Pharmacological Effects from Drugs Injected Intracerebrally in Unanesthetized Animals*

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The intracerebral injection of cardiac glycosides, quinidine sulfate, procainamide, chlorpromazine, reserpine, and lysergic acid diethylamide in unanesthetized dogs produced symptoms of a profound autonomic nervous system stimulation. Many common effects were produced by several structurally unrelated drugs. However, certain drugs had rather specific actions, which seemed to be localized in discrete areas in the brain. Studies with such preparations allow an estimate to be made of central activity without the complicating factors of general anesthesia or diffusion across the blood brain-barrier.

MANY DRUGS have diverse effects on the central and autonomic nervous systems, and by the large it is difficult to separate their central from their peripheral effects. In many instances diffusion of drugs into the central nervous system is so slow that central effects appear to be entirely absent or appear only at toxic doses. Furthermore, studies are often conducted in the presence of general anesthesia which tends to partially or completely obscure any central effects. In the past many investigations have been conducted on curarized, artificially respired animals in an effort to obtain estimates of central activity of drugs. Recently, Feldberg and Sherwood (1–4) devised a cannula for injection of drugs into the lateral ventricle of the conscious cat. Haley and co-workers (5–9) employed a similar cannula in studies with the unanesthetized dog. It is the purpose of this paper to summarize these dog experiments to date and point out the similarities of response elicited by drugs of unrelated chemical structure as well as the differences in response which appear to be related to certain drugs. In addition an attempt will be made to relate pharmacological effects with possible sites of action in the brain.

EXPERIMENTAL

Healthy, adult dogs of either sex were prepared for implantation of a cerebral cannula according to the method described previously (3, 9). Aspiration of cerebrospinal fluid as well as roentgenograms showed that the cannula penetrated into the third cerebral ventricle. Intraventricular injections varied in volume from 0.2 to 1 ml. Intravenous injections within comparable dosage ranges were made via the anterior subcutaneous vein of the foreleg. Electrocardiographic records were obained with lead II using a Sanborn Viso-Cardiette. Figure 1 shows a schematic drawing of the needle in position and some of the areas in the ventricular system which could be affected by the injected drugs.

RESULTS

Cardiac Glycosides.—Intraventricular injection of 3.2 to 4.4 mcg./Kg. of tryptamine-strophanthidin or 6.4 to 8.4 mcg./Kg. of strophanthin-K produced bradycardia and depression of the ST segment of the electrocardiogram characteristic of digitalis. Secondary effects were: salivation, defecation, mydriasis, shivering, generalized tremor, and mucous membrane and retinal pallor. All of these effects disappeared after 11 minutes and the animals appeared normal. With larger doses, 10.9 to 17.2

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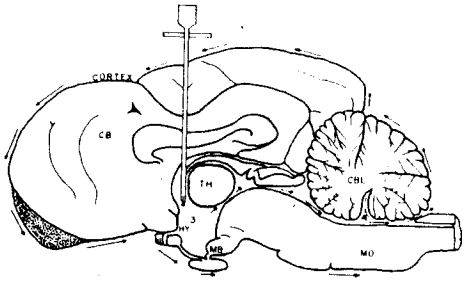

Fig. 1.—Median sagittal view of dog brain showing indwelling cannula. Arrows indicate circulation of cerebrospinal fluid; cerebrum, CB; cerebellum, CBL; thalamus, TH; hypothalamus, HY; third ventricle, 3; fourth ventricle, 4; mammillary body, MB; medulla, MO.

mcg./Kg. of tryptamine-strophanthidin or 31.4 to 57.4 mcg./Kg. of strophanthin-K, ventricular extrasystoles and paroxysmal ventricular tachycardia appeared in three minutes. After two to nine minutes, some animals had bigeminy, trigeminy, sinus tachycardia, multifocal ventricular tachycardia and periodic P-wave suppression. Death resulted from respiratory paralysis and ventricular fibrillation. Additional secondary effects were: barking, generalized excitement, lateral and vertical nystagmus, opisthotonus, tense abdominal musculature, retching, emesis, micturition, tachypnea, and orbicularis muscle twitching. These effects must be centrally induced because intravenous injection of 8.9 to 9.8 mcg./Kg. of tryptamine-strophanthidin or 31 mcg./-Kg. of strophanthin-K had no effect. Doses of 20.1 to 26.8 mcg./Kg. of tryptamine-strophanthidin produced a deep Q-wave and a biphasic T-wave or an inverted T-wave with a late sagging ST segment and a bradycardia. Such effects had a duration of only ten minutes. Strophanthin-K, 77 mcg./Kg. produced only a bradycardia of nine minutes duration. Secondary effects were not observed.

Injection of the vehicles into the third ventricle produced no effect. The intravenous administration of 15 to 37.3 mg./Kg. of hexamethonium chloride completely abolished the secondary effects and re-established normal cardiac rhythm within eight minutes. Chlorpromazine, 20 mg./Kg., also was effective. Furthermore, anesthetization with pentobarbital decreased the cardiac rate and induced a regular sinus rhythm.

Quinidine Sulfate.—Intraventricular injection of quinidine sulfate in doses ranging from 0.45 to 4.0 mg./Kg. produced paroxysmal ventricular tachycardia, alternating nodal extrasystoles or auricular tachycardia followed by a diminishing sinus tachycardia. Immediate secondary effects consisted of retching, micturation, defecation, mydriasis, nystagmus, respiratory depression, mucous membrane pallor and Stage III, Plane II general anesthesia with corneal reflexes still present. None of these effects were seen after intravenous injection of 2.8 to 8.1 mg./Kg. of the drug. Furthermore, intraventricular injection of 0.5 ml. of propylene glycol, which composed 20% of the vehicle, produced none of the above effects. Quinidine sulfate did not cause any fatalities.

Procainamide. Intraventricular injection of 5.2 to 7.1 mg./Kg. of procainamide had little or no effect on the electrocardiogram. Side effects were limited to defecation, nystagmus, slight twitching of the facial musculature and Stage III, Plane II anesthesia. None of these effects were seen after 10.3 mg./Kg. intravenously.

Chlorpromazine. Intraventricular injection of 0.3 mg./Kg. tranquilized the animal for 16 minutes and produced a lowered, biphasic T-wave. No other effects were observed. When the dose was increased to 0.93 to 1.10 mg./Kg. the following cardiac effects occurred: bradycardia; an inverted, lowered or biphasic T-wave; followed by tachycardia; series of one, two, or three ventricular extrasystoles and coupled normal beats. After about 20 minutes the T-wave became upright. Side effects were: analgesia and tranquilization, shivering, decreased respiratory rate, defecation, mydriasis and occasional barking. Body temperature fell 0.3 to 1.6° over a period of 35 minutes and then returned to normal 15 minutes later. Ten to 12 hours later the animals appeared normal. Intravenous injections of 20 mg./Kg. produced variability in the height of the T-wave with tachycardia followed by bradycardia. Normal electrocardiograms were obtained 11 to 20 minutes later. Secondary effects were: attempted emesis, defecation, vertical and lateral nystagmus, miosis with reactive pupils, ataxia, micturition, and analgesia with no reaction to painful stimuli. Body temperature decreased 0.6° and a slight respiratory depression occurred.

Reserpine.—Intraventricular injection of 2.2 to 4.5 mcg./Kg. produced salivation, retching, and emesis. No other effects were observed, and the animals appeared normal 20 minutes after the injection. When the dose was 25 mcg./Kg. the following effects were observed: salivation, repeated emesis, slight miosis, and defecation. Electrocardiographic changes were tachycardia, biphasic or inverted T-wave, and an accentuated P-wave. The animals were normal within 24 hours.

Lysergic Acid Diethylamine (LSD–25).—Intraventricular injection of 1.6 to 10 mcg./Kg. produced the following symptoms within one to three minutes: whining, shaking of the head, salivation, retching, emesis, micturition, tachypnea, and ataxia. After six minutes, mydriasis with reactive pupils was observed. Recovery occurred after 15 to 20 minutes, but throughout this period the animals appeared frightened. The animals barked for several hours after the other effects of the drug were gone. The animals reverted from an adult behavior to a puppy one, but there was no impairment of their ability to obey commands or perform simple tasks. This personality change was the most striking effect which occurred.

DISCUSSION

The various pharmacological effects produced by intracerebral injection of drugs in the unanesthetized dog are summarized in Tables I and II. The possible sites of action listed should not be considered as the only sites because activation of receptors in the cerebral ventricles may, through interneuronal pathways, cause more distant centers to be affected. These centers may give rise to the observed effects which are for the most part evidence of a profound

TABLE I.—COMMON EFFECTS FROM INTRACEREBRAL INJECTION OF DRUGS

Effect	Strophanthin-K and Tryptamine Strophanthidin	Procainamide	Quinidine Sulfate	Chlorpromazine	Reserpine	LSD-25	Possible Sites of Action
Salivation	+	+	−	−	+	+	Pre-optic hypothalamus
Retching	+	−	+	−	+	+	Brain stem reticular formation
Emesis	+	−	−	−	+	+	Chemoreceptor trigger zone
Mydriasis	+	−	+	+	−	+	Posterior hypothalamus
Nystagmus	+	+	+	−	−	−	Pontine area or medial longitudinal fasciculus
Defecation	+	+	+	+	+	−	Hypothalamic, pre-optic and supra-optic nuclear areas
Micturition	+	−	+	−	−	+	Pre-optic hypothalamus
Vasoconstriction	+	−	+	−	−	−	Posterior hypothalamus, vasomotor center in medulla
Shivering	+	−	−	+	−	−	Posterior hypothalamus
Tachypnea	+	−	−	−	−	+	Respiratory center in medulla
Bradypnea	−	−	−	+	+	−	Respiratory center in medulla

+ Present; − absent.

autonomic nervous system activation. Furthermore, it would be inconsistent to insist that certain specific sites in the walls of the third ventricle are the only ones being affected because the brain ventricles form a closed system and the drugs eventually will spread throughout the entire system. The possibility of diffusion into the mass of brain tissue surrounding the ventricles also could play a part in the overall effects observed. As can be seen in Table I, there are many drug effects produced which cannot be related to the chemical structure of the compounds studied. It may be that certain areas in the brain are more susceptible to the drugs than others. On the other hand certain drugs appear to have very specific effects on certain areas (see Table II). Correlation between the central sites of action and the observed peripheral effects may be obtained by comparing our results with those in which the electrophysiological approach has been used.

brain stem reticular formation. Borison and Wang (12) have pointed out the distinction between retching and emesis, relating the latter effect to an activation of the chemoreceptor trigger zone in the wall of the fourth ventricle. From this zone interneuronal fibers activate the emetic center in the dorsal portion of the lateral reticular formation, producing emesis. This may not be the only area involved because Hess (13) has shown that stimulation of the caudal portion of the diencephalon also produces retching and emesis. Ependymal receptors in the lateral ventricles also cause emesis when stimulated (12).

Hess (14) produced mydriasis by stimulation of the posterior hypothalamus, but centers for this activity also exist in the cerebral cortex and the brain stem. In all probability intracerebrally injected drugs act directly on the hypothalamic centers and then the impulses are conducted to the other centers of mydriatic activity. Miosis occurs after

TABLE II.—UNCOMMON EFFECTS FROM INTRACEREBRAL INJECTION OF DRUGS

Drug	Effect	Possible Site of Action
Strophanthin-K and tryptamine-strophanthidin	Abnormal electrocardiogram ending in ventricular fibrillation. Generalized excitation	Anterior and posterior hypothalamus
Procainamide	Stage III, Plane II general anesthesia with corneal reflexes present	Ascending reticular system; hypothalamus
Quinidine sulfate	Stage III, Plane II general anesthesia with corneal reflexes present	Ascending reticular system; hypothalamus
Chlorpromazine	Analgesia and tranquilization. Hypothermia, bradycardia followed by tachycardia	Hypothalamus and brain stem, thermoregulator center, posterior and anterior hypothalamus
Reserpine	Miosis	Optic chiasma, optic tract, pretectal region
LSD-25	Ataxia. Change from adult to puppy behavior pattern	Unknown

Furstenberg and Crosby (10) have related salivation to stimulation of the pre-optic hypothalamus. However, the salivatory nuclei in the medulla may also be stimulated. This may be of particular importance because of the well known relationship between salivation and emesis. Magoun (11) has correlated the postural changes accompanying retching with a facilitatory and inhibitory system in the

stimulation of the optic chiasma, the optic tract or the superior quadrigeminal brachium. Ranson and Magoun (15) also obtained this effect after stimulation of the pretectal region, the posterior commissure or the fibers emerging from the posterior commissure that arch around the ventral aspect of the central gray matter at the upper end of the cerebral aqueduct. Intracerebrally injected

drugs could reach and directly or indirectly activate any or all of these areas. Nystagmus, generally considered to be a pontine effect, may have been brought about through a collateral effect on the medial longitudinal fasciculus, which is represented in the hypothalamus by a nucleus in the posterior commissural area.

Defecation may be considered a peripherally mediated action, but Kuntz (16) states that experimental evidence suggests the existence of a defecation center in the medulla oblongata and of a center in the mesencephalon which exerts a tonic influence on the rectal musculature. Sheenan (17) has summarized the available evidence relating gastrointestinal hyperfunction to stimulation of the hypothalamic preoptic and supra-optic nuclear areas. Uvnas (18) reported that stimulation of certain areas in the hypothalamus results in micturition. However, tonus of the bladder musculature is also regulated through centers in the rostral border of the hindbrain and these centers are subject to influences from the cortical areas of both cerebral hemispheres. Autonomic centers in the diencephalon also influence bladder function.

Mucocutaneous vasoconstriction may be brought about by stimulation of the sympathetic areas of the posterior hypothalamus and also through activation of the vasoconstrictor center in the medulla. Blair and Keller (19) have related shivering to the posterior hypothalamus with its descending pathway through the lateral hypothalamus passing dorsolaterally to the mammillary body and entering the mesencephalic tegmentum. Stimulation of hypothalamic nuclei in the caudal border of the lateral hypothalamus results in hypothermia. The changes in respiratory rate observed may have been related to effects on the respiratory center in the medulla. The changes seen in the electrocardiographic tracing and heart rate are probably due to stimulation of the hypothalamus. Hess (14) has shown that a cardioinhibitory center exists in the anterior hypothalamus and a cardioacceleratory center exists in the posterior hypothalamus.

States of consciousness have been summarized by Magoun (20) as being related to the ascending reticular activating system adjacent to and having effective collaterals in the hypothalamus. Activation of this system could explain the general anesthesia and perhaps the analgesia and tranquilization observed.

As can be seen from the preceding discussion the areas of the brain which can be affected by intracerebrally injected drugs are numerous and diverse in activity. The results obtained by such injections are of central origin because the rapidity of onset of action and the amount of drug producing the observed effects are such to rule out peripheral sites of action. Much larger parenteral doses are required to produce effects and in many instances the effects are diametrically opposite to those obtained by intracerebral injection. Furthermore, the blood-brain barrier would effectively prevent the intracerebrally injected material from entering the blood stream rapidly thus further reducing the overall concentration which could affect the peripheral receptors. The vehicles alone did not produce the effects observed so they must be related to the drugs themselves.

SUMMARY

(1) Studies have been made of the effects produced by the injection of drugs into the third cerebral ventricle of unanesthetized dogs.

(2) Cardiac glycosides, quinidine sulfate, procainamide, chlorpromazine, reserpine, and lysergic acid diethylamide all produced certain effects in common but each drug also appeared to be able to affect certain specific areas in the brain.

(3) The possible sites of action in the brain were discussed and the difficulties of exact localization of such sites of action pointed out.

(4) The intraventricular injection of drugs in the unanesthetized animal allows a true assessment of central activity at doses which produce little or no effect when administered intravenously. Furthermore, the effects produced are not related to the vehicles used.

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