoiding the carotid receptors. Peak-to-peak amplitude of the positive-negative transcallosal response was always reduced, but to various degrees, by 5-HT injected into each of the four points indicated. The injection into the external carotic artery of each side was more effective than the injection into the corresponding common carotids; data which allows us to suspect, in contradiction with that advanced by RODRIGUEZ et al. (1961) that stimulation of the carotid receptors by 5-HT exercises a facilitatory action on the transcallosal response. The injection into the external or common carotid artery of the stimulating side, had the same effect, although of less importance, than the injection into the external or common carotid artery of recording side. Since the blood flowing through a carotid artery does not reach the hemicortex of the contralateral side, this data indicates that 5-HT may affect the transcallosal response acting on structures located elsewhere than at the recording point. It is possible that 5-HT may reduce the electrical excitability of the stimulated cortex reached by the drug injected on the same side and/or, as the AA. sustain, that it may activate inhibitory subcortical structures projecting on both sides of the cortex. Any way these results don't allow to affirm that 5-HT is a neurohumor with inhibitory effect on the cortical synapses.

b) Sensory nerves and sense organs stimulation

MALCOLM (1958) studied the effect of 5-HT on the responses evoked in the sensory cortex, in the ventral thalamus and in the hypothalamus by stimulation of the sural nerve in chloralosated cats. The amine was locally applied on the exposed cortex or injected into a carotid artery or into a lateral ventricle. As arterial injection was made through a catheter tied into the artery, a part of the

volume injected (about one third, according to the A.) was retained in the dead space of the canulation tubing and the artery. 5-HT locally applied ($1:10^3$) did not produce any detectable effect on the cortical evoked responses. 5-HT intracarotidly injected (200—300 μg) first depressed and then enhanced the surface negative component of the cortical response. The depression was over within 3 min, the enhancement was at the peak in 12—16 min but never completely disappeared. The effect on evoked responses in the subcortical structures was solely one of long-lasting depression. The amine (100—200 μg) also caused fall in the systemic blood pressure, marked dilatation of the cortical vessels and oedema of exposed cortex. The vasodilatation lasted 10—15 min; the oedema lasted longer and not easily reversed. 5-HT intraventricularly injected (50 and 200 μg) decreased the amplitude of the surface negative component of the cortical response, left unchanged the initial surface positive component as well as the responses evoked in deeper structures, and abolished (at 200 μg only) the marked facilitation of the thalamic response produced by repetitive stimulation of the sural nerve (10 shocks in 25 msec).

KOELLA and co-workers (KOELLA et al. 1959, 1960; SMYTHIES et al. 1959) described the effects of 5-HT on the responses evoked in the visual areas I of both hemispheres by photic stimulation. The amine (0.53—4.3 μg) was injected into the right or left common carotid artery, one of the carotid sinuses being denervated. The injection into the innervated carotid artery reduced the peak-to-peak amplitude of the positive-negative response not only in the cortex of the injected side but also in the other one. The injection into the denervated carotid was much less effective than the injection into the innervated carotid. This suggests that stimulation of the presso- and/or chemo-receptors of the carotid sinus by 5-HT exercises a bilateral inhibitory effect on the visual areas. 5-HT, even when injected into the denervated artery, depressed the responses of both the visual areas, in spite of the fact that it did not reach the contralateral hemicortex. 5-HT effect on the contralateral cortex may be explained admitting that the amine acts on structures located elsewhere but projecting to the visual areas.

EVARTS (1958) reported that 5-HT (0.1 mg or more) injected into the carotid artery of the recording side did not affect the synaptic transmission in the lateral geniculate nucleus of the cat.

II. 5-Hydroxytryptophan

REVZIN and COSTA (1960) studied, in the cat, the effects of 5-HTP on the potentials evoked in the hippocampus by stimulation of the amygdala. The aminoacid (100—200 mg/kg i.v.) caused a slight depression of the response. Premedication with tranylcypromine (a MAO inhibitor) markedly potentiated the depressant effect of 5-HTP. This potentiation was much more marked in chronic unanaesthetized animals than in "cerveau isolé" preparation. MONNIER (1960) briefly reported that the injection of 5-HTP (50—85 mg/kg i.v.) into unanaesthetized rabbits caused depression of transcallosal responses of somaesthetic and visual cortex, but left unchanged the potentials evoked in the somaesthetic cortex by thalamic stimulation.

III. Other indolealkylamines

EVARTS et al. (1955) studied the effects of bufotenine on the electrical activity in the visual system of anaesthetized cats. The amine was injected into the carotid artery on the recording side. 0.2 mg/kg caused marked depression of the

postsynaptic response evoked in the lateral geniculate by optic nerve stimulation. The response of the visual cortex to stimulation of the optic radiations and the response of the optic tract to retinal photic stimulation were left unchanged by bufotenine even when injected in quantities many times higher than that sufficient to reduce the geniculate response. The effect was at the peak 20—60 sec after the injection and was over within 1 hr. It was independent of any blood pressure and respiratory changes.

Tryptamine and N,N-dimethyltryptamine behaved as bufotenine. N,N-dimethyltryptamine had approximately the same activity as bufotenine, both in terms of peak effect and in duration of action. Tryptamine had a short-lasting effect (about 3—6 min). 5-hydroxy-N,N-dibuthyltryptamine, 5,6-dimethoxy-N,N-dimethyltryptamine, bufotenidine and gramine were inactive (EVARTS 1958).

MONNIER (1959) reported that in rabbits psilocybin (1.5—5 mg/kg i.v.) caused a reduction of the amplitude of the potential evoked in the somato-sensory cortex by stimulation of the ventral-lateral nucleus of the thalamus, while it left unchanged the transcallosal response in the visual and somato-sensory cortex. MATTHEWS et al. (1961) (see also: MATTHEWS 1963) observed no change in the amplitude of the response evoked in the somato-sensory cortex by radial nerve stimulation after α-ethyltryptamine injection (20 mg/kg i.v.) in curarized cats.

H. Effects on the spinal reflexes

I. 5-Hydroxytryptamine

SLATER et al. (1955) briefly reported that intrarterial injection of 5-HT (43—430 μg) in spinal cats resulted in an increase, followed by a depression, of a flexor reflex. Hydrazinophtalazine blocked the pressor action of the amine but did not prevent that on the reflex. Increase in amplitude of the flexor reflex followed by depression was also observed by LITTLE et al. (1957) after 5-HT (50 μg/kg i.v.) in cats with spinal cord transected at T 13 and lightly anaesthetized with dial-urethan. The patellar reflex was momentarily inhibited. KISSEL and DOMINO (1957, 1959) studied the effects of 5-HT on the patellar reflex, the crossed extensor reflex and the reflex inhibition of the knee jerk and the neuro-muscular transmission in spinal cats. Patellar reflex was mechanically elicited, while the crossed extensor reflex and the inhibition of the patellar reflex were evoked by electrical stimulation of a sciatic nerve. 2.1—4.3 μg/kg of 5-HT i.v. produced a marked transitory inhibition followed by facilitation of the patellar and crossed extensor reflexes. 20 μg/kg blocked the patellar reflex as long as 40 sec. 5-HT did not affect the reflex inhibition and the neuro-muscular transmission. The stabilization of arterial pressure or the block of the vascular effects of 5-HT by dibenzyline (5 mg/kg i.v.) failed to prevent the 5-HT effect on the reflexes; chloralose reduced it. Inhibition of patellar reflex after 5-HT in spinal cat was also observed by WEIDMANN and CERLETTI (1959, 1960) (5—10 μg/kg i.v.) and enhancement of the flexor reflex by VANE et al. (1961) (1 mg/kg i.v.).

From the above results it appears that 5-HT injected into the blood stream of the spinal cat has, at first, an inhibitory action on the extensor reflexes (patellar and crossed extensor) and a facilitatory action on the flexor reflex, and later on an opposite action. Moreover these effects seem to be largely independent of the vascular effects of the amine.

In contrast with the above quoted authors, WEIDMANN and CERLETTI (1957) observed inconstant changes of the flexor and crossed extensor reflexes after

5 μg or more of 5-HT i.v. and VANE et al. (1961) obtained enhancement of the patellar reflex after a huge dose of 5-HT (1 mg/kg i.v.) in spinal cats.

As far as the mechanism of the action of 5-HT on the spinal reflexes is concerned, attempts to demonstrate any direct action of the amine on the neurones of the spinal cord were negative in outcome. CURTIS et al. (1955) studied the 5-HT effect on the ventral roots responses evoked in cats by electrical stimulation of the corresponding dorsal roots, the afferent inflow from other structures being prevented by crushing the remaining dorsal roots of the region. Close intrarterial injection of 50—200 μg of 5-HT occasionally depressed the mono- and polysynaptic responses, but, according to the AA., the effect was due to stimulation of the peripheral receptors.

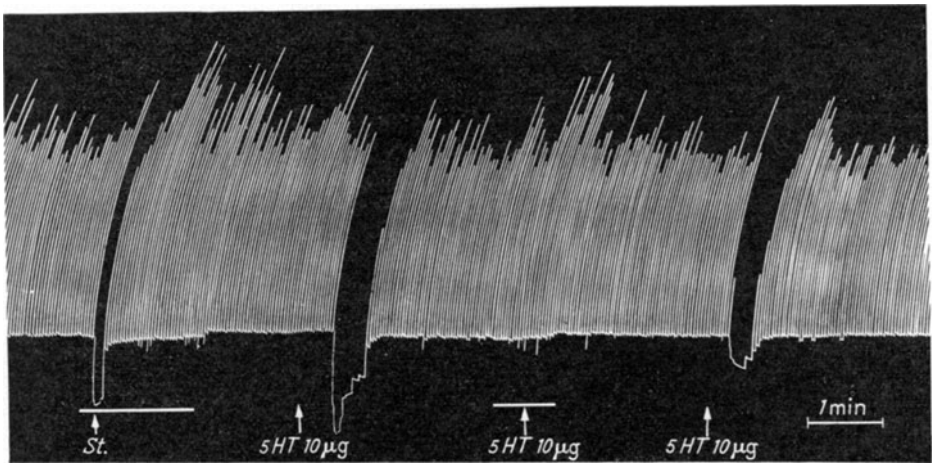

Fig. 2. Effect of the occlusion of the abdominal aorta on the block of the patellar reflex produced by 5-HT in the spinal cat. Aorta occlusion (during the signal line) does not affect the block of the reflex produced by noxious stimulation of the foot (St.), but prevents the blocking action of 5-HT (10 μg) injected into a brachial vein

To by-pass the blood-brain barrier, CURTIS et al. (1961) applied electrophoretically 5-HT on the environment of interneurones in spinal cord of cats, recording their activity with the aid of coaxial microelectrodes. The interneurones were identified by their responses to the stimulation of the dorsal and ventral roots. The inner barrel of the microelectrode, extruding 2—3 μ, was used to record the extracellular spike potentials; the outer barrel was filled with an aqueous solution of 5-HT. 5-HT was applied to 16 different interneurones with currents up to 200 nA for periods as long as 45 sec. In no case did the amine have any effect whatever on the spontaneous activity or on that evoked by the dorsal root stimulation. Diffusional barriers may prevent the 5-HT ejected from the microelectrode to bridge the gap (of a least 3—4 μ) between the tip of the barrel and the neuronal membrane. These results, therefore, do not permit to conclude that 5-HT has no effect at all on the spinal interneurones, but strongly strengthen the suspicion that the effects of 5-HT on the reflexes do not depend on the direct action of the amine on the neurones.

MANTEGAZZINI et al. (1963) observed that the injection of small doses of 5-HT (0.1—0.4 μg) into the femoral artery of the recording side (through a collateral) caused a clear transitory inhibition of the patellar reflex in spinal and eviscerated cats. The intravenous injection of the same doses was totally ineffective. I.v. injection of higher doses (5—10 μg) inhibited the reflex, but the inhibitory effect was completely prevented occluding for a few seconds after injection the abdominal

aorta at the biforcation into the internal iliac arteries (Fig. 2). In such a way the amine reached the spinal cord but not the hind legs. The gentle touching of the foot had the same effect as 5-HT. These results led us to think that the inhibition of the patellar reflex in the cat may be accounted for by afferent impulses discharged by 5-HT in the territories irrorated by iliac arteries. It is quite likely that the effects on the flexor and extensor reflexes may be explained in the same way.

ANGELUCCI (1956) perfused the spinal cord of the frog through a cannula pushed into the vertebral canal; oxygen was supplied through the blood vessels. 5-HT added to the perfusion fluid (up to $1:10^4$) did not affect the flexor reflex nor alter the depressant action of reserpine. Biological assay of the effluent revealed that 5-HT-like substances were released from the spinal cord at rest. The release increased when the reflex was stimulated. CARELS (1962) applied 5-HT to the isolated spinal cord of the frog. 5-HT ($1:10^4$ to $1:10^2$ in the bath) inhibited the monosynaptic component of the response evoked in the ventral roots by stimulation of the dorsal roots or of the descending fibres in the lateral column, but did not affect the response of the motoneurones to antidromic stimulation. These results suggested to the author that the amine acted at presynaptic level.

II. Psilocybin and psilocin

Psilocybin intravenously injected into the spinal cat provoked a steady, long-lasting increase of the patellar reflex (5—10 μg/kg or more) and an increase (up to 0.1 mg/kg) or a decrease (higher doses) of the flexor reflex. The effects did not depend on the blood pressure or neuro-muscular transmission changes (WEIDMANN et al. 1958; WEIDMANN and CERLETTI 1959; CERLETTI 1959; WEIDMANN and CERLETTI 1960). Psilocin behaved like psilocybin, both theamines having an opposite effect on the patellar reflex of that of 5-HT (WEIDMANN and CERLETTI 1959, 1960). When electrophoretically applied on spinal interneurones in the cat, psilocybin and psilocin were inactive (CURTIS et al. 1961).

III. Bufotenine

WEIDMANN and CERLETTI (1959, 1960) reported that bufotenine (20—50 μg/kg i.v.) like 5-HT, temporarily inhibited the patellar reflex in the spinal cat. The esterification of bufotenine with phosphoric acid diminished the activity. CURTIS et al. (1955) failed to observe any change in the poly- and monosynaptic reflexes recorded from the ventral roots in spinal cats, following close intrarterial injection of bufotenine.

IV. Other indolealkylamines

WEIDMANN and CERLETTI (1960) reported that the i.v. injection of 4-HT (20—50 μg/kg), 4-hydroxy-N-methyltryptamine (20—50 μg/kg), 5-hydroxy-α-methyltryptamine (10—20 μg/kg), 5-hydroxy-α-methyl-N,N-dimethyltryptamine (20—50 μg/kg) and 5-hydroxy-β-methyltryptamine (>50 μg/kg) depressed the patellar reflex in spinal cats, while the injection of 4-hydroxy-N-ethyltryptamine (20—50 μg/kg), 4-hydroxy-N,N-diethyltryptamine (20—50 μg/kg), 4-hydroxy-α-methyltryptamine (>50 μg/kg), 4-hydroxy-α-methyl-N,N-dimethyltryptamine (>50 μg/kg) and 4-hydroxy-β-hydroxy-N,N-dimethyltryptamine (>50 μg/kg) enhanced it. The derivatives of N,N-dimethyltryptamine with the following groups — Br, CH_3, OCH_3, $OCH_2C_6H_5$, $OCOC_6H_5$ or $OCONHCH_3$ — in 4 position behaved like psilocybin, i.e. enhanced the patellar reflex.

VANE et al. (1961) reported that tryptamine, DL-α-methyltryptamine, DL-α-ethyltryptamine, N,N-dimethyltryptamine and DL-5-methoxy-α-methyltryptamine (0.5 mg/kg i.v.) facilitated both the patellar and the flexor reflex in spinal or chloralosed cats. They were more potent when injected into a spinal artery. Tryptamine at larger doses abolished the flexor reflex. MATTHEWS et al. (1961), on the contrary, did not observe any change in mono- and poly-synaptic reflexes (dorsal root-ventral root preparation) after 5 and 10 mg/kg i.v. of DL-α-ethyltryptamine in spinal cats. 15 mg/kg gave a slight depression of the polysynaptic discharges.

Tryptamine and α-methyltryptamine were electrophoretically applied to interneurones located in the lumbar segments of cat spinal cord. They failed to affect the responses of the neurones to dorsal root stimulation, even when they were released by currents as large as 150—200 nA. (CURTIS 1962).

To sum up: psilocybin, bufotenine and a number of other indolealkylamines affect the spinal reflexes. There is no proof that the synaptic transmission in the spinal cord is affected by the amines; furthermore any attempt to demonstrate any action on the interneurones was negative in outcome. It is conceivable that, as 5-HT, other indolealkylamines may affect the spinal reflexes changing the pattern of the nervous inflow to the spinal cord. The study of the reflexes after barrage of the impulses arising from the structures located in the injection circuit will throw some light on the mechanism of the action of the amines.

I. Effects on single cellular elements

The data reported in the preceeding sections have been obtained in the course of experiments in which 5-HT reached the CNS through the blood stream, or was applied into the cerebral ventricles or to the exposed cerebral cortex. This section will deal with: I. experiments in which the action of 5-HT and other indolealkylamines on neurones was examined introducing the amines into the extracellular environment and observing the effects upon extracellularly recorded action potentials, and II. experiments in which the action of the amines on brain cells (glia cells and neurones) was studied applying the drug to cultures of nervous tissue "in vitro".

I. Single neurones

CURTIS and KOIZUMI (1961) studied the effect of 5-HT on the spontaneous and synaptically evoked discharges of neurones of mesencephalic reticular formation and inferior colliculi in decerebrated cats. The extracellular fluid surrounding neurones was reached by multibarrel electrodes. One of the barrels contained a saturated aqueous solution of 5-HT creatinine sulphate. The amine was ejected as a cation from the electrode orifice electrophoretically by currents of about 50—250 nA. No change in cellular activity was observed during and after 5-HT application.

The suspicion that 5-HT might not reach a local concentration sufficient to cause a detectable effect is weakened by the fact that amine applied by lower currents (10 to 40 nA) to neurones of the lateral geniculate nucleus greatly affected the synaptic firing of the neurones (CURTIS and DAVIS 1962). 5-HT blocked the post-synaptic spike potentials produced by stimulation of the optic nerve fibres (orthodromic excitation) but failed to influence those produced by stimulation of the optic radiation fibres (antidromic excitation) and those induced by L-glutamic acid electrophoretically applied. When the effect of 5-HT upon

potentials generated by groups of cells (focal potentials) was studied, the observations made upon single cells were confirmed. The amine depressed the orthodromically evoked post-synaptic focal potentials, but was without action upon those generated antidromically. The rate of recovery of the focal potentials, following a depression of 40 to 60% was in the order of 15 to 60 sec. These results suggest that 5-HT does not alter the membrane conductance of geniculate neurones; the amine could affect synaptic transmission by reducing the release of transmitter from the presynaptic terminals or by blocking subsynaptic receptors specialised for combination with the excitatory transmitter.

The amines listed below had the same effect as 5-HT upon the synaptic transmission in the lateral geniculate nucleus of the cat: tryptamine, 4-HT, 6-HT, 7-HT, 4-methoxytryptamine, 5-methoxytryptamine, N,N-dimethyltryptamine, N,N-diethyltryptamine, psilocin, bufotenine, psilocybin, 6-hydroxy-N,N-dimethyltryptamine, 7-hydroxy-N,N-dimethyltryptamine, α-methyltryptamine, 4-hydroxy-α-methyltryptamine, 1-benzyl-2-methyl-5-methoxytryptamine (BAS), melatonin and 4,α-dimethyltryptamine. All the drugs, except 4-HT and 7-HT, were less potent that 5-HT, melatonin and 4,α-dimethyltryptamine being the less active (CURTIS and DAVIS 1962).

KRNJEVIĆ and PHILLIS (1963a) studied the action of 5-HT on single neurones of the cerebral cortex of the cat. The amine at low concentrations lowered the frequency of discharge evoked by the application of glutamate ions as well as that evoked by afferent impulses (orthodromic excitation), but failed to prevent the antidromic excitation of single Betz cells. At relatively higher concentrations it produced paroxysmal cellular discharge, lasting for several seconds after the application and followed by depression of the responsiveness.

KRNJEVIĆ and PHILLIS (1963b) tested a number of derivatives of tryptamine and tryptophan on cortical neurones. 4-HT, 6-HT, tryptamine and tryptophan were as active as 5-HT in inhibiting cellular activity, whereas 7-HT was less active. 4-HTP, 5-HTP, 6-HTP were less active than the parents amines. N,N-dimethyltryptamine, N,N-diethyltryptamine, 4-methoxytryptamine, 5-methoxytryptamine, psilocin, bufotenine, 6-hydroxy-N,N-dimethyltryptamine were less active than 5-HT. Melatonin had no clear action.

CURTIS et al. (1961) applied 5-HT into the environment of interneurones in cat spinal cord. The amine failed to affect the neuronic activity even though it was applied by currents as large as 200 nA. Tryptamine and α-methyltryptamine behaved like 5-HT (CURTIS 1962).

Although the same technique was employed in the above reported investigations, the results differ in important respects. This lends to believe that neurones in various regions of the brain respond in different way to indolealkylamines.

II. Brain cells cultured "in vitro"

BENITEZ et al. (1955) first described 5-HT effect on brain cells of humans and rats cultured "in vitro". 5-HT (2 μg/ml) transformed the spontaneous pulsating movements of the oligodendroglia into a tetanic contraction but was inactive on astrocytes which do not contract spontaneously. NAKAZAWA (1960) confirmed these observations. GEIGER (1957, 1958) briefly reported that 5-HT changed the structure of cortical neurones cultured "in vitro". At concentrations of 0.5—2 μg/ml it induced repetitive pumping movements of the perikarya of the neurones and changed the pattern of movements in the synaptic areas.

J. Effects on sympathetic ganglia

I. 5-Hydroxytryptamine

ROBERTSON (1954) was the first to observe that 5-HT stimulated the perfused superior cervical ganglion of the cat, but it was TRENDELENBURG (1956) (see also TRENDELENBURG 1958, 1959) who extensively studied the ganglionic effects of the amine. 5-HT was injected through the lingual artery into the blood supply of the superior cervical ganglion. As the external and internal carotid arteries were occluded, the drug reached the ganglion but not the nictitating membrane. Preganglionic fibres were sectioned. In the most sensitive preparations 0.43 to 4.3 μg of 5-HT caused a contraction of the nictitating membrane. The ganglionic origin of the effect was definitively demonstrated by the fact that it was abolished crushing the ganglion. Hexamethonium failed to block the 5-HT stimulating action; nicotine and cocaine blocked it. Low doses (0.0043—0.43 μg) which did not stimulate the ganglion by themselves, potentiated the response of the nictitating membrane to submaximal preganglionic stimulation: 0.43 μg increased the response to nearly maximum height. Even in large quantities (43 μg) the amine never produced ganglionic paralysis, nor did it potentiate the response to supramaximal stimulation of the preganglionic fibres. The potentiating action was not due to a lowering of the threshold of the fibres to electrical stimulation. This was demonstrated in experiments in which the cervical sympathetic chain was split longitudinally and a portion of the preganglionic fibres was stimulated supramaximally. Under these conditions 5-HT had the usual effect. The potentiation of ganglionic transmission was reduced by cocaine but not by atropine and mepyramine. In experiments on the perfused ganglion TRENDELENBURG (1956b) demonstrated that 5-HT also potentiated the ganglionic response to acetylcholine, nicotine, carbaminoylcholine, choline and potassium chloride. Vasoconstriction was not responsible for the potentiation. The potentiation of the ganglionic transmission was smaller on the perfused ganglion than on that with normal blood supply. 5-HT differed from nicotine and nicotine-like substances in that it potentiated and never depressed the ganglionic response to preganglionic and to chemical stimulation. Histamine and pilocarpine behaved as 5-HT.

Recording the action potentials of the postganglionic fibres, TRENDELENBURG (1957) demonstrated that 5-HT (like pilocarpine and histamine) potentiated the ganglionic transmission of the impulses travelling on both groups of fibres of the cervical sympathetic chain: the fast-conducting S 1 fibres innervating the nictitating membrane and the slow-conducting S 2 fibres innervating the blood vessels. 5-HT (4.3—8.6 μg) was injected into the central end of the cut lingual artery during occlusion of the external carotid artery. Potentiation occurred 5—15 sec after injection and lasted for about 2—3 min. 5-HT did not once inhibit the ganglionic transmission nor affect the postganglionic response to a supramaximal preganglionic stimulation.

GERTNER and ROMANO (1961) reported that 5-HT had only a slight potentiating effect on the ganglionic transmission through the perfused superior cervical ganglion of the cat. This is in agreement with TRENDELENBURG's observation that the perfused ganglion is much less sensitive to 5-HT than that with normal blood supply.

HERTZLER (1961a, 1961b) studied the effect of 5-HT on the transmission through the stellate ganglion of the rat. The isolated ganglion with a portion of the preganglionic thoracic sympathetic chain and of the postganglionic cervical sympathetic trunk were maintained in a moist chamber and intermittently immersed in physiological saline. 5-HT was added to the saline. Postganglionic

responses evoked by submaximal preganglionic stimulation were recorded. 5-HT (0.21—27 μg/ml) applied for 30 sec increased the amplitude and lowered the threshold of the postganglionic response. After contact with a 2.15 μg/ml solution the effect lasted about 20 min. The response of S 2 slow-conducting fibres was more sensitive to 5-HT than that of S 1 fast-conducting fibres. In the intact animal 5-HT (8.6 μg i.v.) had the same effect.

GYERMEK and BINDLER (1962b) studied the effects of the amine on the inferior mesenteric ganglion of the cat. Postganglionic activity was recorded from small bundles of fibres or single fibres of hypogastric nerve cut distally to the ganglion. Close intrarterial injection of 5-HT (0.54—4.3 μg) produced a marked increase in postganglionic spontaneous activity, leaving the preganglionic activity unchanged. The effect started 3—7 sec after the injection. Preganglionic fibres transection knocked out spontaneous postganglionic activity, but not that produced by 5-HT.

To sum up: 5-HT stimulates the sympathetic ganglia and causes facilitation of ganglionic transmission. The stimulating action of 5-HT is abolished by depolarizing agents but not by competitive ganglionic blocking substances. This leads us to conclude that the amine acts on the ganglionic cells and that it attaches itself to receptors different from the acetylcholine receptors.

GERTNER et al. (1957, 1959) dosed the 5-HT content of the effluent from the perfused superior cervical ganglion of cats. No measurable 5-HT was present in the perfusate at rest and during preganglionic supramaximal stimulation. The addition of iproniazid (200 μg/ml) to the perfusion liquid resulted in an immediate but partial depression of ganglionic transmission (nictitating membrane recording). No 5-HT appeared in the perfusate up to 2 hrs from the beginning of the perfusion with iproniazid. After this period 5-HT began to appear and continued to do so until the end of the experiment (at the rate of about 10 mμ/min). Preganglionic stimulation did not accelerate the appearance of 5-HT nor did it increase its content in the effluent. The addition of iproniazid (200 μg/ml) and 5-HTP (22 μg/ml) to the perfusion liquid resulted in a depression of transmission equal to that produced by iproniazid alone. In this case the 5-HT appeared in the perfusate within 5 min from the beginning of the perfusion, but preganglionic stimulation did not influence the 5-HT release. The significance of these findings must await further experimental results. It must be noted that the use of supramaximal stimuli precluded the possibility to evidentiate a facilitation of the transmission by 5-HT released.

II. Other indolealkylamines

GYERMEK and BINDLER (1962a) (see also GYERMEK et al. 1962) evaluated the ganglionic stimulating activity of a series of indolealkylamines on the inferior mesenteric ganglion of cats; the discharge of the postganglionic fibres was taken as a index of the stimulating actions. The drugs were injected into the cannulated inferior mesenteric artery close to the ganglion. 5-HT (0.43—2.15 μg), N-methyl-5-hydroxytryptamine (2.5—10 μg), bufotenine hydrogenoxalate (1.2—5 μg), bufotenine iodide (0.3—1.2 μg), N,N-dimethyltryptamine (80—1000 μg) and N,N,N-trimethyltryptamine iodide (5—10 μg) caused stimulation of the ganglion. The action of N-methyl-5-hydroxytryptamine, as that of 5-HT, was blocked by 5-hydroxy-3-indoleacetamidine (an anti-5-HT) but not by hexamethonium. The action of the other amines was blocked by hexamethonium. The substances listed below were inactive up to doses of 80 μg or more: N,N-dipropyl-5-hydroxytryptamine HCl, 5-hydroxy-α-methyltryptamine dipicrate, 5-methoxy-α-methyltrypt-

amine HCl, 5-methoxytryptamine, 5-benzyloxygramine, tryptamine HCl, N,N-diethyltryptamine ,N,N-dipropyltryptamine HCl, 6-hydroxytryptamine creatinine sulfate, N,N-dimethyl-6-hydroxytryptamine, 7-benzyloxygramine, 4-hydroxytryptamine oxalate, psilocin, pislocybin.

GERTNER and ROMANO (1961) briefly reported that tryptamine (10 μg/ml) blocked the ganglionic transmission when perfused through the superior cervical ganglion of the cat. MATTHEWS et al. (1961) (see also MATTHEWS 1963) observed that DL-α-ethyltryptamine, a MAO inhibitor, intravenously injected at a dose of 10 mg/kg caused partial depression of the transmission through the inferior mesenteric ganglion in the cat. Recovery occurred in 60—80 min.

K. Effects on cutaneous sensory endings

The action of 5-HT on the peripheral receptors must be particularly borne in mind in interpreting the central effects of the amine peripherally administered. In fact, amine injected into the blood flow does not reach the CNS only but also peripheral structures with central connections. It is quite likely that afferent discharges play an important part in producing some of the 5-HT central effects (for instance, the block of the patellar reflex). The data concerning the effects of indolealkylamines on the cutaneous nerve endings will be reviewed in this section. The effects on the receptors of the autonomic nervous system will be reviewed in other chapters.

ARMSTRONG et al. (1952, 1953) observed that the application of 5-HT creatinine sulphate in low concentrations (down to 10 ng/ml) to the exposed base of the cantharidin blister in humans caused pain. Tryptamine had the same action as 5-HT, but was more than 10 times weaker than the latter. Tryptophan was inactive even when applied in concentrations up to $1:10^3$. The pain arose 10 to 45 sec after 5-HT or tryptamine application and lasted for a few minutes. Further applications developped a refractory state. Using the blister area technique ARMSTRONG (1958) defined the pain-producing potency of a number of tryptamines. 4-HT, 6-HT and bufotenine were respectively 5,25 and 50 times less active than 5-HT. α,α-dimethyltryptamine, β,β-dimethyltryptamine and N,N-dimethyltryptamine were more than 2000 times weaker than 5-HT. ARMSTRONG et al. (1957) demonstrated that 5-HT could not be identified with the substance responsible for the pain-producing activity of plasma and exudates.

There is convincing evidence that, in animals, close arterial injection of 5-HT activates cutaneous afferent fibres. DOUGLAS and RITCHIE (1957) reported that 5-HT (20 μg) intrarterially injected evoked a powerful long-lasting discharge in non-myelinated afferent fibres in the cat's saphenous nerve. The same fibres also fired in response to gentle mechanical stimulation of the skin and to acetylcholine injection. FJALLBRANT and IGGO (1959, 1961) found that 5-HT (4—40 μg) injected into the saphenous artery evoked an intermittent low-frequency discharge in some fibres in a multifibre-strand of cat's saphenous nerve. The discharge began within 20 sec and persisted for several minutes. Recording from single-unit preparations the AA. found that the amine (1—20 μg) excited myelinated fibres from slow adapting mechanoreceptors and non-myelinated fibres from mechano- and thermo-receptors. Following 5-HT injection the response of the units to mechanical and thermal stimuli passed through a cycle of enhancement and depression. VAN GELDER (1962) injected 5-HT close arterially into a region of the skin of the rat and recorded impulses from a small branch of the saphenous nerve innervating the perfused area. The normal blood supply to the skin was blocked during the injection and during the 2 min which followed it. 5-HT

(1.8 μg) produced a sensory discharge lasting at least 2 min and intervalled by a brief period of diminished activity.

GUZMAN et al. (1962) injected 5-HT into many arteries in dogs and cats under chloralose anaesthesia. The injections were made through catheters tied into collaterals. The injection of 10.7—86 μg of 5-HT into each one of the arteries listed below evoked vocalisation, hypertension and hyperpnea, three symptoms considered by the AA. suggestive of pain: femoral, brachial, splenic, gastric, superior mesenteric and pulmonar. The amine appeared to be less effective when injected into the left coronary artery and into the internal carotid artery. Sectioning the sciatic nerve prevented the response to femoral injection.

From the data reported above it is clear that 5-HT when applied to the exposed base of a blister in humans or when intrarterially injected in animals evokes afferent discharges. The minutiae of the mechanism whereby 5-HT excites sensory nerve endings remain open to investigation.

L. Effects on the central nervous system of lower animals

HORRIDGE (1961) studied the action of 5-HT on the transmission through the cerebral ganglion of the clam *Mya*. A single shock to the cerebro-visceral connective (preganglionic stimulation) evoked a burst of impulses in the postganglionic fibres (anterior pallial nerve) which brought about the retraction of the mantle and the closure of the shell. 5-HT applied to the ganglion at a concentration of 10^{-5} caused a spontaneous discharge of motor impulses and slightly prolonged the duration of the burst induced by preganglionic stimulation.

GERSCHENFELD and TAUC (1961) studied the action of 5-HT on the neurons of the abdominal ganglion of the mollusc *Aplysia depilans* (intracellular recordings). The amine, added to the perfusion fluid, excited the cells having only inhibitory input (H cells) as well as those having only excitatory input (D cells), but its effects was more than ten times more intense on the latter. Furthermore the amine inhibited the H cells by exciting inhibitory interneurons.

SALÀNKI (1963) reported that the application of 5-HT on the cerebral ganglia of fresh-water mussels (*Anodonta cygnea*) provoked at 10^{-6} the relaxation of the contracted posterior adductor muscle and at 10^{-5}—10^{-4} a long lasting activity of the muscle.

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