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Oral and Hypothalamic Injections of Barbiturates, Benzodiazepines and Cannabinoids and Food Intake in Rats[1]

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ANDERSON-BAKER, W. C., C. L. McLAUGHLIN AND C. A. BAILE. *Oral and hypothalamic injections of barbiturates, benzodiazepines and cannabinoids and food intake in rats.* PHARMAC. BIOCHEM. BEHAV. **11**(5) 487–491, 1979.—To evaluate and compare CNS sites of action of chemicals which stimulate feeding, intakes were measured after ventromedial hypothalamic (VMH) and lateral hypothalamic (LH) administration of pentobarbital sodium (PBS), diazepam (D) and the d- and l-isomers of Δ^9-tetrahydrocannabinol (THC); and intragastric administration of D and d- and l-THC. In rats fed ad lib PBS (8 and 16 μg) increased intake tenfold ($p<0.05$) 0.5 hr after injection in the VMH, but not the LH. Intragastric administration of 2.5 and 5 mg/kg D increased intake twofold ($p<0.01$) at 0.5 and 2 hr but did not affect 24 hr intake. VMH injections of D (10 and 20 μg) caused a 15-fold increase ($p<0.05$) at 0.5 but not 24 hr, but LH injection of D did not affect 0.5 or 24 hr intake. Intragastric administration of 4 mg/kg l-THC increased ($p<0.01$) food intake at 1 and 2 hr, but 24 hr intake was not affected; d-THC had no effect. VMH, but not LH, injection of l-THC (0.25 μg) caused a 24-hr increase in intake. d-THC (0.25 μg) caused a decrease ($p<0.05$) in feeding at 0.5 hr, but not 24 hr when administered in the VMH, and increased ($p<0.05$) feeding at 24 hr when injected in the LH. The VMH appears to mediate the action of both PBS and D, but the increased feeding caused by systemic l-THC is not duplicated by VMH administration, thereby suggesting an alternate site of action.

Tetrahydrocannabinol Diazepam Pentobarbital sodium Feeding Intrahypothalamic injections

AMONG the pharmacological agents that can cause an increase in short-term food intake, depending on the dose and species, are the barbiturates, benzodiazepines and cannabinoids. Barbiturates such as sodium pentobarbital (PBS) are used clinically for their hypnotic/sedative effect and can cause increased feeding in various species following oral [11] and cerebroventricular administration [22, 23, 32]. The barbiturates cause a reversible depression in the activity of all excitable tissues. The CNS is especially sensitive, and a hypnotic/sedative dose can have very little effect on skeletal, smooth, or cardiac muscle. Chemical transmission across neuronal junctions is highly susceptible to interference by barbiturates, indicating that the synapse is the site of action [15].

Diazepam (D), a benzodiazepine, is widely used as an antianxiety agent and systemic administration has increased feeding in many species, e.g., rats [34], cats [29], dogs [34], horses [9], chicks, pigs, sheep, cattle [27] and humans [15]. The hunger-satiety mechanism may be directly affected by benzodiazepines, either by suppressing the satiety center or stimulating the hunger mechanism [24]. Benzodiazepines may exert their effect on the CNS through a facilitation of gamma-aminobutyric acid (GABA) transmission [33]. Terminal axons are depolarized by GABA, which might have the effect of releasing inhibition by one center on another, or decreasing the firing of an excitatory center.

Cannabinoids, derivatives of *Cannabis sp.*, are used by humans to achieve a euphoric state, and anecdotal reports of increased consumption of food following inhalation of cannabis smoke are numerous. The few clinical studies conducted under laboratory conditions also indicate increased eating following cannabis administration [1, 2, 16, 17, 18]. Results of studies using animal subjects are conflicting and may depend on the nutritional state of the animal (i.e., fasted or sated), time sequence of data collection (number and size of meals), and motivation [2, 3, 14, 31, 36]. The mechanism of action is poorly understood but the effect of cannabinoids on feeding could be related to the increased rate of catecholamine biosynthesis in the hypothalamus [23]. In chickens cannabinoids increased brain sodium and potassium ions relative to calcium ions [3]. Similar ionic shifts in other species have caused depression of feeding (e.g., [5]), suggesting an explanation for the decrease in feeding following chronic administration of cannabis.

The objective of this study was to determine if three classes of compounds known to stimulate feeding when ad-

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ministered peripherally, affect feeding when injected into either the lateral or ventromedial areas of the hypothalamus.

METHOD

To demonstrate the effect of peripheral administration of D on feeding, twenty-three male Sprague-Dawley rats, initially weighing 360 ± 19 g, were assigned to four groups of approximately equal body weight distribution. Rats were housed individually in wire mesh cages in a room with constant temperature 21°C and 12 hr light-dark. Purina lab chow pellets and water were available ad lib. Each group was randomly assigned to a treatment of 0, 1.25, 2.5 or 5.0 mg/kg diazepam. Treatments of D in 1.0 ml propylene glycol/kg body weight were administered intragastrically with a dosing needle and intake of food (Purina lab chow pellets) was measured after 0.5, 2, and 24 hr. Treatment means were tested for difference using analysis of variance and Duncan's multiple range test [13].

The effects of peripheral administration of d- and l-Δ^9-THC on feeding were tested using eight Sprague-Dawley female rats initially weighing 251 ± 3 g, housed as described above. On the first treatment day four were intragastrically dosed with vehicle (1.0 ml 20% ethanol/kg) and four with 4 mg/kg l-Δ^9-THC. At least 48 hr later the first four were intragastrically dosed with 4 mg/kg d-Δ^9-THC and the second four with vehicle solution. Non-paired *t*-tests were used to compare food intakes 1.0, 2.0 and 24 hr after injection.

For each series of hypothalamic injections a group of female Sprague-Dawley rats approximately 225 g was used. During the experimental period the rats were housed individually in wire mesh cages. Constant light was provided in the experimental room, and the temperature was maintained at approximately 21°C. Purina lab chow pellets and water were available ad lib.

General small animal surgical procedure as described by Cooley and Vanderwolf [10] was used to prepare the animals for implantation of the stainless steel guide cannulas. After administration of sodium pentobarbital (45.0 mg/kg IP) and atropine sulfate (1.0 mg/kg IP), each rat was stereotaxically fitted with either a LH or VMH 22 g bilateral cannula preparation. With the animal's head horizontal, the coordinates for bilateral VMH cannula placement corresponded to: anterior-posterior, 2.8 mm posterior to bregma; lateral, 0.5 mm lateral to mid-sagittal suture; dorso-ventral, 7.4 mm below dura mater. The anterior-posterior and dorso-ventral coordinates for bilateral LH implants were the same as for VMH implants, but were located 1.5 mm lateral to the midline. The cannula preparation was secured to the skull by acrylic dental cement, and 28 g stylets were inserted to keep the cannula lumen open. Animals were allowed several days to recover normal feeding behavior and pre-operative body weight.

Administration of chemicals directly into the hypothalamic areas was by means of a 2.2 cm length of 28 g stainless steel tubing soldered to a 22 g retaining collar. This was in turn connected to a Hamilton microliter syringe by means of polyethylene tubing. To minimize damage to brain tissue, and to limit diffusion of administered chemicals to adjacent brain areas [30], a volume of 0.25 μl/cannula was administered for each treatment. Vehicles used were determined by the solubility of the compounds used and consisted of 100% ethyl alcohol (ETOH), dimethyl sulfoxide (DMSO) and 0.0001 M NaOH with l- and d-Δ^9-THC, D and PBS, respectively.

A typical experiment consisted of intracranial injection of chemical or vehicle at 24 hr intervals on consecutive days according to a randomized design. Immediately prior to the injection each animal was offered fresh lab chow pellets and fresh water. Food consumed was measured at 0.5 and 24 hr intervals, and water intake was measured at 2 and 24 hr. Each chemical (PBS, D, and l- and d-Δ^9-THC) was tested in both the LH and VMH. Treatment means were tested for significance by means of analysis of variance, Duncan's multiple range test [13], and paired *t* values.

To confirm cannula placement, animals were sacrificed with sodium pentobarbital and perfused with 10% Formalin, and the brains were removed. Sections 1.5 cm thick which included the cannula tracts were embedded in paraffin. Thin sections (10–15 μ) were made and stained with cresyl violet. Data from animals with incorrect cannula placement, as determined by comparison of slides with a stereotaxic atlas [21] were not included in the tables which follow.

RESULTS

The effects of no handling, sham injection and DMSO vehicle injection treatments on feeding behavior of both VMH and LH cannulated animals were analyzed, Table 1. Neither sham injection nor DMSO caused a significant change in feeding compared to the no handling treatment. The other vehicles (NaOH and ETOH) were not similarly tested but were included as control treatments in subsequent experiments.

VMH injections of PBS, 8 and 16 μg, caused a tenfold increase ($p<0.05$, paired-*t*) in feeding over the 0.5 but not the 24-hr time interval. Injection of PBS in the LH had no effect on food intake over either the 0.5 or 24 hr intervals (Table 2).

Doses of 2.5 and 5 mg/kg D administered intragastrically increased food intake two-fold ($p<0.01$, Duncan's multiple range test) at 0.5 and 2 hr, but did not affect 24-hr intake (Table 3). VMH injections of D, 10 and 20 μg, caused a 15-fold increase ($p<0.05$, paired-*t*) in feeding over the 0.5 but not the 24 hr interval, although LH injection of D did not affect 0.5 or 24 hr intake.

Intragastric administration of 4 mg/kg l- but not d-Δ^9-THC increased ($p<0.01$, non-paired *t*) food intake after 1 and 2 hr, but 24-hr intakes were not affected (Table 4). l-Δ^9-THC, 0.25 μg, caused a 24-hr increase ($p<0.05$, paired-*t*) in feeding when administered in the VMH (Table 5). There was a strong trend toward increased feeding at 0.5 hr ($p<0.06$, paired-*t*) caused by 0.125 μg of l-Δ^9-THC injected into the VMH. LH administrateion of l-Δ^9-THC did not affect 0.5 or 24 hr intake. The d-isomer of Δ^9-THC, 0.25 μg, caused a decrease ($p<0.05$, paired-*t*) in feeding at 0.5 hr, but not 24 hr when administered in the VMH. The same dose caused increased ($p<0.05$, paired-*t*) feeding at 24 hr when injected in the LH. The relative effects of the microinjections of PBS, D, and d-and l-Δ^9-THC are summarized in Table 6.

DISCUSSION

Although we did not administer pentobarbital orally, rats consuming 100 to 400 mg/kg/day barbitone in water ate more and gained faster than controls [11]. VMH microinjections of PBS caused an increase in 0.5 hr food intake at doses of 8 and 16 μg. The same doses of PBS had no effect when administered in the LH. These results are consistent with previous findings. For example, Wagner and deGroot [38] noted

TABLE 1

THE EFFECT OF INTRAHYPOTHALAMIC SHAM AND DMSO INJECTIONS ON FOOD INTAKE IN RATS

Site of Injection	Time Period (hr)	Food Intake g($\bar{X}$ ± SEM) No Handling	Sham Injection	DMSO Vehicle
VMH (n=7)	0.5	0.9 ± 0.3	1.7 ± 0.6	1.0 ± 0.4
	24	28.4 ± 2.5	24.7 ± 3.3	28.1 ± 2.1
LH (n=7)	0.5	0.9 ± 0.2	1.0 ± 0.5	0.7 ± 0.3
	24	29.9 ± 2.3	24.9 ± 4.6	29.1 ± 2.1

TABLE 2

THE EFFECT OF INTRAHYPOTHALAMIC INJECTIONS OF SODIUM PENTOBARBITAL ON FOOD INTAKE IN RATS

Site of injection	Time period (hr)	Food intake g($\bar{X}$ ± SEM) Dose (μg/cannula) 0	4	8	16
VMH (n=4)	0.5	0.1 ± 0.1	0.7 ± 0.3	1.0* ± 0.4	1.4* ± 0.7
	24	23.0 ± 4.2	18.7 ± 1.8	24.7 ± 4.2	22.6 ± 1.8
LH (n=5)	0.5	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	24	14.3 ± 2.4	15.5 ± 3.0	15.4 ± 1.1	13.7 ± 2.1

*Different from 0 dose, $p<0.05$, paired-t test.

TABLE 3

THE EFFECT OF DIAZEPAM ON FOOD INTAKE IN RATS

Method of administration	Time period (hr)	Food intake g($\bar{X}$ ± SEM) Dose (mg/kg) 0	1.25	2.50	5.00
Stomach tube (n=23)	0.5	1.2 ± 0.6	0.7 ± 0.1	3.1† ± 0.4	4.4† ± 0.6
	2	1.7 ± 1.0	1.0 ± 0.2	3.4* ± 0.4	4.7* ± 0.2
	24	29.4 ± 2.0	28.4 ± 0.9	29.6 ± 1.9	26.4 ± 2.8
		Dose (μg/cannula) 0	5	10	20
VMH injection (n=7)	0.5	0.1 ± 0.1	0.4 ± 0.2	1.5* ± 0.6	2.1* ± 0.8
	24	22.0 ± 2.6	17.7 ± 2.4	22.0 ± 3.2	24.7 ± 2.2
		Dose (μg/cannula) 0	5	10	20
LH injection (n=6)	0.5	0.1 ± 0.1	0.7 ± 0.4	1.1 ± 0.4	1.2 ± 0.3
	24	30.3 ± 1.9	24.7 ± 4.1	30.0 ± 1.6	27.5 ± 3.6

*Different from 0 dose, $p<0.05$, paired-t test.
†Different form 0 dose, $p<0.01$, paired-t test.

increased consumption of liquid food when sated or 20-hr fasted rats were given unilateral microinjections of PBS in the VMH. Injections of PBS in the LH had no effect in these studies. Intraventricular infusions of PBS (65 mg/ml at 5 μl/min) caused a positive eating response in both normal rats and rats recovered from aphagia caused by electrolytic LH lesions [7].

Suppression of VMH inhibition of feeding (i.e., satiety) has been postulated as the mechanism by which intraventricular PBS works [35]. This concept is reinforced by the present findings in that the VMH and not LH was found to be the effective injection site. In addition to verifying the results previously cited, PBS was included in the present study to validate the microinjection technique of direct stimulation of the hypothalamus.

The benzodiazepines are known to increase feeding in rats [34], humans [15] and a variety of other animals [6,33]. The feeding responses following intragastric administration are similar to those elicited by intraperitoneal injections of the same doses of D [25,39]. An increase in 0.5 hr food intake was noted when D (at the highest doses—10 and 20 μg/cannula in 0.25 μl) was administered in the VMH, but not the LH. One interpretation is that the benzodiazepines may directly affect the reciprocal hunger-satiety mechanism by suppressing satiety (VMH), by modifying the concentration of GABA. GABA functions as an inhibitory transmitter in the vertebrate CNS [8] and is found in both the LH and VMH [20]. Bicuculline methiodide (BM), a GABA antagonist, and GABA were microinjected (1 μl) into hypothalamic areas (rat) known to influence feeding behavior [19]. Ingestion of sweetened milk was increased by LH injection of BM and decreased by LH injection of GABA [19]. VMH injections of BM and GABA resulted in decreased and increased milk consumption, respectively [19]. D has been shown to increase GABA levels in the brain (rat and mouse) and the spinal cord (cat) [17], by inhibiting GABA-alpha-ketoglutarate transaminase, the GABA-degrading enzyme [37]. The present findings are consistent with this model for the VMH area.

Reports on the effects of the cannabinoids on feeding are difficult to interpret. Anecdotal accounts of increased food intake following smoking of cannabinoids in humans have been confirmed by Greenberg *et al.* [16]. Chronic and casual marihuana users significantly increased caloric intake and gained body weight during a 21-day period of marihuana smoking under research conditions in a hospital ward [16]. Although the major active component of marihuana is Δ^9-THC [28], these findings conflict with numerous reports that administration of Δ^9-THC or a homologue (parahexyl) causes decreases in both food intake and body weight in rats [4,36]. A number of different possibilities has been suggested to account for the contradictory effects of THC in humans and animal subjects. As reviewed by Abel [2] these include drug dosage, route of administration, secondary effects of decreases in fluid consumption, general malaise, and changes in alimentary tract activity. Difficulties in compar-

TABLE 4

THE EFFECT OF 1-Δ^9-TETRAHYDROCANNABINOL ON FOOD INTAKE IN RATS

Method of administration	Time period (hr)	Food Intake g(X ± SEM) Dose (mg/kg) 0	4
Stomach tube (n=8)	1	0.1 ± 0.0	1.7* ± 0.6
	2	0.1 ± 0.0	2.4† ± 0.5
	24	23.8 ± 1.3	23.6 ± 0.9

Method of administration	Time period (hr)	Dose (μg/cannula) 0	0.125	0.25
VMH injection (n=4)	0.5	0.6 ± 0.2	1.4 ± 0.5	1.2 ± 0.6
	24	27.3 ± 1.4	28.2 ± 1.9	34.5* ± 1.7
LH injection (n=4)	0.5	1.6 ± 0.8	1.6 ± 0.8	0.7 ± 0.1
	24	26.1 ± 4.7	26.3 ± 3.9	23.3 ± 2.6

*Different from 0 dose, $p<0.05$, paired-t test.
†Different from 0 dose, $p<0.01$, paired-t test.

TABLE 5

THE EFFECT OF d-Δ^9-TETRAHYDROCANNABINOL ON FOOD INTAKE IN RATS

Method of administration	Time period (hr)	Food intake g($\bar{X}$ ± SEM) Dose (mg/kg) 0	4
Stomach tube (n=8)	1	0.3 ± 0.3	0.4 ± 0.4
	2	0.6 ± 0.4	0.5 ± 0.5
	24	23.7 ± 1.7	25.6 ± 0.4

Method of administration	Time period (hr)	Dose (μg/cannula) 0	0.125	0.25
VMH injection (n=4)	0.5	1.1 ± 0.3	1.5 ± 0.4	0.4* ± 0.1
	24	21.1 ± 2.1	24.5 ± 0.7	20.3 ± 2.7
LH injection (n=4)	0.5	1.3 ± 0.5	0.7 ± 0.3	1.6 ± 0.7
	24	26.0 ± 3.8	25.6 ± 4.1	29.2* ± 3.3

*Different from 0 dose, $p<0.05$, paired-t test.

TABLE 6

SUMMARY OF THE RELATIVE EFFECTS OF HYPOTHALAMIC MICROINJECTIONS OF BARBITURATES, BENZODIAZEPINES, AND CANNABINOIDS ON FOOD INTAKE IN RATS

Chemical	Area LH 0.5 hr intake	LH 24 hr intake	VMH 0.5 hr intake	VMH 24 hr intake
Pentobarbital sodium			↑*	–
Diazepam	–		↓*	–
1-Δ^9-Tetrahydrocannabinol		–	↑†	↓*
d-Δ^9-Tetrahydrocannabinol		↓*	↓*	

*Different from control, $p<0.05$, paired-t test.
†Different from control, $p<0.06$, paired-t test.

ing human and laboratory animal responses to THC may be illustrated by the fact that smoke inhalation is the main route of administration of THC in humans, while rats are typically given THC via intraperitoneal, subcutaneous, or intramuscular injections.

THC has been shown to increase food intake in experiments with laboratory animals. Drewnowski and Grinker [12] have reported that seeming inconsistencies between previous reports for the feeding effect of THC may be largely due to differences in the post-injection time period for which intake was recorded. By using a computer to continuously monitor eating, drinking and general activity, Drewnowski and Grinker [12] demonstrated that during the 3-hr post-injection period THC failed to reduce food intake but shifted feeding towards more numerous, smaller meals and, in fact, showed a trend toward increased intake.

Gluck and Ferraro [14] have demonstrated increased food intake with oral administration of Δ^9-THC in rats on a food-deprivation regimen. In addition as little as 10 μg 1-Δ^9-THC/kg administered intravenously has increased food intake in sheep [26]. In our experiments intragastric administration of 4 mg 1-Δ^9-THC, but not d-Δ^9-THC, in sated rats increased 1 and 2 hr intake, but did not affect 24-hr intake. Microinjection of 1-Δ^9-THC into the VMH caused a non-significant, short-term increase (0.5 hr) in food consumption for the two doses tested, and the higher dose caused a 24 hr increase in food consumption. The d-isomer of THC caused a depression in feeding for 0.5 hr when administered into the VMH, and an increase in feeding for 24 hr when administered into the LH. It is interesting that the d- and l-isomers of THC have opposite effects in the VMH, and d-Δ^9-THC causes increased intake, but 1-Δ^9-THC has no effect, when these compounds are microinjected in the LH.

Based on its action in the LH and VMH 1-Δ^9-THC is proposed to have an inhibitory effect on VMH satiety neurons. The same effect on LH feeding neurons would cause either no effect or a depression in intake (not observed). The d-Δ^9-THC appears to have an opposite, stimulatory effect. The action occurs over a short time period in the VMH (resulting in decreased feeding) and over a longer time period in the LH (resulting in increased feeding).

It has been proposed that the cannabinoids act on the LH and VMH by either facilitating or inhibiting neural activity. The mechanism of action of these agents cannot be defined by the present studies. This study has demonstrated, however, that pharmacological agents known to influence feeding when administered peripherally have localized effects on brain feeding centers that are consistent with the widely-accepted model of LH and VMH function. How these centers function at a molecular level to influence feeding remains to be determined.

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