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Effects of GABA Receptor Blockade on Stimulation-Induced Feeding and Self-Stimulation[1]

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PORRINO, L. J. AND E. E. COONS. *Effects of GABA receptor blockade on stimulation-induced feeding and self-stimulation.* PHARMAC. BIOCHEM. BEHAV. **12**(1)125–130, 1980.—Frequency thresholds for eating elicited by electrical stimulation of the lateral hypothalamus of rats decreased in a dose-dependent manner after intraperitoneal (IP) administration of picrotoxin, a γ-aminobutyric acid (GABA) antagonist that blocks GABA-mediated synaptic inhibition. Strychnine IP, a glycine antagonist that blocks glycine-mediated synaptic inhibition, had no effect. By contrast, frequency thresholds for self-stimulation at the same electrode site significantly increased after picrotoxin. Again, strychnine had no effect. These findings indicate that GABAergic mechanisms are involved in both electrically-elicited feeding and self-stimulation. They also suggest a dissociation of the neural substrates which subserve these behaviors.

GABA Picrotoxin Self-stimulation Stimulation-induced feeding Hypothalamus

EVIDENCE now exists to suggest that γ-aminobutyric acid (GABA) is an important inhibitory transmitter in the mammalian central nervous system [20,32]. However, information is just beginning to become available on the role GABA plays in behavior and the exact nature of its interactions with other neuronal systems. GABA is widely distributed in mammalian brain [1,10], and is highly concentrated in structures which have been associated with electrically elicited motivated behaviors, in particular the lateral hypothalamus [18,33]. Anatomical and pharmacological experiments point to a GABA-mediated descending pathway from the caudate to the substantia nigra [17,31]. This pathway is thought to provide feedback regulation of the cells in the substantia nigra, thereby controlling the activity of dopaminergic neurons in the nigrostriatal system. This system which is considered a possible substrate for self-stimulation and stimulation-induced feeding [11, 28, 29] courses with the medial forebrain bundle through the lateral hypothalamus.

In light of this, it is the purpose of these experiments to assess the effects of GABA receptor blockade on electrically elicited motivated behaviors, lateral hypothalamic stimulation-induced feeding (LH-SIF) and self-stimulation (LH-SS). In the first experiment picrotoxin, a specific postsynaptic GABA antagonist [5, 9, 24] was administered systemically in three doses and frequency thresholds for LH-SIF were determined. Picrotoxin was chosen in preference to bicuculline, another GABA receptor blocker, [20], because of picrotoxin's relative specificity and because bicuculline is known to have effects on other transmitter systems [20]. In addition, because of the convulsant nature of picrotoxin [6], strychnine which also acts as a convulsant but does not alter GABAergic systems [6,7], also was administered as a control for non-specific behavioral side effects. In the second experiment frequency thresholds for LH-SS were assessed following systemic picrotoxin and strychnine injections.

EXPERIMENT 1

The effects of picrotoxin on LH-SIF thresholds were examined. It was hypothesized that GABA receptor blockade would reduce the efficacy of inhibitory mechanisms in the hypothalamus, thereby lowering thresholds for LH-SIF.

METHOD

Animals

Five adult male Sprague-Dawley rats weighing approximately 300 g at the time of surgery were used as subjects. Rats were maintained in individual cages in a room with controlled temperature (22.2° ± 1.1° C) and light (12:12 hr). Food and water were available ad lib at all times.

Surgery

Rats were anesthetized with sodium pentobarbital (60 mg/kg) and placed in a Kopf stereotaxic instrument.

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Monopolar electrodes which consisted of size 00 insect pins insulated to within 0.2 mm of the tip were implanted bilaterally. The stereotaxic coordinates used were: 3.0 mm posterior to bregma, ± 1.6 mm lateral to the midline, and 8.6 mm ventral to the dorsal surface of the skull. The incisor bar was adjusted so that both the bregma and lambda sutures lay in the same horizontal plane. An uninsulated jeweler's screw placed rostrally in the skull served as the ground.

Histology

Upon completion of behavioral testing rats were sacrificed by sodium pentobarbital overdose and perfused intracardially with 0.85% saline followed by 10% formalin. Brains were removed from the skull and placed in 10% formalin for at least 7 days after which 40 μm sections were cut and every third section mounted and stained with cresyl violet. Verification of electrode placements was made with reference to the König and Klippel [19] rat brain atlas.

Apparatus

Digibit logic units (BRS Electronics), a 1.0 μF capacitor, and a 68 K resistor were arranged in series [8] to produce capacitance-coupled, negative-going pulses delivered to the animal in continuous trains. The current amplitude of the pulses was controlled by a 50 K variable resistor. All stimulation parameters were monitored continuously by an oscilloscope.

Testing was conducted in a 34×34×46 cm Plexiglas chamber. Pulses were conducted from the unit to the implanted electrodes via flexible wires and a mercury commutator which prevented twisting of the wires.

Drugs

The drugs employed were picrotoxin (Sigma, 0.5, 1.0 and 1.5 mg/kg) and strychnine (Sigma, 0.75 mg/kg). Both were dissolved in sterile physiological saline and prepared just prior to injection. The saline vehicle alone was used as a control. Drugs and controls were administered intraperitoneally one half hour before behavioral testing.

Procedure

Selection criteria and training. One week after surgery, animals were screened for stimulation-induced feeding behavior. Each animal was tested for a minimum of three daily sessions consisting of 15 30-sec periods of continuous brain stimulation (40 pulses per sec) with 60-sec interstimulation intervals. The testing chamber contained a dish of wet mash. During screening the current intensity was increased from 20 μA in 10 μA steps until stimulation-induced feeding was displayed or 100 μA was reached. Animals which displayed consistent eating for at least 10 sec during 7 or more 30-sec trials were retained for further testing.

Rats were trained for two weeks prior to testing. With a fixed frequency of 40 pulses per second (pps) a current was selected which would sustain 10 sec of eating in a 30-sec trial with a latency of 10 sec or less. Following this, animals were trained in a threshold procedure in which the frequency of pulses in the stimulation train was varied while the current level was kept constant at all times [4]. A method of limits procedure was employed in which the frequency of pps of brain stimulation was increased following trials in which the animal failed to reach criterion and decreased following successful trials. The cirterion for success was eating wet mash for at least 10 sec during the trial with a latency of 10 sec or less. The pps threshold was the average of 15 30-sec trials each separated by a 30-sec intertrial interval.

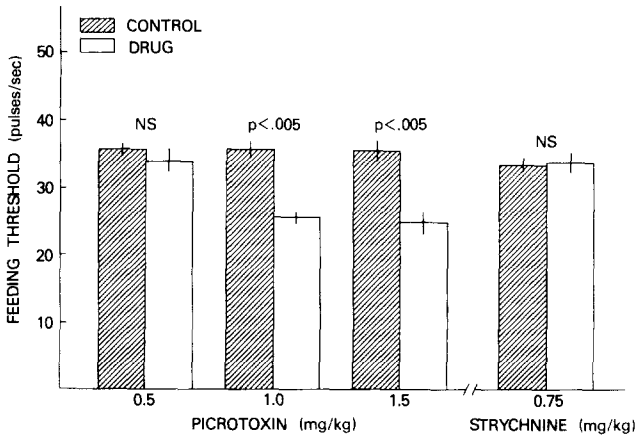

FIG. 1. Effect of picrotoxin and a CNS stimulant control, strychnine on stimulation-induced feeding thresholds. Drug tests are compared to vehicle controls just prior to tests. Error bars represent S.E.M.

Testing. Following stabilization of pps thresholds (3 consecutive threshold determinations within 10% of the mean) animals were tested in the following conditions: picrotoxin (0.5, 1.0 and 1.5 mg/kg), strychnine (0.75 mg/kg), and a saline vehicle. Drugs were administered in a random order with a vehicle test always occurring between drug tests. At least two days interposed between test days. To insure satiety all animals were given one hour free access to wet mash (the test substance) and water before the pps threshold determinations. Current intensities in the testing sessions ranged from 40 to 80 μA.

RESULTS

Picrotoxin lowered pps thresholds for LH-SIF as compared to vehicle controls in a dose related manner. These results are seen in Fig. 1. The 1.0 and 1.5 mg/kg doses significantly lowered LH-SIF thresholds (matched pairs t-test, $t(4)=7.55$, $t(4)=9.00$ respectively, $p<0.005$), while the 0.5 mg/kg dose produced little or no effect (matched pairs t-test, $t(4)=1.41$, N.S.). This effect was consistent across animals; high and moderate doses of picrotoxin decreased feeding thresholds in every animal when compared to the vehicle control run just prior to each drug test. Latencies to begin eating following the onset of stimulation were also reduced at the moderate and high doses and animals tended to eat for longer periods of time. During drug testing, particularly at the high dose, animals would sometimes continue eating following the offset of stimulation, even though satiation was complete prior to testing. Poststimulation feeding never occurred during baseline or vehicle tests or at the 0.5 mg/kg dose.

No effects on LH-SIF thresholds were seen following syrychnine administration (matched pairs t-test, $t(4)=0.65$, N.S.) at a dose high enough to cause facilitation of other behaviors [30]. Therefore, the facilitation of LH-SIF by picrotoxin could not be attributed to its convulsant properties. Neither drug caused any long term alterations in feeding thresholds, as animals showed no significant changes in control thresholds over time.

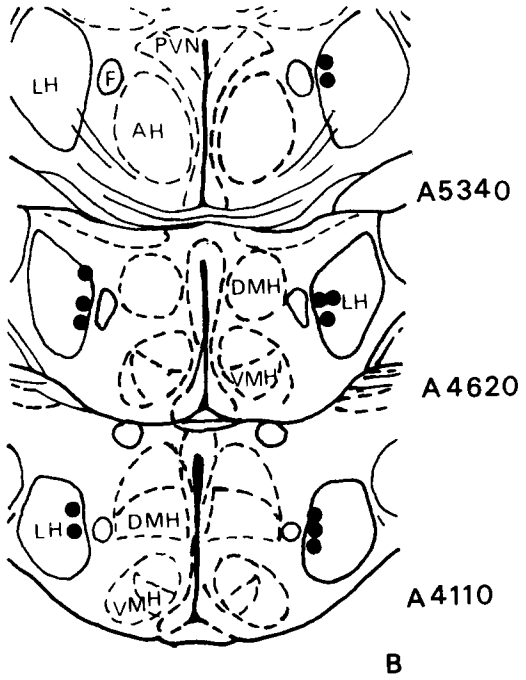

FIG. 2. Locations of electrode tips of animals, A. in Experiment 1, B. in Experiment 2, shown in schematic representations of coronal sections of rat hypothalamus after König and Klippel [19]. Abbreviations: AH, anterior hypothalamus; DMS, dorsomedial hypothalamus; F, fornix; LH, lateral hypothalamus; PVN, paraventricular nucleus; VMH, ventromedial nucleus of the hypothalamus.

Histological examination revealed that the electrodes were similarly located in the lateral hypothalamus of all animals, as illustrated in Fig. 2A. The electrode tips were located anterior-posteriorally at the level of the ventromedial nucleus, in the medial forebrain bundle just medial to the internal capsule.

DISCUSSION

Systemic administration of the GABA antagonist, picrotoxin, was shown to lower thresholds for electrically elicited feeding in the LH in a dose-related manner. This facilitation was not attributable to a drug-induced, generalized decrease in central inhibition or to the convulsant properties of picrotoxin, since administration of strychnine, an antagonist of the inhibitory transmitter glycine and also a convulsant drug, did not have any effect on thresholds for LH-SIF. Therefore, these data strongly suggest that the facilitation observed following picrotoxin administration is due to an interaction of this drug and GABA-mediated neurons rather than to some non-specific stimulation of the CNS. GABA, then, it can be concluded, has a role in the control of the integrated behavior patterns which are elicited by electrical stimulation of the LH.

Since there is evidence to suggest these behaviors are linked to ascending dopamine pathways [27, 28, 29] that course through this region [22], one possible explanation of the facilitation found here is the suppression of GABA-mediated inhibitory feedback mechanisms which regulate dopaminergic activity in these pathways. This results in increased turnover in dopamine neurons [2,21] which could account for the reduced number of pps required to elicit feeding from the LH. Electrical stimulation of a system which is already active because of reduced feedback inhibition should further increase dopaminergic activity and lead to a greater probability of the release of a complex behavior pattern such as feeding.

However, because of the ubiquitousness of GABA as an inhibitory transmitter, interference with inhibitory inputs from other GABA neurons other than those involved in dopaminergic regulation may be responsible for the release of LH-SIF. In particular, a local hypothalamic effect is possible, since high concentrations of GABA have been found in the LH [18,33] and Porrino (in preparation) has found that microinjections of picrotoxin directly into this region elicit feeding in satiated animals while systemic injections (1.0 or 1.5 mg/kg doses) do not.

EXPERIMENT 2

Because LH-SIF and LH-SS are known to covary under most circumstances [12, 13, 14], and because in the previous experiment it was found that picrotoxin facilitated LH-SIF, it was hypothesized that LH-SS would also be facilitated by picrotoxin. Pilot data, however, in which the rate of LH-SS was measured in a free-responding situation, did not confirm this hypothesis. Rates of lever pressing for 0.5 sec trains of 50 pps electrical stimulation at current intensities which supported moderate rates of LH-SS (30 presses/min) were significantly reduced by doses of picrotoxin equivalent to those used in the first experiment. This is in agreement with the findings of Kent and Fedinets [16] who also found a reduction in the rate of LH-SS in a free responding situation. These authors attributed this decrease to a reduction in the reward value of LH-SS and not to a performance deficit since lever pressing for escape from footshock was unaffected by picrotoxin administration. However, since strychnine which does not affect GABAergic mechanisms also depressed lever pressing for LH reward, it was felt that a performance deficit resulting from an interaction of electrical brain stimulation and drug administration could not be ruled out. In order to reduce the possibilities of this sort of confounding interaction, thresholds for LH-SS which involved constant minimal levels of electrical stimulation were measured [4].

METHOD

A total of eight male Sprague-Dawley rats, prepared and maintained as in the first experiment were the subjects for this experiment. Three of these animals had been subjects in the first experiment. Self-stimulation testing was conducted with the same stimulation apparatus and testing chamber as described in Experiment 1. A retractable lever, which when depressed by the rat activated the stimulation unit thereby delivering a train of electrical pulses to the animal, was added to the chamber.

Rats were screened for self-stimulation and those which displayed consistent lever-pressing rates for one-sec trains of brain stimulation at a rate of 40 pps at current intensities below 100 μA were included in the study. Rats were trained in a frequency threshold procedure for self-stimulation essentially the same as that outlined previously for feeding. A prime, two seconds of continuous stimulation presented prior to the beginning of each trial, was added to signal the start of a trial and to inform the animal of the kind of stimulation which would be received if the lever was depressed

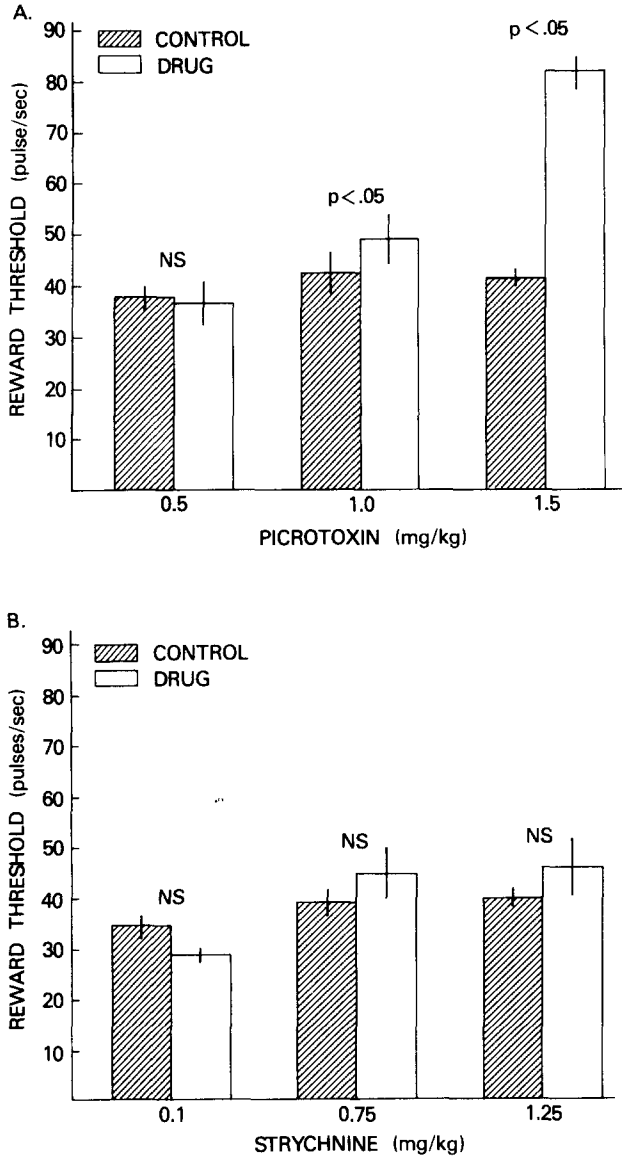

FIG. 3. Effects of A. picrotoxin and B. strychnine on frequency thresholds for self-stimulation. Drug tests are compared to vehicle controls run just prior to test. Error bars represent SEM.

during the trial. A successful trial was one in which ten or more one-sec reinforcements were obtained and the threshold was defined as the average of 15 30-sec trials each separated by a 60-sec intertrial interval. Each animal was tested at a constant current intensity which ranged from 75–110 μA.

Following the stabilization of frequency thresholds, animals were tested in the following conditions: Picrotoxin (0.5, 1.0 and 1.5 mg/kg), strychnine (0.1, 0.75 and 1.25 mg/kg) and saline vehicle. Drugs were prepared and administered as in the first experiment. All animals were not tested in all conditions, although each animal received at least one dose of each drug and corresponding vehicle tests.

RESULTS

A dose-dependent increase in thresholds for LH-SS was evident in all animals following picrotoxin administration. The data from this experiment are depicted in Figs. 3A and 3B. Using a matched pairs t test, there were no detectable effects at the 0.5 mg/kg dose ($t(3)=0.25$, N.S.), a moderate but significant increase at the 1.0 mg/kg dose ($t(4)=3.68$, $p<0.05$), and a large and significant increase in threshold levels at the 1.5 mg/kg dose ($t(3)=3.73$, $p<0.05$). At the highest dose, on several occasions animals would not respond at all to any frequency of stimulation, making accurate threshold determinations impossible. A maximum score of 100 pps was arbitrarily assigned in these instances. Although all animals showed rises in threshold levels, there was some variation in the strength of the response. Some animals uniformly showed larger increases than others.

Again using a matched-pairs t-test, no consistent nor significant effects on LH-SS thresholds were found at any of the strychnine doses tested (0.1 mg/kg $t(2)=2.25$, N.S.; 0.75 mg/kg $t(3)=1.75$, N.S.; 1.25 mg/kg $t(4)=1.19$, N.S.). There was some trend toward suppression at the two higher doses and some hint of facilitation at the lower dose. Because the strychnine effects were non-evident at doses which produced clear behavioral effects in other paradigms [30], the quite evident increases in thresholds seen with picrotoxin cannot be readily ascribed to disruptive non-specific CNS excitatory over-stimulation which could conceivably arise from some generalized blockade of inhibition. If such a generalized blockade explained the results obtained using picrotoxin, observable changes in behavior should have also been obtained using strychnine at the dose at which it was administered.

Animals were observed carefully during the testing sessions for any abnormal behaviors. In the picrotoxin conditions, behaviors such as grooming, licking, chewing, and sniffing were seen more frequently and were more intense than in control sessions. Mild behavioral convulsions occurred occasionally at the highest dose, but only during electrical stimulation. If the animals were treated but not stimulated, it was not possible to distinguish them from controls. Animals were sometimes easily distracted and not attentive to the start of trials in the strychnine conditions, but did not have any other overt behavioral or motor side effects which might have interfered with responding.

Histological examination revealed that all electrodes were located in the lateral hypothalamus as shown in Fig. 2B, in an area extending anteriorly from the level of the paraventricular nucleus, posteriorly to the level of the posterior hypothalamus.

DISCUSSION

Thresholds for LH-SS were increased in a dose-related manner following the administration of the GABA antagonist, picrotoxin. This is in direct contrast to the facilitation of LH-SIF found in the first experiment, suggesting a dissociation between LH-SS and LH-SIF which are usually thought to covery positively. These findings are consistent with previous work which has shown decreases in LH-SS responding following picrotoxin injections by a systemic route [16]. The conclusion that blockade of GABA-mediated synapses suppresses SS in the LH has been strengthened here by this experiment's use of thresholds as an alternate response measure and the addition of drug controls for possible generalized side effects of picrotoxin. Since strychnine, administered in a broad range of doses as such a control, had no real effect on LH-SS thresholds, it is difficult to attribute the picrotoxin-induced increases in thresholds to

a simple performance deficit resulting from overall stimulation of the CNS. For assessing the effects of inhibitory blocking agents on SS, frequency thresholds may be a better measure than rate of lever pressing, since performance deficits seem less likely to occur in this paradigm.

The increases in LH-SS thresholds were surprising for two reasons. First, it was expected that the effects of picrotoxin on LH-SS would be similar to the effects on LH-SIF, since manipulations which change the strength with which feeding can be elicited electrically generally produce parallel changes in the strength with which self-stimulation can be elicited. Second, it was expected that the increased turnover of dopamine [2,21] which occurs with picrotoxin administration, would result in facilitation of reward. Since the opposite effects were observed, this means GABA-mediated inhibitory mechanisms other than those involved in dopamine regulation are more likely to be responsible for the threshold increases. However, other possibilities for the apparent dissociation must also be considered. Self-stimulation behaviors may have been interfered with by the release from inhibition of stereotyped motor patterns such as grooming, chewing and licking which were seen frequently during the drug test sessions. Or perhaps, as the data from the first experiment suggest, picrotoxin in conjunction with electrical stimulation of the LH releases vigorous respondent consummatory behavior, the presence of which may be incompatible with the initiation or expression of operant self-stimulation behaviors. Hence the increases in thresholds may have resulted not from a loss in the rewarding character of the stimulation, but rather from the elicitation of behaviors which made it impossible for animals to engage in the complex lever-pressing response. If that be the case, GABA-mediated inhibition may have no direct effect on LS-SS behavior at all. Whatever the explanation, the effects of picrotoxin on LH-SS are clearly different from those on LH-SIF.

Animals were not homogeneous in the strength of their increases in thresholds following picrotoxin. Those animals which showed the largest increases in thresholds had electrode placements in the posterior portion of the LH at the level of the posterior ventromedial nucleus. The electrode placements of those animals which showed the smallest increases were in the anterior LH at the level of the paraventricular nucleus (see Fig. 2B). This anatomical specificity of response is interesting in light of electrophysiological studies by Ito [15], who found different inhibitory characteristics of cells in the anterior and posterior LH. Specifically, the number of cells exhibiting suppression of their spontaneous firing rates upon stimulation of the posterior hypothalamus decreased as one moved rostrad in the lateral hypothalamus.

GENERAL DISCUSSION

The results of the present experiments clearly demonstrate differential effects of GABA receptor blockage on electrically elicited feeding and self-stimulation in the LH of the rat. Picrotoxin administration led to decreases in thresholds for LH-SIF and increases in the thresholds for LH-SS. These effects were not attributable to some general consequences of blocking inhibition within the CNS, inasmuch as strychnine, another inhibitory blocking agent, had little effect in either paradigm. Some of the animals from which these inverse results were obtained participated in both the feeding and the self-stimulation experiments, thus ruling out the possibility that different placements in different animals were responsible for these differential effects.

These results are important for two reasons. First they demonstrate the involvement of GABAergic mechanisms in the modulation of electrically-elicited consummatory behaviors. This does not prove but is consistent with a current idea that the dopaminergic nigrostriatal pathway, the activity of which is regulated by GABA-mediated inhibition, is the neural substrate of LH-SIF.

If LH-SIF is looked upon as a reflection of a natural motivational process [3,34], the further implication of these data is that GABA-mediated inhibition is not only involved in the modulation of consummatory behaviors in the broad sense but also has a specific function in the regulation of elective food intake. For example, it has been proposed [26] that lateral hypothalamic mechanisms subserving feeding are more or less chronically active but are prevented from constant access to behavioral expression by inhibitory mechanisms arising from a variety of sources such as oropharyngeal monitoring of food intake, the learned patterning of meal times, and even perhaps from competing goal systems. In the present experiment the lowered LH-SIF thresholds may well represent a release of this chronically active feeding system from one or more of such inhibitory mechanisms by the GABA-antagonist, picrotoxin.

LH-SIF threshold remained unchanged following the glycine-antagonist, strychnine. This suggests that glycine-mediated mechanisms of inhibition do not play an important role in the modulation of feeding, at least at hypothalamic levels.

Second, these data are further evidence that LH-SS and LH-SIF are not dependent on the same neural substrate. Since the experimental manipulations of most prior studies have tended to affect both behaviors similarly, it has been thought that the activation of the same system was responsible for both [13,14]. But recent evidence on differential rates of functional recovery of the two behaviors following 6-hydroxydopamine injections [27,28], as well as the pharmacological dissociation of LH-SS and LH-SIF observed with amphetamine administration [3,23] have disputed this view. In addition, it has been possible to isolate regions of the hypothalamus in which consummatory behaviors can be elicited electrically without self-stimulation and in which self-stimulation can be elicited without drive behaviors [25]. The dissociation observed here following picrotoxin administration adds to these findings and confirms the view that LH-SS and LH-SIF are subserved by neural substrates that are at least somewhat independent.

The exact mode by which picrotoxin lowered the LH-SIF threshold while raising the LH-SS threshold remains to be determined experimentally. However, the following hypotheses should be tested. First, it may be that, as previously suggested, because of response competition for the final common path, the picrotoxin-produced disinhibition of food seeking automatically results in a lessened probability (i.e. higher threshold) that the act of bar pressing for self-stimulation can express itself. This possibility necessitates no direct role of GABA in the synaptic modulation of self-stimulation. According to a second hypothesis, GABA is indeed directly involved in modulating self-stimulation as well as in modulating feeding. As already mentioned, a difficulty with entertaining this hypothesis a priori arises because its implications are in conflict with present notions regarding the excitatory role of dopamine in mediating self-stimulation and the evidence that GABA circuits play a negative-

feedback role. A prediction that follows from these notions is that picrotoxin should block the GABA-mediated negative feedback onto the dopamine system thereby lowering rather than producing, as we found, a rise in the self-stimulation threshold.

Finally, the difficulty which the present results pose for this second hypothesis may be explained away by supposing both hypotheses to be true, but the first to be more dominant in this test situation than the second. The rise of the LH-SS thresholds as a response-competition consequence of lowering the LH-SIF threshold may override the predicted direct action of GABA-receptor blockade in lowering the LH-SS threshold. Or, possibly, the role of the GABA mechanisms in the negative feedback circuitry of the dopamine pathways mediating self-stimulation is more complicated than currently supposed. Regardless of what hypothesis future experimentation favors, it is clear here from the dissociation observed between LH-SS and LH-SIF thresholds following picrotoxin administration that there are probably different inhibitory mechanisms which influence each behavior.

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