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SEROTONIN AND NOREPINEPHRINE AS ANTAGONISTIC CHEMICAL MEDIATORS REGULATING THE CENTRAL AUTONOMIC NERVOUS SYSTEM

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OUR STUDIES WITH RESERPINE, serotonin, LSD-25, and chlorpromazine have led Dr. Shore and me to speculate that serotonin and norepinephrine are antagonistic chemical mediators that regulate the central autonomic nervous system. I wish to stress that our concept is admittedly oversimplified, but as a working hypothesis it does permit us to link a number of seemingly unrelated observations, and it suggests experiments within the framework of the concept. Like all concepts it will require change as new information emerges, and when the time comes that it no longer answers questions or suggests experiments we shall be perfectly satisfied to see it buried in that Potter's field especially reserved for ideas that have been slain by a fact.

Our interest in serotonin arose from studies of the properties of reserpine as a potentiator of hypnotics. Since reserpine and serotonin are both indoles, the suggestion arose that the potentiating effects of reserpine might be mediated through the release of serotonin, which is normally present in the brain in a bound form. To test this possibility, serotonin was administered intraperitoneally to mice and was found to induce sedation and to potentiate the action of barbiturates and alcohol. These effects of both serotonin and reserpine are antagonized by LSD-25 (1,2).

Following this, reserpine administered to animals was shown to release serotonin from its various body depots: intestinal mucosa (3), platelets (4), brain (5), and stomach mucosa.

A study was made on the action of reserpine on tissue cells (6). As shown in Table XV, the platelets from guinea pigs, pretreated 16 hours previously with reserpine, are markedly impaired in their capacity to

TABLE XV

Uptake of Serotonin by Platelets of Normal Guinea Pigs and of Animals that Received Reserpine (5 mg/kg) 16 Hours Previously*

Platelets from Normal Animals (μg/mg protein)	Platelets from Reserpine-Treated Animals (μg/mg protein)
1.45	0.19
1.34	0.21
1.48	0.11
0.86	0.20
0.60	0.13
1.35	0.10
1.39	0.14
Average 1.21 ± .33 (SD)	Average 0.15 ± .05 (SD)

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take up added serotonin *in vitro*. Similarly, rabbits pretreated with reserpine and then given 5-hydroxytryptophan, which crosses into brain and is decarboxylated to serotonin, show little capacity to store the serotonin in the brain, as compared to animals untreated with reserpine (Table XVI). Although the type of brain cells that store serotonin and the nature of the anchorage surface are not known, it is clear that reserpine alters the binding sites so that they can no longer hold on to serotonin. This does not seem to be a simple antimetabolite relationship as shown by Carlsson *et al.* (7), who demonstrated that one molecule of reserpine liberates from platelets *in vitro* a great many serotonin molecules. We have done a considerable amount of work in an attempt to establish the nature of the binding sites. The results do not as yet allow definite conclusions to be made but it has been found that homogenization of

*4 ml of platelet-rich plasma and 1 ml of isotonic saline containing 25 μg of serotonin were incubated in siliconed beakers for one hour at 37°C. Values represent net increase in serotonin concentration.

TABLE XVI

Increase in Brain Serotonin Following Administration of 5-hydroxytryptophan to Normal Rabbits and to Rabbits that Received Reserpine 5 mg/kg 16 Hours Previously*

Normal Animals (μg gm)	Reserpine-Treated Animals (μg/gm)
1.55	0.19
0.75	0.21
1.00	0.58
1.53	0.24
Average 1.21 ± .40 (SD)	Average 0.30 ± .18 (SD)

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tissue results in the rapid metabolism of serotonin by monoamine oxidase, suggesting that during homogenization a serotonin complex has been split, or that the integrity of the cell membrane is required to maintain the localization of serotonin. Also, differential centrifugation of tissues has thus far failed to show that serotonin has any particular affinity for a single part of the cell.

As a consequence of the action of resperine on the capacity of the cells to store serotonin, a certain amount of serotonin, depending on the dose of reserpine, will be liberated and rapidly metabolized by the action of monoamine oxidase. Figure 115 shows the depletion of serotonin in rabbit brain that results from the administration of a large dose, from 1 to 5 mg./kg., of reserpine. The serotonin is rapidly depleted and in about one hour reaches a concentration of about 10 per cent of the normal value. The concentration remains at this low level for about 48 hours and then gradually rises, reaching the original level in from 5 to 7 days.

Considerable evidence indicates that the pharmacologic effects of

*Rabbits were given 50 mg/kg of 5-hydroxytryptophan and were killed one hour later. Values represent net increase in serotonin concentration.

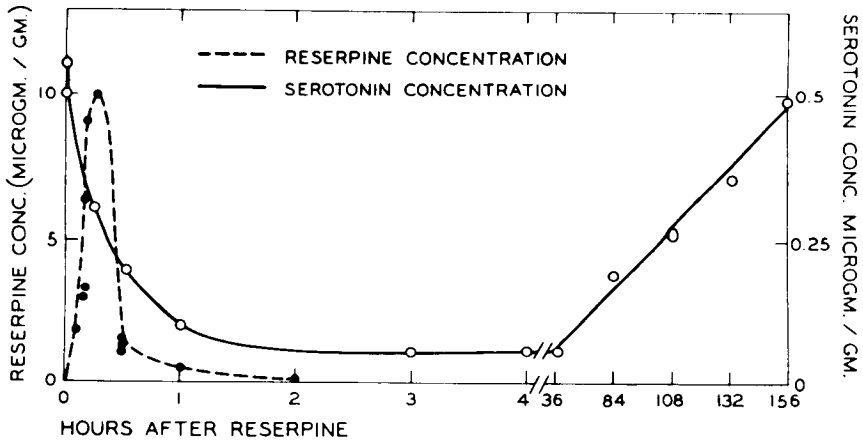

FIGURE 115. Concentrations of serotonin and reserpine in rabbit brain after injection of reserpine (from 1 to 5 mg./kg. I.V.). Reprinted, by permission, from Hess, S. M., Shore, P. A., and Brodie, B. B.: Persistence of reserpine action after the disappearance of drug from brain; effect on serotonin. *J. Pharmacol. & Exper. Therap.* **118**, 84 (1956).

reserpine are a consequence of the change in brain serotonin and not merely concurrent with it. For example, the sedative and potentiating effects of both administered serotonin and reserpine are blocked by LSD-25. Again, as seen in Figure 115, extractable reserpine rapidly disappears from brain because the drug is rapidly metabolized *in vivo*, yet the change in brain serotonin persists (8) as do the pharmacologic effects of the drug (9). Also, of a number of compounds tested, only the pharmacologically active reserpine alkaloids release serotonin from brain (10), *in vivo* or from platelets *in vitro* (7). Particularly striking is the observation that isoreserpine, a pharmacologically inactive stereoisomer of reserpine, and isoraunescine, an inactive isomer of the active compound raunescine, fail to release serotonin. Furthermore, rescinnamine, which shows relatively little pharmacologic activity in the mouse, releases only small amounts of serotonin in the brain of this animal while in the rabbit, in which it shows considerably more activity, it releases much more serotonin.

Investigations in progress show that even after the administration of doses of reserpine that almost deplete the serotonin depots, the amine continues to be formed in the body. Thus, following reserpine, serotonin may be considered to be continuously liberated from brain cells because of their impaired capacity to store the amine. The low levels of serotonin in brain after the administration of a large dose of reserpine would then represent a balance between its rate of synthesis and its rate

of destruction. The low serotonin levels persist until the binding sites regain their capacity to bind serotonin, or new sites are formed.

The question now arises as to whether the pharmacologic manifestations of reserpine should be attributed to a persistent low level of highly active free serotonin or to a decrease in the total amount of serotonin in brain. The evidence favors the former hypothesis. Briefly, in all experiments in which serotonin is used as a pharmacologic agent, only the free form seems active. (*a*) The sedative and hypnotic potentiating effects of reserpine are simulated in mice shortly after an intraperitoneal injection of 20 mg./kg. of serotonin. The sedative effects of serotonin are noted for about 60 minutes. Analysis of brain shows that small amounts of serotonin enter brain so that the brain level increases by about 20 per cent. Two hours later, when the sedative effects have disappeared, most of the increment in serotonin is still present. These sedative effects are presumably caused by the free serotonin that passes into the brain and they disappear when the serotonin becomes bound. (*b*) D. F. Bogdanski and S. Udenfriend* have shown that after rats are injected with 100 mg./kg. of the serotonin precursor, 5-hydroxytryptophan, the serotonin content of the uterus becomes quite high, about 2.5 γ/gm. This tissue shows no contractile activity when suspended in Locke's solution. But when serotonin is added in a concentration of only 0.01 γ/ml. a strong contraction results. (*c*) Both serotonin and reserpine increase the motility of intestines *in vivo*. The reserpine presumably acts by causing an increase in the level of free serotonin in the intestines, although the total serotonin (bound and free) decreases. (*d*) In addition, if the change in the concentration of total serotonin were the determining factor in the action of reserpine, the changes in the level of bound serotonin in brain should parallel the pharmacologic effects. This is not so. Thus rabbits are heavily sedated 30 min. after reserpine administration (1 to 5 mg./kg.) when the serotonin level in brain has declined to about 0.2 μg./gm. of tissue (Figure 115). Yet no sedation is apparent in 72 hr., although the serotonin level has returned to the same level, about 0.2 μg./gm. This apparent paradox can be explained by assuming that free serotonin is the cause of sedation. Shortly after reserpine administration, serotonin is still being released and therefore some free serotonin is present; in 72 hr., although the total serotonin level is again 0.2 μg./gm., a negligible amount of free serotonin is probably present because the serotonin binding sites are recovered sufficiently to take up the indole as it is formed in brain.

Hoagland: You don't think the bound serotonin has any activity at all, then?

*Unpublished data.

Brodie: I do not think so. If we consider serotonin to be a neurohumoral agent, then the bound form could be considered as the stored form. Like bound acetylcholine, it would be released as the free diffusible form by a nerve impulse.

Cantoni: I should like to say that these two arguments which you have presented, namely, that the physiologic state of the animal is different at the two times, and that injecting serotonin into the rats seems to cause no real change after 2 hours, do not seem particularly compelling.

Brodie: Why?

Cantoni: Because if this assumption is not made, these results can be explained as not being related to serotonin. The presence of free serotonin can be proved in a different way. Have you done anything on these lines? If you have not perhaps I could suggest an experiment. You should be able to get the amount of free serotonin by injecting radioactive serotonin. The bound serotonin probably would not mix with the free serotonin. I do not know exactly how you would get that, but you could probably get a more convincing and direct result if there were two pools of serotonin (free or bound) which could be demonstrated by such a technique.

Brodie: That is a good thought. However, we already know from experiments with injected 5-hydroxytryptophan that part of the free serotonin formed by decarboxylation in the brain from this compound becomes bound. From this point of view, therefore, free serotonin can mix with a bound pool of serotonin. I would now like to cite still additional evidence that free serotonin induces a reserpine-like effect. Cronheim and Gourzis (11) have reported that serotonin, infused intravenously to dogs pretreated with reserpine, causes a profound drop in blood pressure. No such effect was noted in normal dogs. This result may be interpreted by assuming that a small amount of free serotonin penetrated the brain, where it could not be readily bound in the reserpine-treated dog, thus adding to the hypotensive effect of the free serotonin already present as a result of reserpine action.

The question now arises as to the normal role of serotonin in brain. Woolley and his collaborators (12) have proposed that the role of serotonin may be to regulate the pulsations of oligodendroglia and Marrazzi and Hart (13) have proposed that serotonin is a humoral inhibitor. I do not therefore propose to discuss these possibilities here. Instead I shall speculate on the possibility that serotonin has a role in the central representation of the parasympathetic nervous system like that of acetylcholine in peripheral synaptic transmission. Thus, it might ordinarily be liberated in a free, active form, momentarily only, and then be rapidly

destroyed. Reserpine, by impairing the sites that store serotonin, but not affecting synthesis, could present a low but continuous concentration of free serotonin to subcortical centers. As a consequence, a continuous volley of impulses would bombard the centers and result in the usual manifestations of reserpine action.

Let us consider the minimal criteria discussed by Dr. Elkes for acetylcholine for a transmitter role in the central nervous system and how serotonin satisfies these criteria:

a) Presence of substance in brain. Serotonin was first demonstrated in brain by Twarog and Page (14) and by Amin *et al.* (15) by bioassay procedures. Using a specific fluorimetric assay for the determination of serotonin, its presence in brain has definitely been identified in our laboratory by countercurrent distribution and by fluorescence and activation spectra (16).

b) Presence must vary with function. Serotonin is unevenly distributed, being highest in the more primitive parts of the brain and lowest in the cortex and cerebellum (Table XVII). Reserpine, which acts centrally to produce marked parasympathetic effects, apparently acts through serotonin in those parts of the brain where serotonin concentration and 5-hydroxytryptophan activity are highest.

c) Presence of enzymes for destruction. Monoamine oxidase is present in all parts of the brain but it is especially concentrated in the hypothalamus (Table XVII).

d) Presence of enzyme for synthesis. There is a fairly good correlation between the activity of 5-hydroxytryptophan decarboxylase and the concentration of serotonin in brain (Table XVII). Those areas in brain that are high in serotonin are high in synthesizing activity while for those low in serotonin the reverse is true (17,18).

e) Demonstrable effect of addition of hypothetical agent to nervous tissue. As previously discussed, when a large dose of serotonin is administered to mice, intraperitoneally, a small quantity of the amine crosses the blood-brain barrier. The animals are sedated and the action of hypnotics is potentiated.

f) Effect of enzyme inhibitor. It is generally considered that acetylcholine acts as a chemical transmitter through membrane depolarization of nerve cells. If the presence of acetylcholine is persistent, for instance, as a result of the presence of a cholinesterase inhibitor at ganglia, a volley of postganglionic impulses may be produced. However, in the presence of an excess of acetylcholine, the ganglion cells are flooded with acetylcholine which results in persistent depolarization, and nerve impulses along the presynaptic fibers will no longer affect the post-

TABLE XVII

Distribution of Serotonin and Enzymes Involved in its Synthesis and Metabolism in Dog Brain

Tissue	Serotonin*	5-Hydroxytryptophan Decarboxylase†	Amine Oxidase**
Hypothalamus	1.6	117	1,660
Midbrain	1.0	98	1,254
Septum pellucidum	1.5	109	1,145
Thalamus	0.5	38	940
Medulla	0.6	32	977
Pons	0.3	28	882
Optic tract	0	7	768
Cerebellum	0.07	<9	930
Cortex	<0.17	7	843

*Serotonin—μg/gm tissue
†5HTP decarboxylase—μg serotonin formed per hr per gm of tissue
**Amine oxidase—μg serotonin destroyed per hr per gm of tissue

synaptic fibers. Thus, the same effect is obtained with too much acetylcholine as with no acetylcholine at all.

Marrazzi: What do you mean when you say the same effect with no acetylcholine as with too much?

Brodie: With no acetylcholine, depolarization would not occur; with too much, depolarization will be persistent.

Marrazzi: But they are not the same.

Brodie: No. I said you would get the same result.

Marrazzi: No, it is not the same result. One is paralysis, and the other is a state of full potentiality for being activated.

Brodie: By the same result, I mean the inability of the impulse to cross the synapse. In the intact animal, if no acetylcholine were liberated, the nerve impulse would not cross the synapse. However, if the synapse is flooded with acetylcholine, again the nerve impulse would not pass. It will not pass to the postsynaptic nerve.

Though we realize the danger of thinking by analogy from findings at the peripheral nervous system, we wished to determine whether a large amount of free serotonin would also counteract its own action in the central nervous system. Rabbits were pretreated with 100 mg./kg. of marsilid (iproniazid), a compound that inhibits monoamine oxidase and consequently the metabolism of free serotonin.

Three hours later the animals were given reserpine to release brain serotonin. These animals showed only a slight decline in serotonin and, instead of having the usual reserpine effects, were extremely agitated. Indeed, they exhibited typical LSD-like effects. Animals given iproniazid alone showed little change in brain serotonin but no overt pharmacologic effects. On the other hand, animals given reserpine first to liberate serotonin and then given iproniazid showed the same drop in serotonin and sedative effect as the animals given reserpine alone (Table XVIII).

Fremont-Smith: What is marsilid?

Brodie: Marsilid or iproniazid is isopropyl isonicotinylhydrazide, a compound once used to treat tuberculosis. The rabbit on the left in Figure 116 had reserpine only and is obviously disinterested in its surroundings. The other animal was pretreated with iproniazid and then

TABLE XVIII

Effect of Iproniazid on the Concentration of Serotonin in Brains of Normal and Reserpine-Treated Rabbits*

Drug	Brain Serotonin (μg/gm) (average)	Effect
None	0.55	—
Reserpine	0.10	Sedation
Iproniazid	0.63	None
Iproniazid followed by reserpine	0.42	Excitement
Reserpine followed by iproniazid	0.10	Sedation

*Rabbits were given 5 mg/kg reserpine I.V. Iproniazid (100 mg/kg) was given 3 hr before or after reserpine. Animals were sacrificed 1 hr after last drug administration.

FIGURE 116. Effect of iproniazid plus reserpine on rabbits. Both animals were given reserpine (5 mg./kg. I.V.) but animal on right was pretreated with iproniazid 2 hr. previously. Reprinted, by permission, from Brodie, B. B., and Shore, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. *Ann. New York Acad. Sc.* **66**, *631 (1957).*

given reserpine. A motion picture would show how active this animal was. It actually bucked like a bronco and was difficult to hold, so intense was its motor activity.

Olds: What was the reserpine dose there?

Brodie: We gave from 1 to 5 mg./kg. These doses are sufficient to release all the stored serotonin.

Jarvik: Does marsilid have any effect on epinephrine levels in the brain?

Brodie: I do not know, but I doubt it, since all the indications point toward iproniazid's being a rather poor inhibitor of epinephrine metabolism in spite of its potent inhibitory effects on monoamine oxidase.

Marrazzi: Did it activate the adrenal medulla? Is that what you mean?

Jarvik: I was thinking of amine oxidase inactivation of epinephrine.

Brodie: I mean that the metabolism of epinephrine and norepinephrine seems to be catalyzed only slightly by monoamine oxidase. Excess

free serotonin in the brain can be produced in still another way. Dr. Udenfriend and his colleagues (19) in our laboratory have shown that 5-hydroxytryptophan given to rabbits or dogs passes quickly into the brain, where it decarboxylates over a considerable period of time to form serotonin. Small doses of 5-hydroxytryptophan show no action or have a slight sedative effect. If the dose of 5-hydroxytryptophan is large enough, serotonin is formed in considerable amounts and, presumably by saturating the storage depots, results in a considerable level of free serotonin. Again, the animals are excited and behave as though they have received LSD-25.

Thus, it would appear that excess serotonin can block its own action. There is still another indication of this. We have shown that 100 mg./kg. of serotonin induce less potentiation of barbiturates in mice than 20 mg./kg. do.

It is of considerable interest that similar central effects are induced by a functional deficiency of free serotonin presumably brought about by LSD-25, and by an excess of free serotonin. LSD-25 perhaps acts by interfering with the normal depolarizing action of serotonin released at synaptic junctions, and excess serotonin by inducing a persistent state of depolarization. But an important fact to consider is that LSD-25 does not merely neutralize the effects of serotonin centrally, as it does in the case of smooth muscle, but it actually induces the opposite effects (Table XIX). It suggests that in the brain stem there are two mutually antagonistic systems, and if one is blocked the other is unmasked.

Hoagland: In our laboratory Dr. Alan Slocombe has extracted monoamine oxidase from rat brain and measured its inactivation action on serotonin *in vitro*.* He finds that marsilid blocks this inactivation because of its inhibitory effect on monoamine oxidase. He also finds that LSD-25 is almost as successful as marsilid in blocking the destruction of serotonin by the enzyme by competing with serotonin for the enzyme. Here there appears to be direct *in vitro* confirmation of what you are saying from the point of view of a real antagonism, but both marsilid and LSD-25 produce effects in the same direction. LSD-25 acts so as to increase serotonin.

Brodie: I do not think you are indicating, though, that LSD-25 might act that way, are you?

Hoagland: It may be possible.

Brodie: The amount of LSD-25 in brain would be orders of magnitude lower than that of marsilid, and it might be too small to affect monoamine oxidase. But this should certainly be checked.

Hoagland: Yes, it is of a different order of magnitude. But in the

*Unpublished data.

TABLE XIX

Comparison of Pharmacologic Effects of Reserpine (Persistent "Low" Free Serotonin), "Excess" Free Serotonin, LSD-25, and Amphetamine

Effect On	Persistent "Low" Free Serotonin (Reserpine)	Persistent "Excess" Free Serotonin (Iproniazid + Reserpine or 5-Hydroxytryptophan)	LSD-25	Amphetamine
Alertness	Decrease	Increase	Increase	Increase
Motor activity	Decrease	Increase	Increase	Increase
Temperature	Decrease	Increase	Increase	Increase
Depth and rate of respiration	Decrease	Increase	Increase	Increase
Blood pressure	Decrease	Increase	Increase	Increase
Pupil	Constriction	Dilation	Dilation	Dilation
Eyelid	Ptosis	Exophthalmos	Exophthalmos	Exophthalmos
Nictitating membrane	Relaxation	—	—	—
Heart rate	Decrease	Increase	Increase	Increase
Erection of hair	—	Piloerection	Piloerection	Piloerection

Reprinted, by permission, from Udenfriend, S., Shore, P. A., Bogdanski, D. F., Weissbach, H., and Brodie, B. B.: Biochemical, physiological and pharmacological aspects of serotonin. *Recent Progr. Hormone Research* 13, 1 (1957).

electrical responses from the brain, practically all here confirm each other on the fact that LSD-25 and serotonin have similar inhibitory effects on both spontaneous activity and on the transmission of the transcallosum response in pentothalized animals.

Brodie: One might expect similar effects if there were an excess of free serotonin in the transcallosal pathway.

Hoagland: That is the point. If LSD-25 inhibits amine oxidase that destroys serotonin, the latter will accumulate.

Marrazzi: But with minute doses of serotonin.

Brodie: How much is too much?

Marrazzi: You tell us.

Brodie: Unfortunately, I do not know, since our analyses do not distinguish total from free serotonin. However, our experiments suggest that while a small level of free serotonin produces a sedative action, only a slight additional rise in serotonin is necessary for its action to be reversed.

Marrazzi: The point we are trying to make is that the smallest doses we have used, and they are very small, give pure inhibition. I do not see that you are making a very appropriate analogy. You are making use of the fact that with an excess dose of an excitatory substance, paralysis results, and you say this is irreversible. True, but there are no known instances where you start with an inhibitor and get an excitation by the same mechanism. An excitation is caused by introducing a new mechanism. So I do not think the argument works backward.

Brodie: How about acetylcholine?

Marrazzi: Acetylcholine is excitatory first and paralytic in large doses.

Brodie: Just as serotonin may be. Serotonin can be considered as activating synapses in the central parasympathetic nervous system at low concentration and paralyzing them at high concentration.

Marrazzi: We can reproduce exactly our serotonin-inhibitory effect on the transcallosal preparation, by putting in marsilid.

Brodie: Incidentally, is there any serotonin in the transcallosal pathways?

Marrazzi: Since marsilid acts in the only way we know it acts, by inhibiting monoamine oxidase, and it produces the same effect as serotonin, I would assume that serotonin was present.

Brodie: That is an interesting point, but might it not be possible that free serotonin protected by iproniazid in one part of brain is able to diffuse to the transcallosal pathway? A problem that concerned us is how chlorpromazine and reserpine both act centrally to produce reduced sympathetic predominance, but chlorpromazine obviously does not act through serotonin. A number of observations make it appear that reserpine and chlorpromazine act by different mechanisms. First, they induce a potentiation of the action of hypnotics, but only that of reserpine is blocked by LSD-25 (Table XX). Second, the action of reserpine is irreversible in that its effects last far beyond the time the drug is detectable in tissues; chlorpromazine on the other hand seems to act reversibly; that is, its effects are dissipated as the drug disappears from the body. Third, the LSD-like effect in rabbits induced by excess of free serotonin (whether produced by the administration of ipron-

TABLE XX

Effect of LSD-25 on Ethanol Potentiation by Reserpine and Chlorpromazine*

Drugs	Duration of Hypnosis† (min, average)
Ethanol (controls)	40
Ethanol + reserpine	> 300
Ethanol + LSD-25 + reserpine	54
Ethanol + chlorpromazine	150
Ethanol + LSD-25 + chlorpromazine	147

†Time from loss to return of righting reflex

iazid followed by reserpine or by an excess of 5-hydroxytryptophan) is not blocked by reserpine. It would not be expected that reserpine, if it acts through free serotonin, would be a sedative agent in this situation, since there is already too much free serotonin present. On the other hand, chlorpromazine rapidly sedates the rabbits (Figures 117 and 118).

The difference in the modes of action of chlorpromazine and reserpine can perhaps be explained by assuming that they act on physiologically antagonistic systems in the brain stem, these systems being the central representations of the sympathetic and parasympathetic nervous systems. Drug-induced paralysis of one system would unmask the opposite system and allow it to predominate. Figure 119 shows a chemist's conception of what brain centers look like. Stimulation of the central parasympathetic system will, for example, constrict the pupils, while stimulation of the sympathetic system will dilate them. If serotonin is the neurohumoral agent for the central parasympathetic system, we can satisfy Dr. Marrazzi's objection, since serotonin may now be classed as a stimulatory agent.

Now reserpine is postulated to stimulate the parasympathetic system by causing a persistent release of serotonin from its storage depots.

*Adult male mice were given the various drugs intraperitoneally. Reserpine (5 mg/kg) was administered 1 hour before ethanol (4 gm/kg). Chlorpromazine (5 mg/kg) was given simultaneously with ethanol. LSD-25 (10 mg/kg) was given in two divided doses 1 hour before and simultaneously with ethanol. Mice given ethanol alone served as controls; LSD-25 by itself had virtually no effect on duration of hypnosis produced by ethanol.

FIGURE 117. Effects of reserpine on rabbit with excess serotonin in brain. Animals were pretreated with iproniazid (100 mg./kg.) followed in 1 hr. by reserpine (5 mg./kg. I.V.). Thirty minutes later the excited animal was given further administration of reserpine (5 mg./kg. I.V.). Reprinted, by permission, from Brodie, B. B., and Shore, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. *Ann. New York Acad. Sc.* 66, *631 (1957)*.

LSD-25 by blocking the action of serotonin normally released at the synapses, would unmask the action of the opposing sympathetic system and produce its typical sympathomimetic responses.

Chlorpromazine could be assumed to inhibit the sympathetic system by blockade of the chemical mediator that activates the sympathetic centers. It is possible that this mediator is norepinephrine. This substance has been found by Vogt (20) to have almost the same pattern of distribution in the brain as does serotonin. Thus just as LSD-25 may block the action of serotonin both peripherally and centrally, chlorpromazine may be considered to block epinephrine both peripherally and centrally.

It is true that chlorpromazine does not have much effect in blocking the pressor response to injected norepinephrine. Thus, with respect to chlorpromazine the term *adrenergic blocking agent* does not have the usual meaning since it does not block peripherally the chemical arterial

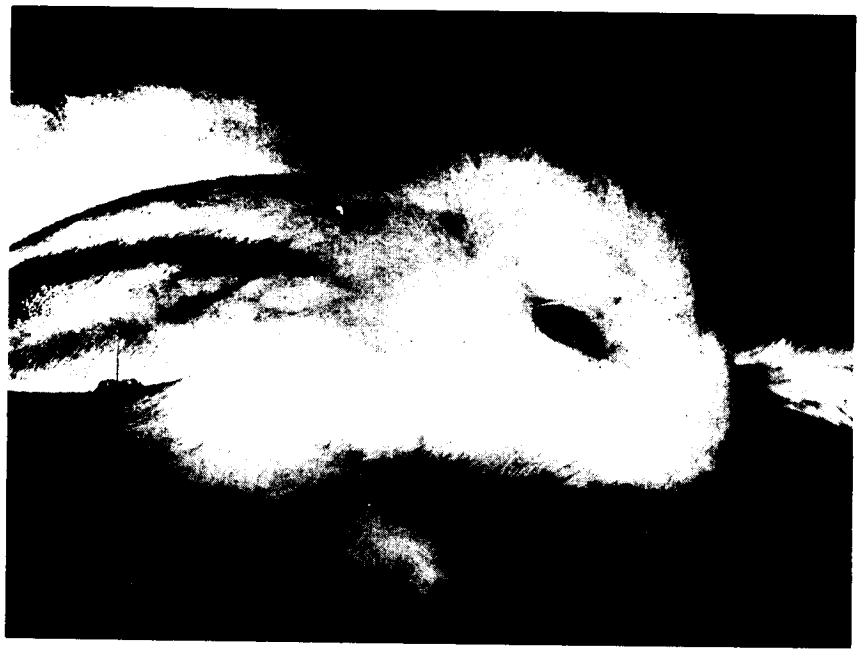

FIGURE 118. Effects of chlorpromazine on rabbit with excess serotonin in brain. Animal was pretreated with iproniazid (100 mg. kg. I.V.) followed in 1 hr. by reserpine (5 mg. kg. I.V.). Thirty minutes later the excited animal was given chlorpromazine (5 mg. kg. I.V.). Reprinted, by permission, from Brodie, B. B., and Shore, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. *Ann. New York Acad. Sc.* 66, 631 (1957).

transmitter, norepinephrine. But since it produces all the signs of an adrenergic blocking agent, it presumably does so by exerting a central action, perhaps by blocking norepinephrine centrally. In acting thus it would unmask the central parasympathetic system. I have stretched the meaning of the term *central parasympathetic* to include the sleeping or sedative centers postulated by Hess and the term sympathetic to include centers involved in arousal or wakefulness.

The concept of mutually antagonistic autonomic centers modulated by serotonin and norepinephrine allows speculation on the mechanism of action of a number of drugs. Amphetamine and ephedrine, because of their phenylethylamine structures, have been assumed to act centrally only in respect to their stimulant actions, but to act directly on various autonomic effector organs. These compounds have in general the same spectrum of effects as LSD (Table XIX) and indeed have been reported to produce hallucinations. But the effects on isolated organs are less than in the whole animal, and are decreased *in vivo* after sympathetic

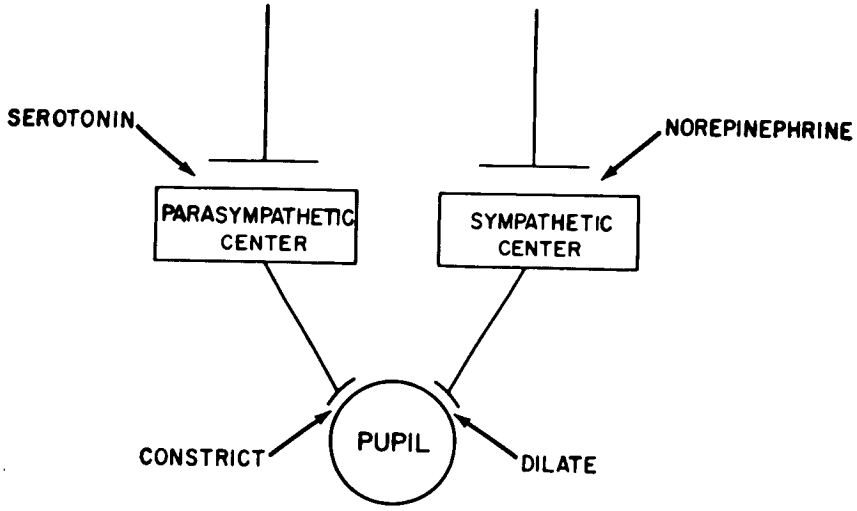

FIGURE 119. Mutually antagonistic brain centers in subcortical areas. Reprinted, by permission, from Brodie, B. B., and Shore, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. *Ann. New York Acad. Sc.* 66, *631 (1957)*.

denervation of the peripheral effector organ. The usual explanation is that the amines act indirectly on effector organs by protecting norepinephrine at sympathetic nerve terminals from the action of monoamine oxidase. But ephedrine and amphetamine exert only weak inhibitory effects on monoamine oxidase. Is it not possible that the peripheral actions of ephedrine and amphetamine are in part centrally mediated where they would simulate the action of norepinephrine on sympathetic centers? Recent work indicates that ritalin, also a phenylethylamine, is an antagonist of reserpine *in vivo*, and induces a number of peripheral sympathomimetic effects by acting within the central nervous system (21).

As mentioned before, the effects of chlorpromazine on peripheral organs is probably almost entirely central in origin. Thus it does not block the pressor actions of administered norepinephrine. It has been shown by Dasgupta and Werner (22) that the injection of small doses of chlorpromazine intracisternally into monkeys causes a fall in blood pressure and a blockade of the carotid sinus reflex, while the pressor response of systemic injections of epinephrine remains unaffected. Also, Jourdan *et al.* (23) state that chlorpromazine is inactive in the spinal dog at a dose that is hypotensive in an intact animal. Of special interest are the observations of Moran and Butler (24) in this laboratory,

who have shown that chlorpromazine sulfoxide, a major metabolite of chlorpromazine, produces sedation, orthostatic hypotension, and partial blockade of the carotid sinus reflex by a central action.

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