Pharmacology Biochemistry & Behavior, Vol. 12, pp. 729–733. Printed in the U.S.A.

Pain Modulating and Reward Systems: A Single Brain Mechanism?

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Received 4 February 1980

LE MAGNEN, J., P. MARFAING-JALLAT, D. MICELI AND M. DEVOS. *Pain modulating and reward systems: A single brain mechanism?* PHARMAC. BIOCHEM. BEHAV. 12(5) 729–733, 1980.—The hypothesis that brain rewarding and pain modulating systems could involve a common opiate system, identically blocked by naloxone, has been tested in three experiments. The preferences or aversions for sapid solutions in rats have been employed as reliable measures of responses to rewarding or nociceptive stimulations. In the first experiment, it was shown that the spontaneous aversion to a quinine HCl solution was enhanced when rats were offered the solution 30 min after naloxone at a dose of 1 mg/kg. The same enhanced aversion was observed in the second experiment towards a sweet solution previously made aversive through a conditioned taste aversion paradigm. In the third experiment, by using two different procedures and saccharin or glucose solutions, it was found that naloxone acutely abolished the preference for sweet solutions versus water in rats. It is concluded that: (1) the enhancement by naloxone of the aversion to a sapid solution, similar to the naloxone induced hyperalgesia, allows to assimilate this aversion to other responses to nociceptive stimulations; (2) this suggests that, like other responses to nociceptive stimulations, this aversion is normally attenuated through the release of brain or pituitary opiates; (3) the suppressant effect of naloxone upon both this attenuation of aversion and a preference for a sapid solution supports the notion of a biochemical and functional community between rewarding and pain modulating systems.

Taste preference and aversion Opiate systems Naloxone Brain rewarding system Pain modulating system

A ROLE of brain opiate receptors and their ligands and presumably of enkephalinergic neuronal systems in the attenuation of behavioral responses to pain is now well documented [8]. It has been demonstrated convincingly that, in the rat, painful stimulations such as foot shock produced the release of pituitary and brain opiate substances [2, 3, 4, 31, 38, 39]. The analgesia which follows a painful stimulation [2, 3, 9, 10, 11] and the hyperresponsiveness to pain observed after the blockade of opiate receptors [26,27] by naloxone are consistent with the notion that some undefined brain neuronal system (or systems), in which endogenous opiates are involved, acts as a pain modulating mechanism. The observed analgesia and the development of tolerance following various nociceptive stimuli, as well as the effects of naloxone suggest that the same system might be involved in responses, not only to pain but also to stresses and to nociceptive stimuli in general, [2, 3, 9, 10, 11, 24, 34].

Independently, a notion of "brain rewarding systems" had emerged from studies of intracranial self-stimulation (ICSS) [37]. Evidence has been provided that dopaminergic systems play a role in supporting the rewarding effects of ICSS [22]. Just as naloxone inhibits the pain attenuating system, neuroleptics which are dopaminergic blockers alter self-stimulation [19,47]. This has been interpreted as an effect of the drug, not on performance but rather on the rewarding aspect of electrical stimulation [46]. Beyond this artificial stimulation behavior, the notion of "brain rewarding systems" has been extended recently to natural approach responses. The role of the same dopaminergic system which appears involved in ICSS has been supported for example by the fact that dopaminergic blockers suppress the rewarding effect of food stimuli as revealed by the extinction of instrumental responses reinforced by the delivery of foods [41,47]. However, it is not clear whether the drug acts by suppressing the rewarding effect of food sensory stimuli, i.e. the palatability of a "prefered" food, or by counteracting hunger motivation.

The role of opiates and opiate receptors in the brain rewarding systems involved in ICSS has received some support [14, 16, 18, 28, 30, 45]. Naloxone, like neuroleptics, depresses ICSS while morphine facilitates it [13, 17, 36]. This has been interpreted in terms of a possible relationship between dopamine and enkephaline biosynthesis [21]. The involvement of opiate systems and in naturally rewarded behavior is also suggested for example by the inhibiting effect of naloxone on ad lib intake in rats [12, 20, 23, 25, 42].

However, it has not been suggested that opiates contribute simultaneously to the attenuation of responses to aversive stimuli and to the support of positively reinforced responses. More generally, the question has not been raised of the possible relationship between the "brain rewarding" and the "brain pain modulating" systems.

Rats, as other species, exhibit clear cut and reliably measurable ingestive responses to aversive sapid solutions such as quinine or ethanol solutions. The involvement of the same brain mechanism in such ingestive responses and other escape responses to nociceptive stimuli has been suggested by various experimental data. It has been shown, for exam-

ple, that the strength of the individual response of naive rats to an aversive ethanol solution was positively correlated with both their responses to a bitter solution and their capacity to learn an active avoidance of electric shock [1, 29, 32, 33]. Rats also exhibit clear cut and reliably measurable innate "preferences", i.e. approach responses to certain sapid solutions such as sweet solutions. These preferences can be transformed easily in aversion through the "conditioned taste aversion" (CTA) paradigm.

The experiments reported here aimed at testing the hypotheses that:

(1) The aversion response to a bitter solution as it is enhanced by naloxone might be assimilated with other responses to nociceptive stimuli.

(2) A brain rewarding system which supports the "preference" to a sweet solution involves opiates and opiate receptors as revealed by the abolition of preferences by naloxone.

Results have led to the conclusion that the suggested "brain rewarding" and "pain modulating" systems are a single system which can be presumably identified with an opiate system.

The effects of naloxone upon (1) the innate aversion to a quinine solution, (2) the acquired aversion to a sweet solution and (3) the spontaneous preference to a saccharin or glucose solution, have been tested in 3 experiments.

In Experiment 1, 10 adult male Wistar rats, weighing 254 g ± 2 at the beginning of the experiment were housed individually. They had free access to their familiar stock-diet at all times. Twice a day, a graded drinking tube was presented from 10 to 10:30 a.m., and from 3 to 5 p.m. In the 2 hour period of the afternoon, tap water was available throughout the experiment. The rats were then water-deprived overnight. In the morning, they were presented with either a 0.0024% quinine HCl solution, or with tap water, on alternate days. After 4 days of habituation to this schedule, an IP injection of saline was administered 30 min before the beginning of the morning drinking session for 8 consecutive days. The liquid intake for the 4 quinine presentations and the 4 alternate water presentations served as baseline. For the following 8 days, the morning drinking periods were preceded, 30 min before, by an IP naloxone injection (1 mg/kg). Finally, 8 daily sessions of alternate quinine and water presentations were again preceded by a saline injection.

In Experiment 2, 20 rats were habituated to the same drinking schedule as above and were submitted to a "conditioned taste aversion" paradigm. Saccharin (0.1%) was presented in the morning. During 3 days, the 30 min morning session was immediately followed by an IP injection of LiCl (1.2 mEq/kg 0.1M) in 10 rats and by an IP injection of saline in 10 control rats. Then the rats of the two groups were assigned to 2 sub-groups of 5 rats each. In all sub-groups, rats were offered alternately the saccharin solution during the morning session. In the first sub-groups, a saline injection was administered 30 min before the saccharin drinking session. In the second sub-groups of 5 rats, an injection of naloxone (10 mg/kg) preceded saccharin sessions. Saccharin and water intake on alternate days were recorded for 12 days. The injections of naloxone were then discontinued and alternate presentations of saccharin and water were continued until the extinction of the aversive response to saccharin in rats treated with LiCl during training.

In the third experiment, the effects of naloxone (1 mg/kg) were tested in a first group of 10 rats presented with a 0.1% saccharin solution and water on alternate days. In a second group of 10 rats, the same procedure was employed with a 5% glucose solution. In a third group of 12 rats, the effect of naloxone was tested in a 2 bottle-choice situation, where a saccharin solution (0.05%) and water were presented simultaneously for 1 hour. After habituation, the rats of this last group were observed for 4 daily sessions, 30 min after a saline injection; the next 4 days, the one hour session was preceded by a naloxone (1 mg/kg) injection and finally, for the last 4 days, by a saline injection again. As usual, the respective positions of the solution and water bottles were alternated on 2 consecutive days. As usual also, the preference for the sweet solution was expressed in percentage of intake of the solution of the total fluid consumption.

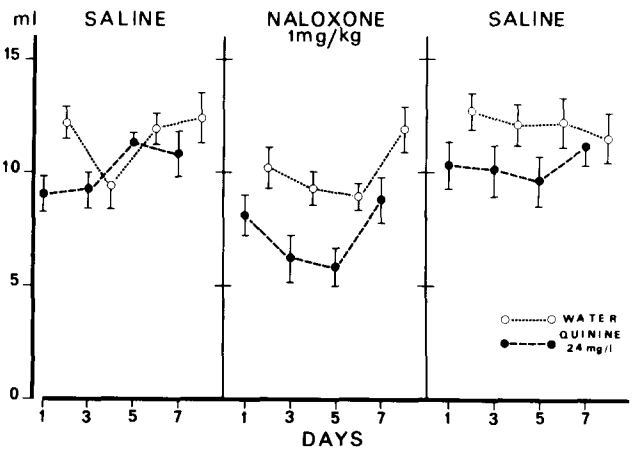

FIG. 1. Thirty min intake of a quinine HCl solution versus water after an acute Naloxone (1 mg/kg) injection (central section) or after an injection of saline (pre and post naloxone controls).

RESULTS

In Experiment 1, rats exhibited during the initial saline control a slight and nevertheless statistically significant aversion to the quinine solution vs water ($t=2.92$; $p<0.01$—Student t-test difference method) (Fig. 1). Under the acute effect of naloxone, the intake of quinine solution was reduced by 28.5% and the intake of water on alternate days by 12.2%. The difference between quinine and water intake was then highly significant ($t=5.75$; $p<0.01$). The quinine to water ratio, which gives a measure of the aversion, drifted from 0.895 at baseline to 0.72 under naloxone. The initial aversion was almost reestablished during the post-treatment saline control (10.27 vs 10.1) ($F_{1\text{-}60}=0.07$ NS).

In Experiment 2, the pairing of saccharin intake with LiCl conditioned a strong aversion to the sweet solution. For the subgroups in which the presentation of saccharin was preceded by a saline injection, the extinction of this conditioned taste aversion occurred within 8 days. In the other subgroups, naloxone injected 30 min prior the oral intake of saccharin enhanced the aversion and blocked its extinction completely. This extinction occurred rapidly as soon as the naloxone treatment was discontinued. In the control group which was trained with a saline injection after the presentation of saccharin and which therefore had not developed an aversion, naloxone, during the subsequent phase, suppressed the preference to the sweet solution over water whereas the saccharine preference was increasing overtime in the saline controls (Fig. 2).

Experiment 3 confirmed this suppressing effect of

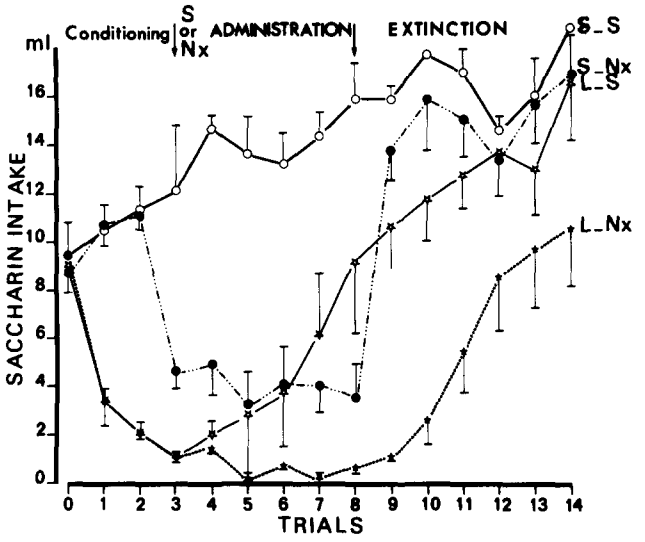

FIG. 2. Comparison of the effects of 10 mg/kg Naloxone (LNx) and saline (LS) on a LiCl induced aversion to a saccharine solution, and of the effects of naloxone (SNx) and saline (SS) on the saccharin preference of unconditioned controls.

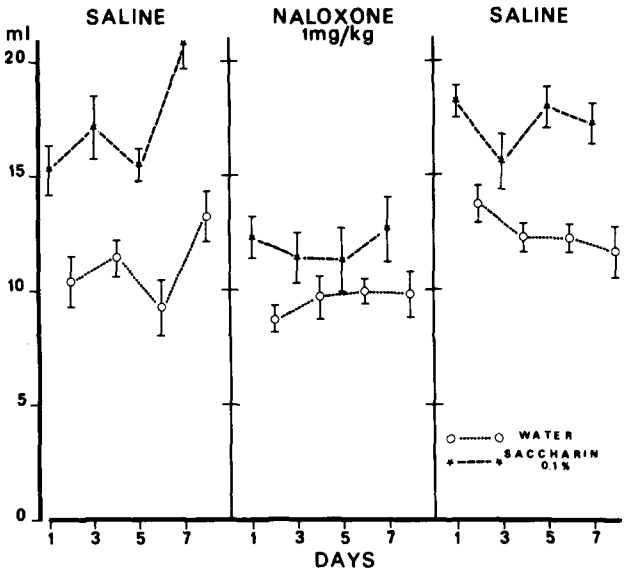

FIG. 3. Thirty min intake of a saccharin solution versus water after an acute Naloxone (1 mg/kg) injection (central section) or after an injection of saline (pre and post naloxone controls).

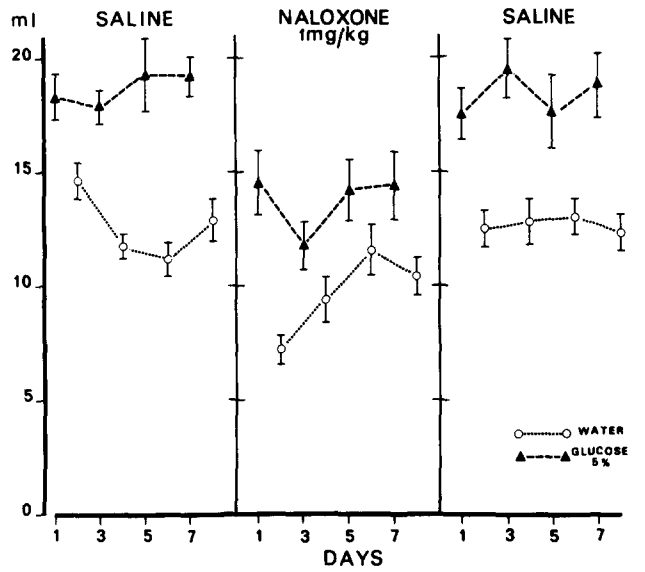

FIG. 4. Thirty min intake of a glucose solution versus water after an acute Naloxone (1 mg/kg) injection (central section) or after an injection of saline (pre and post naloxone controls).

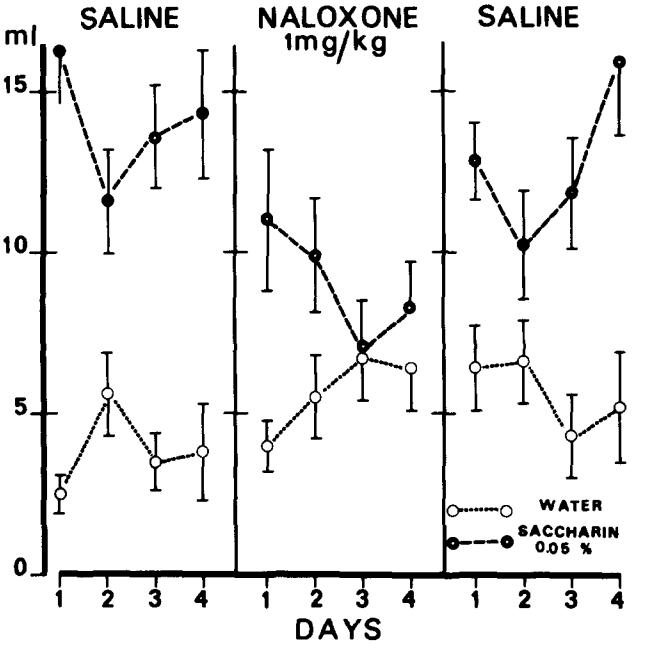

FIG. 5. One hour preferential intake of saccharin over water after an acute Naloxone (1 mg/kg) injection (central section) or after an injection of saline (pre and post naloxone controls).

naloxone on preference. In the single bottle saccharin water preference tests, rats initially exhibited a strong preference for the sweet solution: 17.2/11.1 ($t=9.73$; $p<0.01$), 30 min after saline injection. After naloxone, the 30 min intake of the saccharin solution dropped to the control level of water intake observed after saline (11.9 ml versus 11.1; $F_{1\text{-}60}=0.59$ NS) (Fig. 3). But naloxone also reduced the water intake by 14% so that the intakes of the two fluids remained statistically different ($t=4.19$; $p<0.01$). The initial intake of the saccharin solution was reestablished during the final saline days and the water intake was elevated by 12%. Comparable results were obtained with glucose. The initial preference of 18.7/12.6 ($t=9.93$, $p<0.01$) fell to 13.7/9.7 ($t=6.04$; $p<0.01$) under the acute action of naloxone. Again the intake of the sweet solution after naloxone was not statistically different from that of water during the previous saline phase ($F_{1\text{-}60}=1.5$ NS). Again the initial intake of the two fluids was reestablished during the last saline phase (Fig. 4). When presented with the saccharin solution and water simultaneously, the rats consumed almost 80% of their total fluid intake from the saccharin bottle. Under naloxone, the intake of the sweet

solution dropped by 35.2% (9.04 ml vs 13.95 ml; $F_{1\text{-}72}=17.7$; $p<0.01$) while water intake increased by 46.6% so that only 61.6% of the total intake was drawn from the saccharin bottle, which, according to a previous work, is near the range 40–60% of no preference. A 68.9% saccharin preference was reestablished during the 4 day-post-treatment (Fig. 5).

DISCUSSION

Thus, naloxone enhances the aversiveness of a bitter solution while it abolishes the spontaneous preference for a sweet solution. The fact that a CTA for an initially preferred sweet solution was magnified by naloxone shows that the hyperresponsiveness to aversive solutions induced by naloxone is not specific to taste, sweet or bitter, but to aversiveness. In another study, it has been shown that naloxone combined with LiCl or ethanol during a CTA training enhanced the aversion induced [35]. Thus, naloxone enhances and opiate receptors counteract both the conditioning of an aversion and the exhibition of this acquired aversion. In other words, naloxone acts identically in primary and secondary reinforcement.

This enhancement of avoidance responses to aversive solutions might be assimilated with the hyperalgesia which is induced by naloxone. Therefore, such responses may be identified with responses to pain, stress and other nociceptive stimuli. Like these responses, it is suggested that they are attenuated physiologically by the release of endogenous opioïd substances. It has been shown that the aversion to bitter and other solutions was enhanced after hypophysectomy and that this enhancement was abolished by injections of ACTH [5,44]. This could suggest the involvement of opioïds of brain or pituitary origin in as much as $ACTH_{1\text{-}24}$ which is a partial agonist of opioreceptors could act as a substitute to reestablish a normal attenuated response.

The suppression by naloxone of the preference for a sweet solution substantiates the assumptions that "brain reward system" analogous or identical to those which underly ICSS, supports such preference responses and that opioreceptors, blocked specifically by naloxone, are involved in such neuronal mechanisms. The finding that naloxone abolished preference for both saccharin and glucose rules out the possibility that it acts by enhancing the aversion to the bitter component of saccharin. The suppression of preference is not probably due to an effect of naloxone on the internally aroused stimulation to eat or to drink, or hunger and thirst motivation. Rats, after being water- but not food-deprived overnight, are more thirsty than hungry at the time of testing. Such a condition has been shown to reduce the relative preference of a sweet solution vs water, [43]. If naloxone acted on the thirst arousal of drinking, its effect would have been to enhance the relative preference for saccharin. On the contrary, a specific effect on hunger arousal would have induced an aversion to the sweet solution. This aversion was not observed since naloxone only abolished the preference response and made the rat drink the sweet solution just as much as water. This effect was fully apparent as early as the first injection and there was no indication of a learning process on the subsequent days.

Thus, brain rewarding systems, in which opio-peptidergic neurons seem to be involved, are suggested to underly the naturally rewarding aspect of sensory stimuli which trigger approach or appetitive behavior. This suggestion and the fact that naloxone blocks both the attenuation of responding to nociceptive stimuli and the approach response to rewarding stimuli, leads to the hypothesis that reward and pain modulating systems of the brain belong to a biochemical continuum in a functionally unique brain mechanism. The effects of naloxone imply that an identical role is played directly or indirectly by brain receptors which are pharmacologically blocked by naloxone in both reward and the antagonism of aversion. It is possible that both positively and negatively reinforced sensory stimuli activate an identical receptor system. However, this does not preclude a possible difference of the endogenous ligands involved and a definite difference of brain sites and neuronal pathways. In addition, it leaves open the question of the specific brain mechanisms subserving the responses to pain or to other nociceptive stimuli.

A functional community between cerebral reward and pain modulating systems is supported by the finding that a stress, such as foot-shock, facilitates subsequent ICSS [15]. It is as if rats stimulated the release of an endogenous substance by increasing their ICSS in order to complement the release of the substance elicited by the foot-shock. Overeating of highly palatable foods and other excessive appetitive behaviors induced by tail-pinching may be also interpreted as a search for an over-compensation for the nociception through the activation by both stimuli of a unique mechanism [6, 7, 40]. Many trivial aspects of normal human behaviors seem consistent with this model as well as semipathological states in which, like after naloxone, an exaggeration of all aversive reactions is associated with the suppression of rewarded behaviors.

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