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Naltrexone Fails to Suppress Spontaneous Locomotor Activity in Hamsters

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LOWY, M. T., S. SANGIAH AND G. K. W. YIM. *Naltrexone fails to suppress spontaneous locomotor activity in hamsters.* PHARMACOL BIOCHEM BEHAV 22(3) 399–401, 1985.—The increased spontaneous locomotor activity (SLMA) of rats exposed to a novel environment is decreased by opiate antagonists. In the present study, naltrexone (1.0–40 mg/kg) failed to reduce the SLMA of hamsters exposed to the novel environment of activity cages. The SLMA of another group of untreated hamsters declined following 4 consecutive exposures to the activity cages. Thus, the novelty-induced increase in hamster SLMA is not sensitive to opiate antagonism. The differential sensitivity of rats and hamsters to opiate effects on activity and feeding may be due to the presence of an opiate-sensitive hibernation system in hamsters.

Hamsters Locomotor activity Naltrexone Opiates Species differences

A large amount of evidence suggests that endogenous opioids (EO) modulate feeding behavior in rats and mice [12]. In general, opiate agonists increase food intake, whereas opiate antagonists decrease feeding behavior. However, there are apparent species differences concerning EO involvement in consummatory behavior. In particular, we have reported that the golden hamster (*Mesocricetus auratus*) fails to respond to various opiate-induced feeding conditions (i.e., food deprivation, 2-deoxy-D-glucose administration) and is insensitive to naltrexone-induced anorexia [6]. Moreover, hamsters in contrast to rats, do not increase food intake following administration of various opiate agonists [7]. These studies suggest that EO do not function as feeding inducers in hamsters.

Opiates also have pronounced effects on spontaneous locomotor activity (SLMA) of rats and mice. Various exogenous and endogenous opiate agonists produce biphasic effects on rat and mouse SLMA with low doses producing a stimulatory effect, while higher doses depress activity [4, 13, 16]. In addition, opiate antagonists, such as naloxone and naltrexone, decrease activity of rats and mice exposed to a novel environment or stress [3–5, 14, 15]. The present study was designed to determine if hamsters differ from rats in their sensitivity to the effect of naltrexone on SLMA.

METHOD

An initial group of 28 male golden hamsters (*Mesocricetus auratus*) weighing 90–110 g were purchased from Engle Breeding Laboratory (Farmersburg, IN) and housed in groups of 6–8 with ad lib access to Wayne Lab Blox and water. Illumination was on a 12/12 hr schedule with light onset at 0800 hr. Room temperature was maintained at 23–26°C.

On test day hamsters were randomly assigned to experimental groups (N=7) and given injections of saline or naltrexone HCl (1.0, 10, 40 mg/kg) 10 min prior to testing using a balanced design. Naltrexone was dissolved in 0.9% saline immediately prior to use and injected subcutaneously in a volume of 3 ml/kg. Doses are expressed as the salt. Hamster SLMA was monitored in round photoelectric activity cages (Woodard Research Corp., Herndon, VA) identical to those previously described in this laboratory [18]. Measurements were taken every 10 min for 1 hr. Testing was initiated between 1000–1400 hr. Prior to testing, the hamsters had never been exposed to the activity cages.

An additional group of 7 hamsters was purchased and maintained as described above. These hamsters were exposed to the activity cages for 4 consecutive sessions to determine if initial exposure to the testing apparatus results in increased exploratory behavior. Data was analyzed using a 2-way analysis of variance with repeated measures.

RESULTS AND DISCUSSION

The effect of naltrexone on the SLMA of hamsters exposed to the novel environment of the activity cages is summarized in Fig. 1. Note that naltrexone, in doses as high as 40 mg/kg, did not suppress the SLMA of hamsters. A 2-way ANOVA with repeated measures indicated no significant treatment effect, $F(3,24)=0.12$, but a significant effect of time, $F(5,120)=25.9$, $p<0.01$. Naltrexone appeared to

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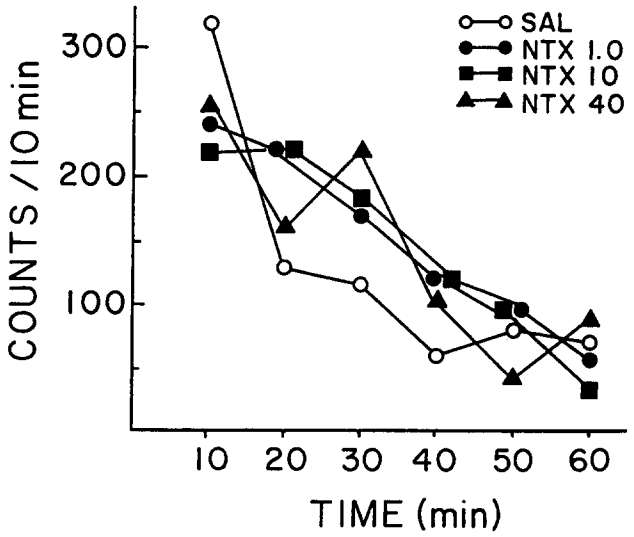

FIG. 1. Lack of suppression by naltrexone (NTX) on activity of hamsters exposed to the novel environment of the activity cages. NTX (1.0, 10, 40 mg/kg) or saline (SAL) was injected 10 min prior to placement in cages. Points represent the mean number of counts per 10 min for 7 hamsters.

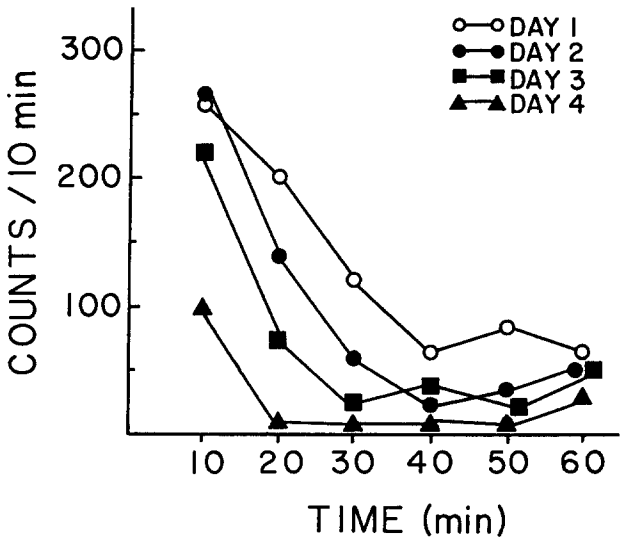

FIG. 2. Adaptation of the exploratory behavior of hamsters repeatedly exposed to the activity cages. Points represent the mean number of counts per 10 min for 7 hamsters.

produce a slight decrease in activity at 10 minutes, but this effect was not dose-related and was shortlived. If anything, there was a tendency for naltrexone treatment to increase activity at 20–30 minutes.

In order to determine if hamsters do indeed increase their SLMA following exposure to a novel environment, another group of hamsters was exposed to the activity cages over 4 sessions. As can be seen in Fig. 2, subsequent exposures of the hamsters to the activity cages resulted in progressive decreases in activity. ANOVA indicated an effect of both treatment, $F(3,24)=8.5$, $p<0.01$ and time, $F(5,120)=32.2$, $p<0.01$. Thus, initial exposure of the hamsters to the activity cages did result in increased levels of SLMA.

The results of the present study indicate that the opiate antagonist, naltrexone, fails to suppress the SLMA of hamsters exposed to a novel environment. This contrasts with the efficacy with which low doses of naloxone or naltrexone attenuate activity in rats and mice in novel test situations [3–5, 14, 15]. The ineffectiveness of naltrexone was not due to the lack of a response of the hamsters to the novel exposure to the activity cages, since repeated exposure to the activity cages resulted in an adaptation of the SLMA response. Neither is the lack of effect of naltrexone due to an absence of opiate receptors or increased drug metabolism, since low doses (1.0 mg/kg) of naltrexone attenuate stimulated drinking over a 4 hr test period in hamsters [6].

The lack of effect of naltrexone in decreasing both feeding [6] and activity in hamsters raises the question of whether opiate antagonists might produce anorexia in rats indirectly by decreasing activity. However, a recent study indicates that naloxone can produce anorexia without suppressing wheel running in rats [1]. Morley *et al.* [11] have reported that naloxone suppresses food intake and activity in wolves, but that the anorexic effect of naloxone was not secondary to the decreased activity. In addition, naltrexone suppresses daily food intake in white-footed mice without altering hoarding behavior [17]. Thus, opiate antagonists can suppress feeding behavior without concomitant decreases in activity.

The differential response of hamsters and rats to opiate effects on activity and feeding may be due to the presence of an endorphin-mediated hibernation system in hamsters. It has been postulated that endogenous opiates are involved in a multitude of processes mediating hibernation [9]. In support of this, naloxone induces cardiovascular changes and premature awakening in hibernating hamsters [10]. However, it should be pointed out that the behavioral events preceding hibernation is not the same for all species. This has been well described by Lyman [8] in a comparison of ground squirrels and golden hamsters. Ground squirrels become extremely obese prior to hibernation and when exposed to cold temperature immediately go into hibernation and consume very little food during hibernation. Golden hamsters, on the other hand, do not become obese prior to hibernation, but engage in hoarding behavior to store food which is consumed periodically during the course of hibernation. If food is not available, hamsters will not hibernate. It would be of interest to examine the effect of opiate antagonists on the hoarding and feeding behavior of hamsters during the induction of hibernation.

Since cold temperature and a decreased photoperiod are physiological parameters which induce hibernation, these events may alter EO systems mediating metabolic and behavioral events related to energy expenditure and conservation. In support of this, torpid bears have increased circulating levels of plasma β-endorphin compared to non-torpid bears [2]. Of particular interest is the report that short photoperiods increase the number of opiate receptors in the whole brain of hamsters [19]. Thus hibernation may be accompanied by increased levels of EO as well as an increase in the number of central opiate receptors. These changes would be expected to increase the sensitivity of the organism to opiate antagonists. This could explain why opiate antagonists produce cardiovascular changes in hibernating

hamsters, but not in non-hibernating hamsters [10]. Similarly, this same phenomena could contribute to the lack of effect of opiate antagonists on the feeding and activity of non-hibernating hamsters. Thus, the presence of an opiate-sensitive hibernation system in hamsters, but not rats, may explain the differential effect of opiate antagonists on the behavior of these two species of rodents.

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