Rats Self-Administer Nonrewarding Brain Stimulation to Ameliorate Aversion

Abstract. *Hypothalamic stimulation in rats both reduces escape from noxious hindbrain stimulation and sustains self-administration only when hindbrain stimulation is inescapable. Self-administration reflects an aversion-ameliorative action of brain stimulation and not a positive reinforcement process. The psychophysical testing used is offered as a model for establishing the analgesic properties of brain stimulation.*

Electrical brain stimulation is a useful starting point in identifying neural systems that mediate analgesia. Several brainstem loci, when electrically stimulated, reliably suppress reactions to somatic pain (*1, 2*). Stimulation-produced suppression of pain responses is not necessarily indicative of pain amelioration and is not, therefore, a sufficient criterion for demonstrating analgesic action. Brain stimulation may suppress responses without ameliorating pain. For example, brain stimulation might disorganize neural transmission of the command signals upon which execution of the response to pain depends. Or, stimulation could activate other goal motives, such as the search for food, which wrest control of the final common path from the behavioral expression of pain. However, to the degree that the suppressive actions of brain stimulation on pain arise from such effects instead of pain amelioration, we would not expect the organism to administer the brain stimulation to itself. Thus a crucial behavioral criterion for establishing brain stimulation as ameliorative is what we will call self-administration; it should occur only when pain is present. We know of only one report of a single rat which, when in pain, would press a lever to obtain the same midbrain stimulation which, when delivered by the experimenter, had suppressed pain responses (*2*).

We have used the behavioral criterion of self-administration to evaluate a possible role of the lateral hypothalamus (LH) in supraspinally ameliorating the perception of pain. Stimulation of the medial forebrain bundle (MFB) of the LH has been reported to inhibit instrumentally conditioned escape and certain unlearned responses to somatic pain stimuli (*3*), but the relation between these effects and the well-documented rewarding (*4*) and motivating (*5*) properties of LH stimulation is not clear. The question of whether the apparent pain-reducing effects are due to a specific ameliorative action of LH stimulation, to masking of pain by reward, or to competitive behavioral or motor effects of stimulation which interfere with aversive responses has not been resolved. Because LH stimulation does not alter spinal pain reflexes, as does midbrain periaqueductal stimulation, it has been proposed that if the LH does ameliorate pain perception it must do so through the operation of a supraspinal mechanism (*6*). In our study, escape from stimulation of a supraspinal pain-implicated structure—the nucleus reticularis gigantocellularis (NGC) (*7*)—was suppressed by concurrent electrical LH stimulation. Applying the behavioral criterion described above, we demonstrated that, during inescapable NGC stimulation, rats would self-administer trains of LH stimulation set at the same current that had earlier suppressed escape. The currents to the LH were too low to support self-administration in the absence of NGC stimulation. However, by raising the current to the LH we were able to establish self-administration for classical reward in the absence of aversive stimulation and compare it with self-administration of lower currents during aversive stimulation. We report that aversion-ameliorative effects of LH stimulation do not depend on the process that mediates classical self-stimulation reward.

Monopolar stimulating electrodes were implanted in the MFB of the LH and the ipsilateral NGC of six male Sprague-Dawley rats (400 to 450 g) (*8*). The rats were first trained to press a lever to escape for 3 seconds from trains (25 pulses per second) of 0.1-msec square wave pulses delivered to the NGC. After several days of escape trials, a current to the NGC was assigned to each rat which supported a mean rate of 12 3-second escapes per minute. A series of 1-minute escape trials was then run in which the LH was stimulated as well as the NGC. Pulses to the LH were delivered at the same basic frequency as pulses to the NGC and were timed so that during periods between escapes each pulse to the NGC was preceded by a pulse to the LH at an interval of 10 msec. (During escape periods LH stimulation was continued.) Data for the 10-msec LH-NGC interpulse interval are reported because in a pulse-pair analysis we have shown that this interval produces maximal interactive effects between the LH and the NGC (*9*). In four rats with LH electrodes in verified self-stimulation reward sites we determined a current to the LH which, when delivered concurrent with NGC stimulation, reduced the rate of escape. Two other rats with hypothalamic electrodes medial and dorsal to the MFB, which did not support self-stimulation, did not show this effect. In the four with electrodes in reward sites, a current to the LH was determined that reduced the rate of escape to about 50 percent of the rate in controls. The reliability of this escape reduction was confirmed in sessions of 1-minute escape trials conducted over the next 4 days in which trials of escape from pure NGC stimulation as well as from concurrent LH and NGC stimulation were randomly presented (Fig. 1A) ($P < .01$, $t(3) = 6.3$, matched-pair, two-tailed test). The finding that LH stimulation reduces escape from supraspinally elicited aversion extends the observations that LH stimulation reduces escape from somatic pain and adds further support to the proposal (*6*) that the LH ameliorates somatic pain through operation of a supraspinal mechanism.

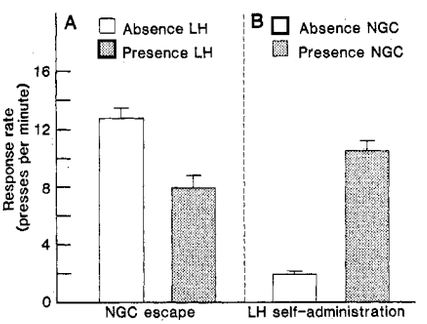

Fig. 1. (A) Mean rates (and standard errors) of lever-pressing for 3-second escapes from NGC stimulation in the absence and presence of continuous LH stimulation are shown for repeated measurements made on four rats. (B) Mean rates (and standard errors) of lever-pressing for 3-second trains of LH stimulation in the absence and presence of continuous NGC stimulation are shown for repeated measurements made on the same four rats as in (A). The self-administered currents to LH are those which reduced escape, and the currents to NGC are those which motivated escape.

We noted that the currents to the LH that reduced escape were lower than those which supported classical self-stimulation reward. Despite this, we reasoned that rats should press a lever to self-administer low currents to the LH in the presence of inescapable NGC stimulation if, in fact, the escape reduction was due to amelioration of aversion rather than competitive behavioral or motor effects of LH stimulation. We therefore used the same four rats in a test in which each 1-minute trial consisted of inescap-

0036-8075/82/0319-1516$01.00/0

able NGC stimulation, and pressing a lever produced a concurrent 3-second train of LH stimulation. The same frequency, phasing, and intensities of NGC and LH stimulation were used as in the preceding experiment. For five consecutive days a minimum of 14 trials were run per day. All rats pressed at high rates for the LH trains, and the rates did not decline over the course of a session or over days. For the next 4 days sessions of randomly ordered 1-minute trials were conducted in which rats either pressed for LH trains in the presence of inescapable NGC stimulation or were given the opportunity to press for these same LH trains in the absence of NGC stimulation. (The latter trials were conventional self-stimulation reward trials in format, although the amount of current was different, and they were initiated with up to three priming trains, as necessary, to bring a rat to the lever to make the first response.) In the absence of NGC stimulation the currents to the LH elicited negligible rates of self-stimulation although they reliably supported high rates of lever-pressing in the presence of NGC stimulation (Fig. 1B) ($P < .01$, $t(3) = 7.7$, matched-pair, two-tailed test). This finding—that escape-reducing currents to the LH are below the threshold for sustaining all but the lowest rates of classical reward but support higher rates of self-administration during NGC stimulation—suggests that subrewarding currents have an aversion-ameliorative property which accounts for reduction of escape and motivates lever-pressing when escape is not possible.

Since tail pinch can facilitate food intake (*10*), it is possible that in our study aversive NGC stimulation facilitated reward and thereby accounted for the self-administration of currents to the LH that were otherwise below the threshold for maintaining classical self-stimulation. In such a case the differential lever-pressing for current to the LH during NGC stimulation would not necessarily arise from an ameliorative action but be due to the reward to be obtained. In such a case, a manipulation such as gastric loading, which reduces classical self-stimulation reward (*11*), should also reduce the lever-pressing.

To discover whether the reinforcing property of low-intensity LH trains in the presence of NGC stimulation depends on the substrate that also mediates classical self-stimulation at higher currents, a third experiment was performed. Three rats from the preceding experiments plus two more were trained to press a lever for 3-second trains (25 pulses per second) under two conditions:

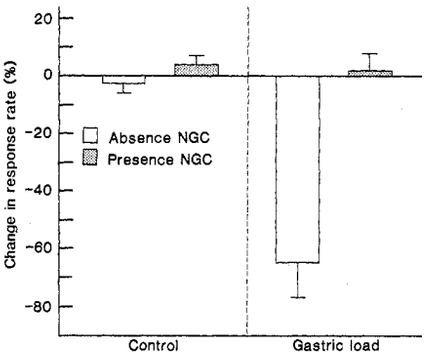

Fig. 2. Mean percentage of change (and standard errors) in rates of lever-pressing for 3-second trains of LH stimulation in the absence and presence of continuous NGC stimulation following treatment. Repeated measurements were made on five rats.

(i) to obtain low-intensity LH trains in the presence of NGC stimulation, and (ii) to obtain higher intensity LH trains in the absence of NGC stimulation—a conventional self-stimulation reward condition. Tests were conducted in blocks of randomly ordered 3-minute trials. Currents to the LH were set to elicit approximately equal rates of pressing in the two conditions. The first block was followed either by gastric loading with 10 cm^3 of sweetened condensed milk or a control procedure entailing insertion of the esophageal tube. A second, identically ordered block of trials then followed. Each rat received three gastric loading and three control treatments within a 2-week period.

The gastric load, as expected, reduced the rate of lever-pressing for classical self-stimulation reward in the absence of NGC stimulation ($P < .01$, $t(4) = 5.6$, matched-pair, two-tailed test). It did not, however, alter the rate of lever-pressing for low-intensity LH trains in the presence of NGC stimulation (Fig. 2). This dissociation is not explained by differential extinction characteristics of an aversively and appetitively motivated response because three rats, given extinction testing in the presence of NGC stimulation, reduced their rate of lever-pressing or ceased pressing the lever. Thus, self-administration of low-intensity LH trains in the presence of NGC stimulation apparently relies on a process that is not subject to modulation by gastrointestinal factors and is therefore dissociable from the classical self-stimulation reward process.

From the psychophysical testing described we have enabled the animal to behaviorally indicate that there is a lateral hypothalamic substrate for the supraspinal amelioration of aversion. The question as to the ameliorative substrate's significance and relation to other LH behavioral systems arises. A strong inferential case can be made, which we have done elsewhere (*9*), that the LH aversion-ameliorative mechanism is associated directly with an appetitive motivational system and only indirectly with the classical reward system by virtue of its association with the motivational system. Perhaps the association between the LH aversion-ameliorative mechanism and the appetitive motivational system is concerned with the adjudication of priority between goal motives of conflicting behavioral polarity.

KENNETH D. CARR*
EDGAR E. COONS
Department of Psychology,
New York University,
New York 10003

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8. Electrodes were constructed of size 00 insect pins and insulated to within 0.5 mm of the tip. For LH implantation skull-flat coordinates were: 3.0 mm posterior to bregma, 1.6 mm lateral of midine, and 8.4 mm below skull surface. For NGC implantation, incisor bar was raised 5.0 mm above interaural plane and coordinates were: 11.6 mm posterior to bregma, 0.7 mm lateral of midline, and 9.1 mm below skull surface. An uninsulated jeweler's screw placed rostrally in the skull served as ground.
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12. This report is dedicated to Neal E. Miller in honor of his superb qualities as a scientific mentor to E.E.C. Supported by NIMH predoctoral fellowship F31 MH07302 to K.D.C. and NIH biomedical institutional award RR-07062 to E.E.C.
* Address reprint requests to K.D.C. at New York University Medical Center, Millhauser Laboratories, New York 10016.

20 October 1981