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Effects of transmitter mimickers at sites of angiotensin-induced drinking in the cat*

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A variety of mimickers of synaptic transmitter activation were tested at neural sites in the cat effective for the elicitation of drinking by angiotensin-II. The angiotensin-II was administered in a dose of 1,000 ng and the mimickers, norepinephrine, epinephrine, isoproterenol, dopamine, 5-hydroxytryptamine, and carbachol, in doses of 10 micrograms. None of the putative neurotransmitter agonists elicited water ingestion. The carbachol produced parasympathetic arousal, emotional activation, convulsions, and circling behavior. The catecholamines produced drowsiness and sleep. The isoproterenol and 5-hydroxytryptamine were without obvious behavioral effects. The role of brain synaptic transmitter systems in the mediation of thirst by angiotensin is discussed.

Angiotensin-II (AII) is an endogenous dipsogen found in the blood and brain of mammals (Booth, 1968; Fitzsimons, 1972; Ganten, Boucher, & Genest, 1972; Ganten et al, 1971). This substance is produced in a two-step process. First, renin from the kidneys acts on angiotensinogen from the liver to form angiotensin-I. Second, this substance is altered by converting enzyme to form AII (Goodman & Gilman, 1970; Gross, 1971; Guyton, 1971). Since microinjection of AII into the brain produces water ingestion, one important question is whether this substance acts via one of the biochemical synaptic transmitter systems presently known, and if so, which one (or ones).

A number of studies have employed the "blocking technique," administering chemical agents known to inhibit one or another of the chemical transmitter systems and evaluating the inhibition of the drinking elicited by AII. Inhibitors of acetylcholine (antimuscarinics) and norepinephrine (both alpha and beta blockers) have not inhibited AII-elicited drinking (Fitzsimons & Setler, 1971; Giardina & Fisher, 1971; White, Levitt, & Boyer, 1972). However, catecholamine mediation may be suggested by the findings that 6-hydroxydopamine or lateral hypothalamic lesions inhibit AII-elicited drinking (Fitzsimons & Setler, 1971; B. J. Rolls, personal communication). In one study, an AII antiserum was found to block the elicitation of drinking in the rat following the intracranial microinjection of AII or renin substrate (angiotensinogen). This suggests, also, the necessity of conversion of this AII precursor to AII for dipsogenic activity (Epstein, Fitzsimons, & Johnson, 1973).

Neuroanatomical and dose-response analyses of drinking elicited by AII and renin have recently been reported for the cat (Brophy & Levitt, in press; Sturgeon, Brophy, & Levitt, 1973; Sturgeon & Levitt, in press). This report is a preliminary study of the behavioral effects in the cat of a variety of putative neurotransmitters when administered to brain sites at which AII is an effective dipsogen.

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METHOD

Subjects, Surgery, and Histology

Ten adult male or female cats participated in this study. They were also used in two other experiments reported separately (Brophy & Levitt, in press). The cats were housed individually with continual access to Purina Cat Chow and tap water. Surgery, consisting of the implantation of six to eight guide shafts (23 ga) for the delivery of chemicals into the brain, was conducted under Nembutal anesthesia, using aseptic precautions. Data reported are based on stimulations at 30 neural loci in the 10 cats. Five sites of stimulation were employed: septum (seven placements), preoptic area (seven placements), caudate nucleus (six placements), lateral hypothalamus (five placements), and lateral cerebral ventricle (five placements) (Jasper & Ajmone-Marsan, 1961).

At the conclusion of the experiments, Ss were anesthetized with an overdose of Nembutal, red ink was injected into the sites of stimulation, and then saline followed by Formalin was perfused via the innominate artery. Frozen sections were cut (40 micra) and stained by the Kluver and Barrera technique. A representative photomicrograph has recently been published (Sturgeon, Brophy, & Levitt, 1973). Drawings showing the placements of the 30 stimulation sites in the five neural structures may be found in the original dissertation (Brophy, 1973).

Test Procedures

Testing began at least two weeks after surgery. Chemical injections were then begun, at 48-h intervals. Each drug injection was preceded by a 30-min pretest, during which water intake was measured and behavior was evaluated. The cat was then removed from its cage and held while the drug injection was made into the brain. The brain injection was made with a 30-ga needle cut to the appropriate length and fitted to a Hamilton Company

Table 1
Behaviors Produced by the Drug Injections

	Responses Elicited by CARB			Sleeping and Drowiness Following Catecholamines		
Structure	AA	Rage	CS	NE	E	D
Septum (7)*	6	6	0	1	0	1
Caudate Nucleus (6)	4	4	0	3	2	1
Lateral Ventricle (5)	4	3	2	0	1	0
Preoptic Area (7)	3	3	0	0	0	2
Lateral Hypothalamus (5)	2	0	0	2	1	0

Note–AA = autonomic arousal, CS = convulsive seizures.
**Number of stimulations*

microsyringe. The needle was held in place for 5 sec after the injection and then replaced by a stylette. Cats were then observed for 30 min (water intake and behavior were recorded). A modified Kimax drinking tube was used for measuring water intake.

Drugs

The drugs and doses used were angiotensin-II amide in a dose of 1,000 ng, and 1-norepinephrine hydrochloride (NE), epinephrine bitartrate (E), dopamine hydrochloride (D), dl-isoproterenol hydrochloride (ISO), carbachol (carbamylcholine chloride, CARB) and 5-hydroxytryptamine creatine sulfate complex (serotonin, 5HT) in doses of 10 micrograms each. Drugs were injected dissolved in 1.0 microliters of a 5-ion isotonic artificial cerebrospinal fluid containing primarily sodium and choloride ions, with trace amounts of potassium, calcium and magnesium ions. For injections into the lateral cerebral ventricle, the same dose of drug (1,000 ng of AII or 10 micrograms of the transmitter mimickers) was injected in a volume of 16 microliters, so as to facilitate the spread of the solution within the ventricular system. Molarities of the injected solutions varied between 269 and 322 milliosmoles.

RESULTS

All 30 sites reported on were positive for the elicitation of drinking by AII. An arbitrary criterion of at least 30 ml during the test has been used to define a drinking response. Sites were first tested for drinking with AII and then stimulated with the other six drugs in a random order. AII was the only drug to reliably elicit water ingestion. No difference in the volume or latency of the AII drinking response was found as a function of site of stimulation. This finding has been reported separately (Brophy & Levitt, in press). Water consumption elicited by AII averaged 90 ml. None of the other drugs produced a significant drinking response. However, water intake following ISO approached statistical significance (mean = 26 ml). Following the other five drugs, mean intake ranged from 8 ml (E) to 15 ml (D) (CARB and NE = 9 ml each, 5HT = 10 ml).

Three types of behavioral responses, other than drinking, were observed: emotional behavior, motor effects, and drowsiness and sleep (Table 1). CARB, but none of the other drugs, elicited signs of parasympathetic arousal, rage, and in two cases, convulsive seizures. The parasympathetic activation included pupillary dilation, salivation, and lacrimation, and was followed by intense scratching and grooming of the head and face. This pattern occurred following 19 of the 30 injections of carbachol. Signs of increased emotionality or rage accompanied the parasympathetic arousal on 16 of the 19 trials. This behavior included growling, hissing, and piloerection, and appeared to be defensive since the cats did not attack mice placed in the cage or a piece of rubber tubing waved in front of them. The rage occurred at all sites except the lateral hypothalamus. Typically, the parasympathetic arousal and rage began within about 5 min of injection and lasted for 30 to 90 min.

Strong tonic-clonic convulsive seizures, beginning about 40 min after drug injection, occurred twice following CARB injection into the lateral ventricle. The seizures lasted 2 h in one cat, and a second cat expired during the second hour of seizures. Circling behavior, contralateral to the side of injection, occurred with caudate (three times) and preoptic (twice) injections.

What appeared to be drowsiness and sleeping occurred following 14 of the 90 catecholamine injections (NE, E, D; see Table 1). No striking behavioral changes were observed to follow injection of 5HT or ISO.

DISCUSSION

Drinking was *not* reliably elicited by a 10-microgram dose of CARB, NE, E, ISO, D, or 5HT injected into several different neural sites. This dose is large enough for significant diffusion throughout the brain, and also into the general circulation, to be expected (Routtenberg, 1967, 1972). The small, but nonsignificant elevation in water consumption following ISO is likely due to peripheral diffusion. This has been shown to be the case for a similar dose in rats (Giardina & Fisher, 1971; Houpt & Epstein, 1971). The drinking is thought to be the result of beta-adrenergic facilitation of renin release from the kidneys. The gross behavioral effects widely produced by the chemicals suggest a major role for diffusion, and are consistent with previous reports on the effects of intracranial injection (Beleslin, Andjelkovic, & Vasic, 1973; Feldberg & Sherwood, 1954; Meyers, 1964).

One question of interest is whether AII-elicited drinking involves one of the known synaptic transmitter systems of the brain. If the neural firing pattern changes presumed to result from increases in AII and to mediate the drinking response involve one of these transmitter systems, then intracranial injection of the appropriate transmitter mimicker at the *appropriate* dose would be expected to also produce drinking. Since no dose-response study was done here, it is quite possible that one of the tested transmitter systems could still mediate AII-elicited drinking. Further dose-response testing, especially with lower doses, is needed. However, several blocking studies with antagonists of the same transmitter systems tested here have also failed to provide data suggesting a role for one of these systems in AII-mediated drinking (Fitzsimons & Setler, 1971; Giardina & Fisher, 1971; White, Levitt, & Boyer, 1972).

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Impact of sound effects and dramatic speech style on speaker perception, attitudes, and speech recall

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Under the guise of serving in an experiment on speech perception, Ss listened to a short speech under one of four conditions. The speech was spoken either dramatically or seriously, and the speech either was or was not accompanied by sound effects. Measures were taken on Ss' moods, attitude, and recall of the speech. Results showed more persuasion for the serious than for the dramatic version of the speech. However, the serious/dramatic and sound/no-sound manipulations interacted in determining mood ratings. Overall, attitudinal acceptance was independent of the affect expressed by Ss. The results were interpreted as supporting Leventhal's (1970) parallel response model.

In a recent attitude study, Galizio and Hendrick (1972) exposed Ss to four folk songs, each of which either did or did not have guitar accompaniment and each of which was either sung or dramatically spoken. Results indicated that a communication accompanied by instrumental music enhanced both persuasion and

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