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Opiate-Receptor Blockade Reduces Voluntary Running but Not Self-Stimulation in Hamsters

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POTTER, C. D., K. T. BORER AND R. J. KATZ. *Opiate-receptor blockade reduces voluntary running but not self-stimulation in hamsters.* PHARMACOL BIOCHEM BEHAV **18**(2) 217–223, 1183.—Naltrexone HCl, a long-acting opiate receptor blocker was administered to female hamsters at two doses, 10 and 20 mg/kg, IP prior to 12 hr of nocturnal running or every 12 hr during access to hypothalamic self-stimulation to determine whether endogenous opiates played a role in either of these two motivated behaviors. Naltrexone suppressed total running activity and speed, and caused an increase in pause time but did not affect the rate of hypothalamic self-stimulation. Furthermore, weight gain was unaffected by four weeks of self-stimulation but was accelerated during two weeks of voluntary running. Thus stimulation of endogenous opiate receptors helps support high levels of voluntary running but is not involved in initiation of running or in maintenance of intracranial self-stimulation in female hamsters. Furthermore, the association of opiate receptor stimulation and increased somatic growth with voluntary running but not with self-stimulation suggests a possible facilitatory role for endogenous opiates in acceleration of growth by exercise.

Opiate receptors Hamsters Running Self-stimulation Naltrexone

PHYSICAL activity is accompanied by the release of endogenous opiates into the blood stream [2, 10, 12, 14, 16, 39] and within the brain [39]. The significance of these changes is not fully understood, but at least four roles for exercise-induced opiate release have been hypothesized. First, exercise is interpreted by many to be a non-specific stressor. Opiate release during physical activity may reduce discomfort in a manner similar to that seen in other situations evoking stress-induced analgesia [11, 25, 41]. Secondly, opiates may be involved in the activation of physical activity. Low intraventricular doses of opioid peptides enhanced grooming in rats [18] while central injections of enkephalin analogues increased exploratory behavior [24] and motor activity [23] in mice. Conversely, administration of an opiate antagonist lowered open-field activity in rats [38]. Thirdly, endogenous opiates may be acting as reward transmitters for the reinforcing aspects of physical activity. Reports of trance-like states in long distance runners [31], and intrinsic rewards of running, such as "sheer joy" [28] suggest that physical activity may have opiate-like reinforcing properties [1,33]. Finally, endogenous opiates may be involved in some of the neuroendocrine phenomena associated with prolonged physical activity. For example, enhanced opiate release in women participating in an exercise program [10] may be related to the delayed onset of puberty [17, 26, 40] and amenorrhea [13, 15, 27] seen in some women athletes. The pattern of circulating gonadotropin release is altered during the follicular phase of the menstrual cycle in some women athletes [3]: opiates are also known to suppress gonadotropin release [9,34]. In addition, physical activity facilitates growth hormone (GH) release in animals [6] and in man [35], while opiates are also known to facilitate GH and prolactin (PRL) release [9, 32, 37].

To extend our understanding of the biological roles of endogenous opiates in prolonged submaximal physical activity, we examined the effect of naltrexone, a long-acting opiate receptor blocking agent, on spontaneous running in golden hamsters. Spontaneous running in these animals has characteristics analogous to those of long-distance running in man. Running bouts are initiated voluntarily by hamsters and separated by brief pauses. Young adult hamsters run between 11 and 16 kilometers a night [4]. The number of running bouts initiated each night with and without the administration of the opiate antagonist shed light on the role of en-

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dogenous opiates in initiating activity. On the other hand, analysis of the amount of running activity and the duration and speed of running bouts allows us to investigate the role of endogenous opiates in response maintenance through effects on the reinforcing properties of running [4,5]. Finally, we compared the effects of opiate receptor blockade on spontaneous running and hypothalamic self-stimulation in the same hamsters to control against a possible general behavioral sedation by the drug and to determine whether opiate involvement is common to these two types of incentive behavior. In the last experiment, we compared changes in ponderal growth during two weeks of running and four weeks of intracranial self-stimulation to see whether facilitation of somatic growth and endogenous opiate release were common to both of these motivated behaviors.

METHOD

Animals and Maintenance

Female golden hamsters (*Mesocricetus auratus*, Waterhouse) were obtained from Engle Laboratory Animals, Farmersburg, IN, at body weights of about 100 g and age of about 10 weeks. Animals were maintained with Purina Formulab Chow 5008 and water ad lib in rooms with controlled temperature (20–22°C) and light (12L:12D).

Drug Administration

All hamsters received IP injections of isotonic saline or one of two doses of naltrexone HCl (Endo Laboratories, Wilmington, DE) in random order once a day, approximately 20 minutes before the onset of darkness (Experiment 2) or twice a day, before the onset of darkness and before the onset of light (Experiment 1). Naltrexone doses of 10 and 20 mg/kg/12 hr were previously shown to maintain a physiologically effective chronic blockade of opiate receptors in rodents [21, 29, 36].

Electrode Implantation

Ten adult female hamsters anesthetized with sodium pentobarbital (75 mg/kg, IP) had stainless steel stimulation electrodes implanted in lateral hypothalamic sites found previously to support intracranial self-stimulation [8]. A Kopf stereotaxic instrument held the skull horizontal between bregma and lambda. The electrodes were insulated with Epoxylite except for 0.5 mm at the tip. A 1 cm-long copper brush at the distal end of the electrode was permanently mounted on the skull with two screws and further secured with dental cement [21].

Experiment 1: Effects of Opiate Blockade on Self-Stimulation and Effect of Self-Stimulation on Weight Gain in Hamsters

The hamsters were housed in suspended wire cages with metal ceilings. The floor served as the stimulation ground. When the metal brush on the animal's head came in contact with the ceiling, closure of the circuit allowed delivery of electrical stimulation through the head-mounted brushing. Stimulation consisted of a 0.3 second train of 60 Hz sinusoidal current between 25 and 50 μA in intensity as measured on an oscilloscope. Determination of the current intensity that would sustain self-stimulation behavior occurred during the first 21 days of exposure to the cages. An initial current of 50 μA was selected based on previous findings [22]. The current intensity was increased or decreased until the rate of response was stable. After this initial period the hamsters were given four weeks of continuous exposure to self-stimulation. Body weights were recorded daily. During these four weeks, one of the two doses of naltrexone or saline was given to each animal in a randomized order for four consecutive days (Monday–Thursday). Self-stimulation rates were recorded on these days. In addition, self-stimulation rates over a four day no-drug period were also recorded for each animal.

Experiment 2: Effects of Opiate Blockade on Amount and Pattern of Voluntary Running in Hamsters

Five of the animals used in Experiment 1 were given two weeks of orientation to cages containing freely turning horizontal running discs [4]. Wheel turns were recorded on electromechanical counters and on Harvard cumulative event recorders. The running patterns were determined in the following manner. Paper speed was 5 mm/min. A disc turn induced a 0.25-mm sideway pen excursion. Running bouts were defined as episodes of activity consisting of 20 disc revolutions or more, separated by pauses, defined as inactive periods of 150 seconds or longer. Running speed, in revolutions per minute (RPM), was calculated from the rate of sideway pen excursion within individual running bouts. Total activity, in revolutions per day (RPD), was the total number of revolutions during the 12 hour period of darkness.

After orientation, the hamsters had 2 weeks of continuous exposure to the running discs. During this time weight changes and running pattern were recorded as a function of saline injection (1 ml/kg, IP), and injection of 10 mg/kg naltrexone, and 20 mg/kg naltrexone, IP. At least 24 hours were allowed to elapse between drug or saline injections. Each condition was tested twice and mean values were used in data analysis.

Statistical Analysis of the Data

In both experiments the rate of ponderal growth was inferred from a least-squares linear regression analysis of weight changes during the experimental condition. Analysis of covariance and a test for unequal regression coefficients was used to compare the growth rates during the two experiments.

In Experiment 1, self-stimulation rates on days of drug administration are expressed as a percentage of self-stimulation rates during the time prior to drug treatment. Hotelling's T Square Test was used on the raw data to compare drug trials and baseline self-stimulation rates.

In Experiment 2, analysis of variance and Scheffe's *post-hoc* test for multiple comparisons was used to determine the effect of drug treatment on running. Analyses of the effects of opiate blockade on running were done on the entire 12 hour dark period, and on the first 6 hours only, when the effectiveness of the antagonist drug was expected to be maximal.

Histology

Brains, from animals perfused with saline and 10% Formalin were fixed in 10% buffered Formalin for 2–4 days. They were sectioned at 80 μm in the coronal plane. Sections were stained with cresyl violet and were projected onto diagrams of a brain from a 100 g female hamster to determine the location of the electrode tip [7]. Diagrams were drawn in

TABLE 1

EFFECT OF NALTREXONE (10 mg/kg/12 HR) ON HYPOTHALAMIC SELF-STIMULATION

Animal	Pre-Treatment Self-Stimulation Rate (Responses/Day)	Self-Stimulation after 10 mg/kg/12 hr Naltrexone HCl (Percentage of Pre-Treatment Rate) Day 1	Day 2	Day 3	Day 4
1	11,010	65	110	54	119
2	2,760	90	105	132	120
3	4,500	123	150	242	25
4	17,400	87	141	40	90
5	1,710	104	90	54	87
	Mean ± S.E.M.	94 ± 9.6	119 ± 11.3	104 ± 38	88 ± 17

TABLE 2

EFFECT OF NALTREXONE (20 mg/kg/12 HR) ON HYPOTHALAMIC SELF-STIMULATION

Animal	Pre-Treatment Self-Stimulation Rate (Responses/Day)	Self-Stimulation after 20 mg/kg/12 hr Naltrexone HCl (Percentage of Pre-Treatment Rate) Day 1	Day 2	Day 3	Day 4
1	10,770	125	196	180	93
2	3,030	102	87	48	88
3	4,290	85	166	113	70
4	11,100	74	121	112	111
5	1,200	101	143	91	69
	Mean ± S.E.M.	97 ± 8.7	143 ± 18.7	109 ± 21.3	86 ± 7.8

India ink over histological features discernible in photographic prints of sections of this hamster brain in planes ranging between 2 mm anterior to 2 mm posterior to bregma.

RESULTS

Experiment 1: Effects of Opiate Blockade on Self-Stimulation and Effects of Self-Stimulation on Weight Gain in Hamsters

The rate of self-stimulation was unaffected by either dose of naltrexone (Tables 1 and 2) when the rate of response on the days of drug administration was compared to pre-treatment response rates. Four weeks of self-stimulation had no effect on the rate of weight gain in these animals (Fig. 1).

Experiment 2: Effects of Opiate Blockade on Amount and Pattern of Voluntary Running in Hamsters

The lower dose of naltrexone (10 mg/kg, HCl) had no effect on the amount or pattern of voluntary running. However, the higher dose (20 mg/kg, HCl) caused an overall inhibition of voluntary running in hamsters. During the first six hours of the dark period (Table 3), total running activity (disk revolutions) was significantly lower following this dose of naltrexone than under control conditions. In addition, run-

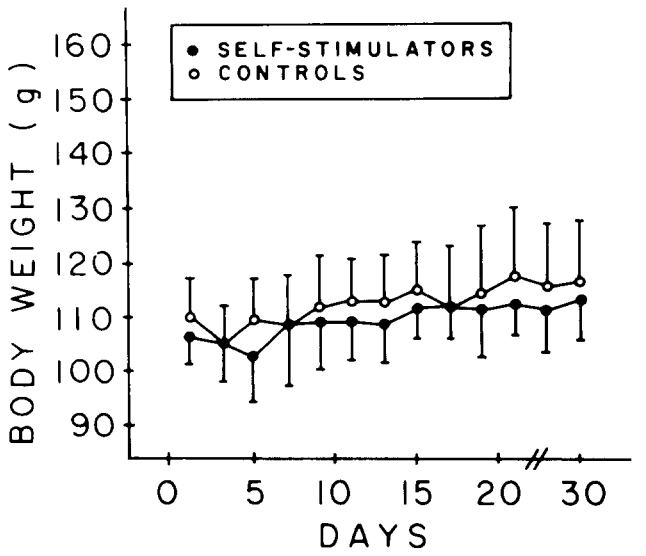

FIG. 1. Weight change of self-stimulating (n=5, solid circles) and control hamsters (n=5, open circles). The regressions of the weight change as a function of time are y=0.27x + 105.2 for self-stimulating hamsters and y=0.31x + 107.9 for the controls. Brackets denote standard errors of the mean.

TABLE 3

EFFECT OF NALTREXONE ON RUNNING PARAMETERS OVER THE FIRST 6 HOURS OF ACTIVITY PERIOD

	Condition 1 Control	Condition 2 Naltrexone 10 mg/kg	Condition 3 Naltrexone 20 mg/kg	Condition Comparisons F-Statistic* Condition 1, 2	Condition 1, 3
Total Activity (Revolutions per Day)	16,733 ± 881	13,178 ± 2,789	10,594 ± 711	2.86	8.45
Number of Running Bouts	7 ± 0.8	4.8 ± 0.7	9.0 ± 0.7	3.79	2.53
Duration of Individual Running Bouts (min)	45.6 ± 6.1	50.9 ± 9	26.4 ± 3.7	0.34	4.5
Total Pause Time (min)	33.8 ± 4.9	57.9 ± 21.5	95.0 ± 26.7	1.24	8.04
Duration of Individual Pauses (min)	5.6 ± 0.8	20.4 ± 11.8	11.3 ± 2.3	3.31	0.49
Speed (RPM)	50.6 ± 2.7	48.3 ± 4.6	42.9 ± 1.3	0.55	5.23

Mean ± S.E.M.

*F(1,8)=5.23, $p<0.05$.

TABLE 4

EFFECT OF NALTREXONE ON RUNNING PARAMETERS OVER A 12 HOUR ACTIVITY PERIOD

	Condition 1 Control	Condition 2 Naltrexone HCl 10 mg/kg	Condition 3 Naltrexone HCl 20 mg/kg	Condition Comparisons F-Statistic* Condition 1, 2	Condition 1, 3
Total Activity (Revolutions per Day)	23,578 ± 2,609	23,386 ± 2,728	15,982 ± 2,107	0.006	8.76
Number of Running Bouts	10 ± 0.88	8.8 ± 0.7	14 ± 1.6	0.4739	5.26
Duration of Individual Running Bouts (min)	40.7 ± 4.4	46.2 ± 2.4	25 ± 3.5	1.23	10.02
Total Pause Time (min)	142.3 ± 19.7	183.6 ± 36.6	279.1 ± 64.3	0.659	7.22
Duration of Individual Pauses (min)	17.4 ± 3.1	24.8 ± 5.2	23.8 ± 8.1	1.06	0.793
Speed (RPM)	52.7 ± 1.8	52.8 ± 2.7	43.6 ± 2.6	0.008	11.3

Mean ± S.E.M.

*F(1,8)=5.23, $p<0.05$.

ning speed was significantly slower and total pause time was significantly longer. When the entire 12 hour period of darkness is considered (Table 4), the significant effects of the higher dose of naltrexone were; reduction in total running activity (disk revolutions), a slower running speed, and a decrease in the duration of the individual running bouts. Also, total pause time was longer and more running bouts were initiated.

The rate of weight gain in the five hamsters was significantly higher during the two weeks of voluntary running (1.1±0.1 g/day) than during the four weeks of intracranial self-stimulation (0.4±0.1 g/day, Fig. 2).

Histological examination of electrode placement was available for all but 2 animals whose brains were inadequately preserved. Effective sites which sustained stable rates of intracranial self-stimulation were in the area of medial forebrain bundle (MFB) between the optic chiasms and the median eminence. Ineffective placements in control animals were generally anterior, dorsal or posterior to the MFB sites (Fig. 3).

DISCUSSION

Our experiments indicate that the endogenous opiates play a facilatory role in the maintenance of voluntary running in female hamsters.

Administration of naltrexone, a long-acting opiate receptor blocker, had an inhibitory influence on the total amount of voluntary running in hamsters. Suppression of running speed and the duration of individual running bouts resulted in fewer disk revolutions and longer pauses. The hamsters initiated more running bouts under the influence of the higher dose of naltrexone than under control conditions, but this increase in running bouts could not counteract the overall inhibitory influence of naltrexone on running.

Since, at the same dose, naltrexone had no effect on the amounts of intracranial self-stimulation, naltrexone did not appear to induce generalized behavioral inhibition or debilitation. The specificity of drug effects on voluntary running, and the nature of changes in the pattern of running behaviors makes us conclude that naltrexone has altered the incentive

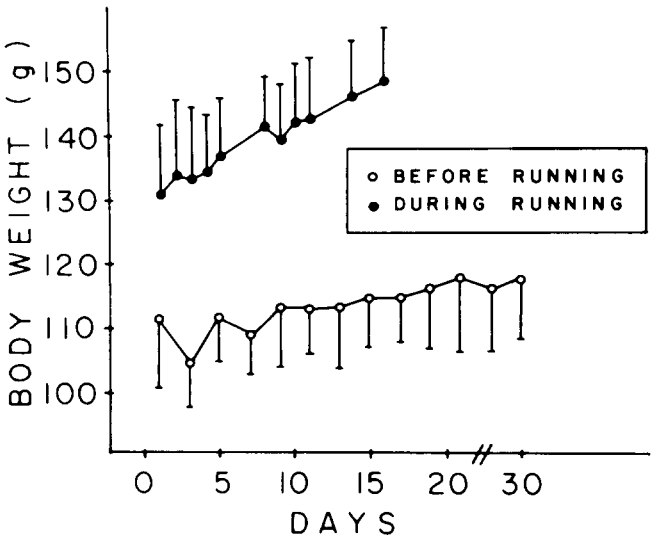

FIG. 2. Weight change of the five hamsters during four weeks of intracranial self-stimulation (bottom) and two weeks of voluntary running (top). The regressions of the weight change as a function of time are $y=0.35x + 108.6$ during the exposure to self-stimulation and $y=1.13x + 130.5$ during voluntary running. Brackets denote standard errors of the mean.

properties of voluntary running. We base this inference on the data from other experiments which suggest that total amount of voluntary running, speed of running, and duration of individual running bouts represent measures of the hamster's motivation to run [5]. For instance, loss of body fat energizes food seeking behavior and increases the motivation for intracranial self-stimulation [19] and voluntary running [5] in hamsters and other rodents as reflected by an increase in the rate and total frequency of these behaviors. Conversely, increases in body fat or body size by means of forced intragastric administration of food [20] or by a variety of endocrine [5] and neurosurgical manipulations ([19] and Potter, Borer and Fileccia, unpublished data, 1981) reduce the motivation for intracranial self-stimulation and voluntary running as demonstrated by a reduction in the rate and total incidence of such behaviors.

Our data are consistent with the hypothesis that the stimulation of endogenous opiate receptors participates in the mediation of motivated running behavior. In particular, release of endogenous opiates and consequent stimulation of opiate receptors by voluntary running in hamsters may maintain and prolong this behavior. Facilitation of the speed of running and maintenance of longer running bouts may occur through the enhancement of incentive properties of this behavior by opiate receptor stimulation.

The apparent independence of hamster's hypothalamic self-stimulation behavior from endogenous opiate influence stands in contrast to the apparent opiate facilitation of this behavior in the rat [29]. This discrepancy may be a function of species difference in the role of opiates in the maintenance of self-stimulation behavior. More likely, the apparent independence of hamster self-stimulation behavior is the function of electrode placement. Even in the rat, self-stimulation rate is ten times more sensitive to the opiate receptor blockade in

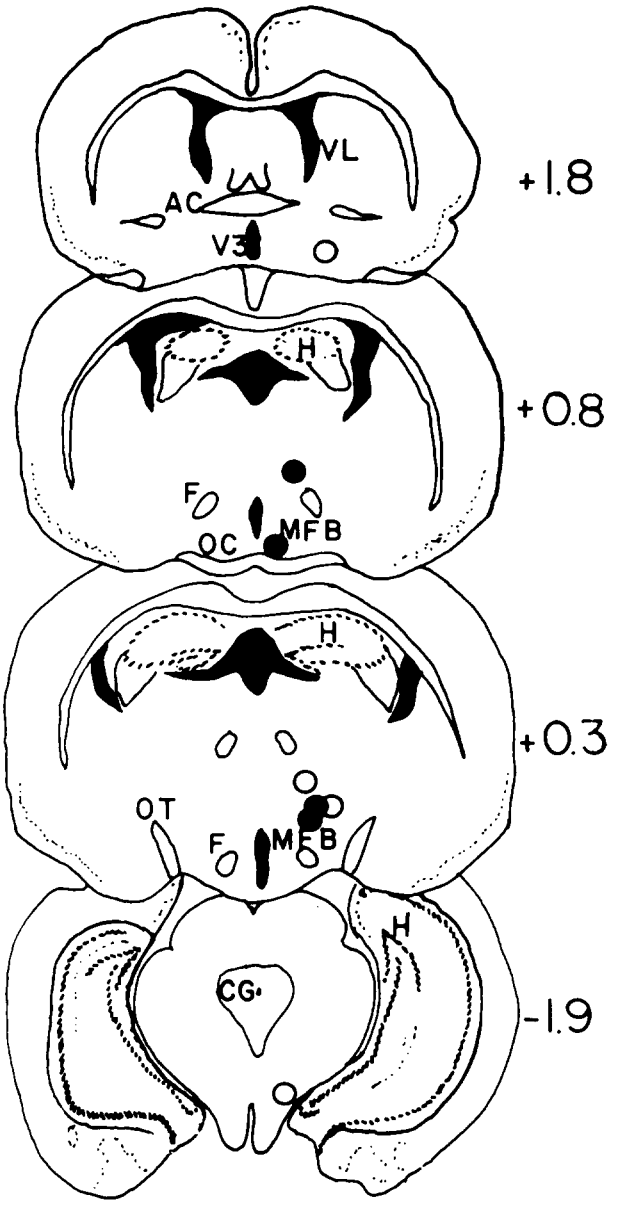

FIG. 3. Location of effective (solid circles) and ineffective (open circles) sites for tips of self-stimulation electrodes. Numbers, in mm, denote the distance of coronal planes anterior (+) or posterior (−) with respect to bregma in brains positioned horizontally between bregma and lambda. Abbreviations: AC, anterior commisure; CG, central gray; F, formix; H, hippocampus; MFB, medial forebrain bundle; OC, optic chiasm; OT, optic tract; VL, lateral ventricle; V3, third ventricle.

the central gray area than in the MFB [29]. Thus, specific opiate facilitation of voluntary running and lack of such an effect on intracranial self-stimulation in hamsters may be an artifact of the location of electrode placement rather than a true difference in the biological role of opiate receptor stimulation in these two incentive behaviors.

The association of voluntary running in hamsters with opiate receptor stimulation as well as with increased release

of growth hormone (GH) and acceleration of somatic growth [6] raises the question whether these two phenomena are causally related. Opiate receptor stimulation facilitates pituitary GH and prolactin release in rodents [9, 32, 37] and may contribute to exercise-induced facilitation of GH secretion and of somatic growth in hamsters. Facilitation of GH secretion and of somatic growth by voluntary exercise in hamsters but not in rats or guinea-pigs [4] may thus reflect differences in the magnitude of exercise-induced opiate receptor stimulation in the three rodent species.

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