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BRIEF COMMUNICATION

The Effects of Exercise on the Oral Consumption of Morphine and Methadone in Rats

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McLACHLAN, C. D., M. HAY AND G. J. COLEMAN. *The effects of exercise on the oral consumption of morphine and methadone in rats.* PHARMACOL BIOCHEM BEHAV **48**(2) 563–568, 1994.—Endogenous opioid peptides have been hypothesised to play a regulatory role in exogenous opiate agonist dependence. It was hypothesised that exercised rats would demonstrate increased β-endorphin (βEP) levels and decreased exogenous opiate intake. After providing morphine or methadone as their sole liquid, drug preference levels were determined by amounts of exogenous opiate consumed when rats were offered a choice between drugged and nondrugged solutions. Treatment animals were exercised in a treadmill and were found to consume significantly less exogenous opiate than control animals. Plasma, pituitary, and whole brain βEP levels were nonsignificantly higher in exercised animals. Differences were observed in the drug ingestion patterns of morphine- and methadone-exposed rats.

Morphine Methadone Sucrose Exercise β-Endorphin Oral ingestion

THE similarities in action and binding sites of endogenous and exogenous opiates (7) suggest a role for endogenous opioid peptides in the physiological mechanism regulating exogenous opiate agonist dependence. Indeed, theories postulating a role for endogenous opioids in the exogenous opiate dependence mechanism abound.

It has been suggested that dependence is mediated by a negative feedback mechanism whereby exogenous opiates inhibit the synthesis and release of endogenous opioids (19). Subsequently, when exogenous opiate administration is terminated, the endogenous inhibitors of acetylcholine and noradrenaline (endogenous opioid peptides) are depressed, resulting in the excitatory symptoms of withdrawal. The locus cerelus (LC) has been proposed as a site at which the excitatory symptoms of withdrawal are mediated (1). Other authors (8) have proposed that exogenous opiate use alters opiate-receptor properties so that normal amounts of endogenous opioids become unable to adequately activate them. This also results in elevations of the actions of acetylcholine and noradrenaline.

Alternatively, it has been suggested that antiopiate peptides including adrenocorticotropin (ACTH) (17), F-8-F-NH_2 (20), β-melanocyte-stimulating hormone, mullerian-inhibiting factor 1, thyroid-releasing hormone, somatostatin, calcitonin, and cholecystokinin (14) (which produce behavioural alterations directly contrasting endogenous opioids) are involved in the dependence mechanism (23). In organisms naive to exogenous opiates, the opiate and antiopiate systems are thought to be in balance, suggesting that each modulates the other. Upon exogenous opiate administration, antiopiate production increases and homeostasis of the organism is maintained (tolerance develops). Cessation of exogenous opiate administration results in an imbalance of endogenous opioids and antiopiates, resulting in withdrawal.

Both the negative feedback and antiopiate hypotheses suggest that increased endogenous opioid secretion and/or ac-

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tivity result in decreased amounts of physiologically required exogenous opiates. Indeed, electroacupuncture in humans increases βEP concentrations in the blood, cerebrospinal fluid (10), pituitary, and hypothalamus (2), and reduces cravings for morphine and alleviates withdrawal symptoms (27). Exercise may produce similar effects because, even though the phenomenon of "runners high" is generally regarded as too vague to be empirically established, some individuals experience endogenous opioid-mediated improvement in affect following vigorous exercise (28).

Increases in serum (11) and CNS endogenous opioid concentrations (5) have been observed after exercise. These increases have been associated with nonspecific factors associated with exercise, such as stress (6), as well as the specific effect of exercise (25). As such, it seems that exercise-induced endogenous opioid increases probably result from additive effects of stress and exercise. This may explain why the effect of exercise on endogenous opioid concentrations varies with exercise intensity (5): The more stressful the exercise, the greater the effect on endogenous opioid concentrations.

The administration of exogenous opiates in drinking water is a simple and economical method, large numbers of subjects can be tested concurrently, and it is effective in producing dependence on methadone (21) and morphine (12). Unlike intrusive delivery paradigms which induce catecholamine, glucocorticoid (3), and endogenous opioid release (9), oral administration does not induce reactions which may interact with treatment effects. Furthermore, it allows the observation of drug-seeking behaviour. Nevertheless, presumably because of the bitter taste of both drugs, experimental animals often refuse to consume sufficient morphine (12) and methadone (21) to become dependent. Mixing the two drugs in sucrose solution has been observed to overcome this problem (12,18).

Unpublished observations in our laboratory have shown a pronounced "binge/recovery" cycle in oral morphine intake. This pattern is characterised by large intakes over two to three days, followed by near abstinence for similar periods. Previous research has overcome this problem by restricting access to morphine (13). Since oral morphine intake is reportedly regulated by water rather than morphine requirement (3), highly concentrated exogenous opiate solutions would ensure increased exogenous opiate consumption, and a pronounced "binge/recovery" cycle. However, low concentrations may result in animals not consuming enough exogenous opiate to induce physiological dependence.

The main aim of this study is to explore the utility of behavioural treatment techniques in reducing morphine and methadone intake in rats. Specifically, the effect of treadmill exercise on exogenous opiate intake will be examined. Furthermore, the utility of the oral ingestion paradigm as a chronic exogenous opiate administration technique is investigated, and the effects of exercise on brain and peripheral βEP concentrations are investigated.

METHOD

Subjects

Forty-eight 84-day-old male Long Evans Hooded rats were used. They were individually housed in a sound-attenuated laboratory with ad lib access to food and maintained in a 12-h light-dark cycle at 20 ± 2°C.

Apparatus

Depending on the experimental stage and treatment group, three solutions were administered: sucrose solution—table sugar (12) dissolved in distilled water (10% by weight); morphine solution—0.5 mg/ml morphine hydrochloride powder dissolved in 10% sucrose solution (18); and methadone solution—0.5 mg/ml methadone hydrochloride powder dissolved in 10% sucrose solution.

A treadmill was constructed, consisting of a compartmentalised PVC fibre belt running on a 12.5° slope (15). A treadmill simulator was also used.

Procedure

To ensure that endogenous opioid concentrations were not affected by nonspecific stress, animals were acclimated to handling and treatment apparatus during pretreatment stages. Fluids consumed by each animal were measured and refilled at the end of the light cycle and at the beginning of the dark cycle for the duration of the experiment. In an attempt to smooth exogenous opiate intake across the day, 40 ml of morphine, methadone, or sucrose solution were provided to each animal every 12 h.

The study consisted of five experimental stages. The preexperiment stage (stage 1, 12 days) allowed the animals to adjust to the laboratory environment. The animals were given ad lib access to food and water. In the acquisition stage (stage 2, 28 days) the animals were provided with either morphine or methadone solutions as the sole source of fluid. Two drinking cylinders (one drug, one sucrose solution), their position alternated daily, were made available to the animals during the choice stage (stage 3, 14 days). After 8 days, two additional measurements of fluid intake were made (2 h after lights off and 2 h after lights on) because many morphine animals consumed all available morphine solution over each 12-h measuring period. This drinking behaviour resulted in a ceiling effect on 12-h consumption levels, and therefore less sensitive measurements of morphine preference levels. Thus, morphine preference was operationalised as amount consumed in the 2 h after replenishment. On the last day of stage 3, the 18 highest morphine and methadone drinkers were ranked by drug consumption and randomly assigned to exercise and nonexercise groups. The treatment stage (stage 4, 16 days) investigated the effect of exercise on drug intake. Since more solution was consumed at night, and therefore greater treatment effects on intake were expected during this time, animals were exercised just before lights off. Exercise intensity was determined by the ability of the animals to keep pace with the treadmill. Its duration and intensity ranged from 5 min at 10 m/min on day 1 to 60 min at 30 m/min on day 17.

Serum, whole brains, and pituitaries were assayed for βEP concentrations directly following the 16th and 17th episodes of exercise (at lights off). Procedures outlined by other authors were used (24).

RESULTS

For convenience, morphine and methadone intake are documented in volumes of solution, rather than weights of drug consumed. Figure 1 illustrates typical examples of the drug intakes of rats from each of the nonexercised groups. It indicates that morphine intake was initially variable, but soon became constant at the maximum amount available. Methadone intake remained variable throughout the experiment, with wide shifts in amounts consumed from day to day.

In stage 2, average morphine intake increased from 7.9 ml on day 1 to a maximum of 71.9 ml on day 27 (average increase of 2.21 ml/day; line of best fit, $r^2 = 0.94$); average methadone intake increased from 21.0 ml on day 1 to 62.1 ml on day

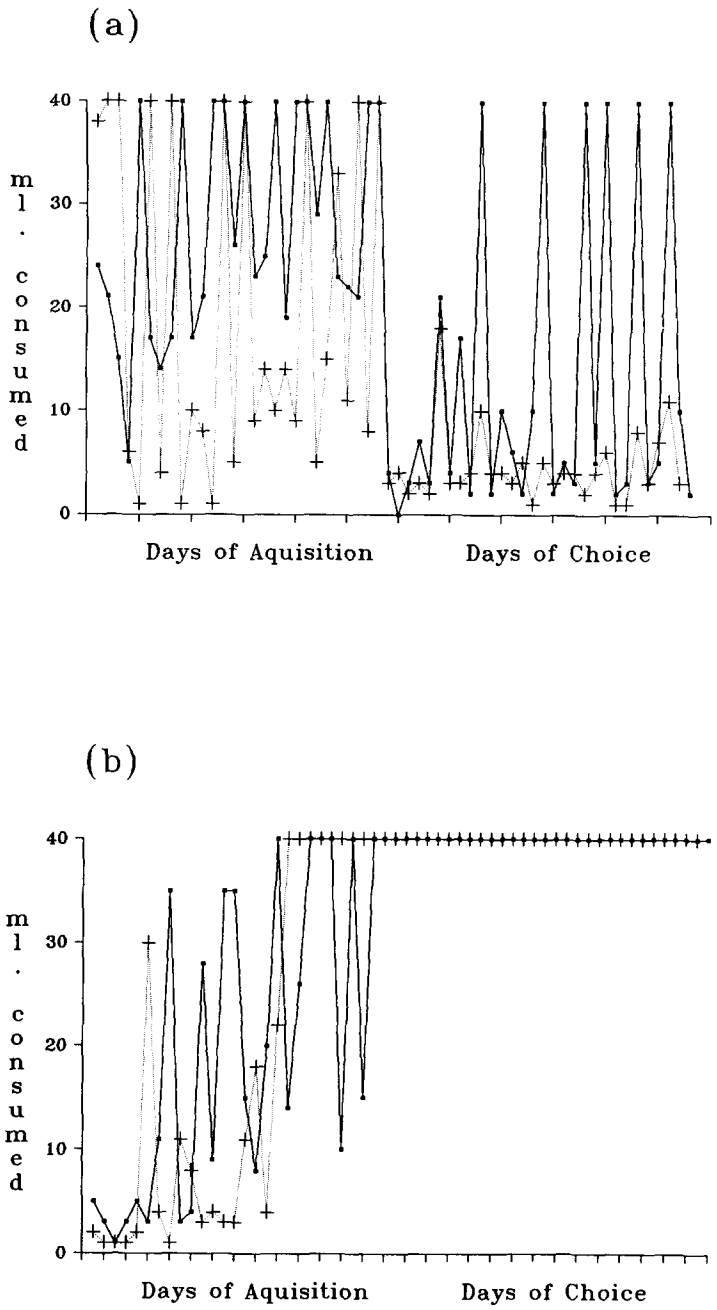

FIG. 1. Typical individual patterns of day and night (12 h) consumption of (a) methadone and (b) morphine by animals in the nonexercised groups (where ■ = night drinking, + = day drinking).

28 (average increase of 0.95 ml/day; line of best fit, r^2 = 0.59). Average intake of morphine and methadone dropped 9.4 ml and 54.6 ml, respectively, when a choice between drug and sucrose solutions was offered (day 1 of stage 3). Upon the provision of a water/sucrose choice, 83.3% and 100% of animals continued to consume morphine and methadone, respectively.

We have previously observed 100-day-old male Long Evans rats to have an average water consumption of 32.24 ml/day over three days. Respectively, maximum daily liquid intakes of the morphine and methadone animals were 123% and 93% higher than this baseline water intake in stage 2, and 319% and 219% higher in stage 3.

Consistently more morphine and methadone was consumed at night than during the day. Differences were small for morphine, the largest being 11.0 ml in stage 2 and 3.1 ml in stage 3. Differences were larger for methadone, the largest being 27.9 ml in stage 2 and 6.9 ml in stage 3.

The average weights of the morphine and methadone animals increased by 32.52 and 62.59 g, respectively, from the

beginning of the experiment to the end of stage 2. This difference in increase was significant, $t(34) = 3.89, p \leq .001$.

Fluid intakes were converted into four-day blocks. The first block represented the average amount of exogenous opiate consumed in the last four days of the choice stage, and the subsequent four blocks represented the average amounts of exogenous opiate consumed in the first, second, third, and fourth four-day blocks of the exercise period. The five blocks were constructed to smooth daily drinking variability, while still allowing the detection of changes in treatment effects over time. Intake was then expressed as a difference score based on the change in fluid consumption from choice baseline (see Table 1), and a four-way, two-repeated-measures analysis of variance (ANOVA) was used to investigate the effect of exercise on morphine and methadone consumption in the 2 h after the 0800 and 2000 replenishments. The independent factors were solution (morphine/methadone) and exercise treatment (exercise/no exercise), and the repeated factors were time of day (day/night) and blocks. A significant main effect for exercise versus no-exercise was observed, $F(1, 30) = 7.14$, $p = .01$, with the no-exercise groups showing a greater increase in intake than the exercise groups (Table 1). A significant main effect for blocks was also found, $F(3, 90) = 2.79$, $p = .05$, with a post hoc Newman-Keuls test indicating that blocks 2 and 4 showed a greater change from baseline than did blocks 1 and 3, which did not differ from baseline (Table 1). A significant interaction between drug and exercise group was found, $F(1, 30) = 6.42$, $p = .02$. This was a result of the morphine no-exercise rats increasing their intake more than the morphine-exercised rats, while no change for either methadone group was observed (Table 1). The interaction between blocks and day/night intake was significant, $F(3, 90) = 18.41$, $p < .01$. The results of a Newman-Keuls post hoc test indicated that night intakes were significantly higher than day intakes in blocks 1, 2, and 3, but that there were no significant difference in block 4 (Table 1). The Block × Group interaction approached significance, $F(3, 90) = 2.43$, $p = .07$, indicating that, compared to the exercise groups, drug intake of the control groups increased across blocks (Table 1). The Drug × Group × Block interaction also approached significance, $F(3, 90) = 2.37$, $p = .07$, reflecting a tendency for the no-exercise morphine group to increase fluid intake across blocks while the other three groups remained fairly stable (Table 1).

Because 2-h methadone intake was low, a three-way, two-repeated-measures ANOVA of 12-h methadone consumption was performed. No significant effects were observed.

Since both drug groups consistently consumed all sucrose solution over 12 h, the effect of exercise on 2-h sucrose consumption was analysed using a four-way, two-repeated-measures ANOVA. The significant drug effect, $F(1, 30) = 8.98$, $p = .02$, observed indicates that the 2-h sucrose consumption of the methadone groups decreased during exercise relative to that of the morphine groups (Table 1). The significant group effect, $F(1, 30) = 4.54$, $p = .04$, indicates that 2-h sucrose consumption decreased more in no-exercise than in exercise groups (Table 1). The significant Drug × Group

TABLE 1

AVERAGE DAY AND NIGHT EXOGENOUS OPIATE SOLUTION (and sucrose) INTAKES DURING TREATMENT IN THE 2 h FOLLOWING REPLENISHMENT

		Blocks*				Average Between Blocks	
Group		1	2	3	4	Day/Night	Total
Morphine control	Day	−0.70 (0.09)	1.47 (−1.03)	0.61 (0.03)	3.75 (0.97)	1.28 (0.02)	4.79 (0.32)
	Night	4.47 (1.78)	10.61 (−0.09)	8.03 (1.47)	10.08 (−0.72)	8.29 (0.61)	
Morphine exercise	Day	−2.90 (−1.94)	2.72 (−1.81)	−1.03 (−0.92)	2.16 (1.00)	0.24 (−0.92)	0.76 (0.02)
	Night	2.40 (−0.33)	3.72 (0.81)	0.50 (3.28)	−1.50 (0.06)	1.28 (0.96)	
Methadone control	Day	−0.72 (−3.69)	−0.67 (−5.47)	−0.44 (−5.53)	1.08 (−2.38)	−0.19 (−4.27)	0.20 (−3.94)
	Night	−0.14 (−2.56)	−0.19 (−4.78)	−0.06 (−1.63)	−0.44 (−5.57)	−0.21 (−3.61)	
Methadone exercise	Day	−0.75 (−2.00)	−0.75 (−0.19)	−1.09 (3.14)	1.16 (3.06)	−0.36 (1.00)	0.31 (−0.36)
	Night	−0.15 (−1.72)	0.04 (−0.53)	−0.50 (0.83)	−0.43 (−5.42)	−0.26 (−1.71)	
Average within blocks	Day	−1.27 (−1.89)	0.69 (−2.12)	−0.49 (−0.82)	2.04 (0.66)	0.24 (−1.04)	
	Night	1.65 (−0.71)	3.55 (−1.15)	1.99 (0.99)	1.92 (−2.89)	2.28 (−0.94)	
	Total	0.19 (−1.30)	2.12 (−1.64)	0.75 (0.09)	1.98 (−1.12)		

*Scores are expressed as differences from choice baseline intake.

interaction, $F(1, 30) = 6.32$, $p = .02$, demonstrates that 2-h sucrose intake of the morphine no-exercise and methadone exercise groups increased relative to the morphine exercise and methadone no-exercise groups. The significant day/night effect observed, $F(1, 30) = 5.75$, $p = .02$, indicates that the overall sucrose intake during exercise decreased more in the day than night. An a posteriori Newman-Keuls analysis showed that the significant block effect, $F(1, 90) = 2.97$, $p = .04$, was the result of the mean sucrose intake in block 3 being significantly higher than the intakes in blocks 1, 2, and 4. The significant Group × Block × Day/Night interaction observed, $F(3, 90) = 4.17$, $p = .01$, is attributable to the increasing difference between the sucrose intake of the exercise and no-exercise groups across the blocks during the day compared to more parallel trends across the blocks during the night.

The morphine exercised animals demonstrated higher average plasma (594.3, 513.3 pg/ml), pituitary (152.4, 140.6 ng/mg), and whole brain (7.3, 4.6 ng/gm) βEP concentrations than the morphine no-exercise animals. The methadone exercised animals had higher average plasma (385.0, 144.4 pg/ml) and brain (6.8, 5.2 ng/gm) βEP concentrations than methadone no-exercise animals, and similar pituitary concentrations (117.3, 117.6 ng/mg). To determine the significance of these differences, two-way ANOVAs were carried out on plasma, pituitary, and whole brain βEP concentrations. No significant differences between exercised and nonexercised animals were observed, although plasma βEP concentrations were significantly higher, $F(1, 32) = 4.3$, $p = .047$, in morphine than in methadone animals.

The failure to observe significant differences was a reflection of large individual differences in βEP concentrations. Standard deviations were high and ranged from 113% of the mean in the morphine exercise group to 35% of the mean in the methadone exercise group. To investigate whether the large individual differences in βEP concentrations were related to the amounts of exogenous opiate consumed by each rat, Pearson product-moment correlations of brain, plasma, and pituitary βEP concentrations and total 2-, 12-, and 24-h morphine and methadone consumptions in the final four days of exercise were calculated. No significant correlations were observed.

DISCUSSION

Although the 2-h drug intake of rats in all groups showed increases over baseline during exercise, nonexercised animals exhibited significantly greater increases than exercised animals. This result supports the hypothesis that exercise is capable of causing relative decreases in voluntary exogenous opiate intake.

The nonsignificance of the increased βEP levels in exercised compared to nonexercised animals suggests that it is premature to attribute exercise-associated exogenous opiate intake decreases to exercise-associated βEP increase. Nevertheless, it is possible that exercise increases endogenous opioid receptor binding more quickly than it increases endogenous opioid concentration. For example, some authors (6) have observed increased endogenous opioid receptor binding after 3 min swimming, while others (22) have documented endogenous opioid concentrations as unaffected after 4.5 min acute running. Therefore, the observed nonsignificant increases in βEP concentrations may have been indicative of increased βEP receptor binding. Measuring βEP in more specific areas (e.g., the LC) may provide more detailed support for endogenous opioid concentration increases following exercise.

In comparing the effects of exercise on morphine and methadone intake, the different drug consumption patterns meant that the most meaningful comparison was between 12-h methadone and 2-h morphine consumptions. From this, it seems that morphine but not methadone intake was affected by exercise. This may have been because the animals were physically dependent on morphine but not methadone. It is difficult to categorically state that this was the case because dependence was not assessed by the quantification of a withdrawal syndrome; however, a number of factors suggest that it was so. For example, although it is usual for rats to consume up to six times more water during the night than during the day (21), the circadian rhythmicity of drinking patterns in exogenous opiate-dependent animals may be dominated by the physiological need for exogenous opiates. If this were the case, exogenous opiate-dependent rats would be more likely to consume more liquid exogenous opiate during the day than would nondependent rats. This was observed in the morphine but not in the methadone animals. Second, upon initiation of the choice stage, methadone intake decreased by greater amounts than did morphine intake. This suggests that, rather than being dependent, methadone animals may have drunk large amounts of methadone solution during the aquisition stage because it was the only liquid available. Third, animals consumed considerably more morphine than methadone.

Despite these factors, it is likely that some methadone dependence developed because animals continued to consume methadone in the choice stage despite its bitter taste, and amounts of methadone consumed increased over the choice period in a manner consistent with the development of tolerance. Furthermore, qualitative similarities in morphine and methadone intake variability patterns also suggest that there was some dependence on methadone. Assuming that intake variability resulted from overdose-induced disorientation, or the fulfilment of physiological exogenous opiate requirements by the consumption of large amounts on previous days, it is possible that intake variability decreased in the morphine group as dependence developed and they became tolerant to the effects of 80 ml/morphine/day. The methadone animals continued to show large variability in intake pattern, suggesting that tolerance did not develop as quickly, so the amounts of methadone available to them continued to fulfil their physiological needs and provided them with enough methadone to follow a binge/recovery ingestion pattern.

The documented patterns of exogenous opiate intake support previous research indicating that oral ingestion is a suitable method for the chronic delivery of morphine and methadone in rats (12,13,21). Upon observing that 83.3% and 100% of animals consumed morphine and methadone, respectively, when offered a nondrugged choice, we demonstrated higher percentages of drug consumption than in other studies (21). This may have been due to the use of sucrose in masking the bitter exogenous opiate taste. Reports of morphine/water and morphine/sucrose intakes 80% (18) and 223% (this study) higher than baseline water intakes, respectively, support this possibility. The difference in amount consumed presumably resulted from the sweetened solution.

The large fluid intake observed in all groups can be partially explained by physiological need for morphine and methadone and partially by previous observations (10) that rats ingest large volumes of sweet solutions in the absence of any physiological need. Despite proving useful in increasing drug consumption, the sucrose may have resulted in less desirable interactions with mechanisms which regulate food-, liquid-, and drug-seeking behaviours. For example, sucrose ingestion

is thought to be endogenous opioid-mediated (4), suggesting the possibility of an interaction between sucrose and exogenous opiate intake. Indeed, significant differences in sucrose intake were observed between exercised and nonexercised animals.

Furthermore, since they are excellent caloric meters, rats consuming large amounts of 10% sucrose solution tend to eat less (18). Since the morphine animals consumed at least as much sucrose as the methadone animals, the finding that their average weight increased significantly less suggests that they may have eaten less solid food than the methadone animals. As opioid agonists are known to regulate feeding (26), this may have resulted from the larger amounts of morphine ingested or the different patterns of morphine and methadone ingestion. Morphine has also been reported to disturb glucose homeostasis through its effects on the endocrine system (16). This may also account for differences in weight gain between the two drug groups.

In observing a significant relationship between exercise and exogenous opiate intake in rats, we have succeeded in illustrating a functional example of endogenous opioid-exogenous opiate interactions. Obviously, the utility of using exercise in the treatment of human exogenous opiate users is limited, although it may prove valuable as an adjunct to other forms of treatment. In documenting the possibility of naturally restoring preexogenous opiate homeostasis, the results of this study suggest that the development of nonintrusive treatments for exogenous opiate dependence is possible.

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