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Opiate Antagonists Stimulate Affiliative Behaviour in Monkeys

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FABRE-NYS, C., R. E. MELLER AND E. B. KEVERNE. *Opiate antagonists stimulate affiliative behaviour in monkeys.* PHARMAC. BIOCHEM. BEHAV. **16**(4)653–659, 1982.—The effects of treating captive talapoin monkeys acutely (twice daily for 7 days) with naltrexone hydrochloride (0.25 mg 0.5 mg and 1 mg/kg intramuscular injections twice daily), naloxone hydrochloride (0.5 mg/kg IM twice daily) and sulpiride (1.5 mg/kg IM twice daily) was studied in social pairs and singly caged animals. The behaviour of social pairs and endocrine changes in all treated monkeys were monitored before, during and after withdrawal of the course of drug treatment. Naltrexone and naloxone, but not sulpiride, significant increased grooming and grooming invitations while aggressive behaviour, self grooming, scratching and general locomotor activity were unaffected. There was an overall increase in LH, testosterone and coritsol in plasma samples taken 60 mins after opiate receptor blockade. Prolactin was unchanged but increased dramatically in animals treated with sulpiride. No significant endocrine changes were observed to precede the increased grooming behaviour which opiate receptor blockade induced. The behavioural changes reported for this primate support the view that positive affect arising from social bonds may be mediated by cerebral endorphin containing systems.

Naltrexone Naloxone Sulpiride Talapoin monkeys Grooming behaviour Testosterone Cortisol LH Prolactin Social bonding

THE discovery of opiate receptors and their endogenous ligands has stimulated many studies and various hypotheses concerning their physiological importance. These hypotheses have ranged from the implication of endogenous opiate systems in psychopathological processes (schizophrenia [5,18] anxiety [30], depression [26]), sexual behaviour [1, 13, 32], stress [2,27], various aspects of neuroendocrinology (LH [3,4], prolactin [11,14], testosterone [8,9], ACTH [17] and cortisol [39]), feeding behaviour [6], exploratory behaviour [35], memory [22], social attachment [20,34], nociception and analgesia [16,27]. Considering the distribution of endogenous opiate receptors, especially in the limbic brain [28], it is perhaps understandable that they can influence such a wide variety of functions. Indeed, electrolytic lesions to a very small proportion of the limbic brain, namely the hypothalamus and amygdala, which are rich in opiate receptors, will affect many of the functions listed above, with the exception of pain perception. It might be anticipated, therefore, that administration of opiate receptor blockers by systemic injection could influence many such functions simultaneously, and in the context of behavioural interactions, the problem arises as to the direct specificity of the opiate system. Thus, when interference of the opiate system changes some aspect of behaviour, the question arises as to whether this is a consequence of endocrine changes, or stress, or pain, all variables known to influence behaviour, or is it indeed a direct action of opiate withdrawal on the behaviour itself?

In many primate species the social structure has profound consequences for behaviour with high ranking individuals achieving priority over behavioural interactions, including sexual [23,24] and grooming interactions [36,37]. It therefore came as a surprise when, in a previous study on a captive group of talapoin monkeys [29], the administration of the opiate receptor blocker, naltrexone, stimulated grooming interactions regardless of social rank. Even the lower ranking males that had not been seen to participate in social grooming did so when given naltrexone. In this social group there were too few monkeys for definitive conclusions to be drawn, and moreover, since they were permanently living together it was not possible to ascertain whether such grooming changes were secondary to other behaviours, or endocrine changes, or were simply a consequence of non-specific sickness as a result of the drug. In view of Panksepp's [20,34] findings that naltrexone increased separation distress, an assessed from vocalisations in guinea pigs, and our own preliminary observations on grooming behaviour in monkeys treated with naltrexone, we decided to closely examine the effects of opiate receptor blockade on attachment behaviour in monkeys. Since our previous study also showed secretion of pituitary hormones changed following opiate withdrawal, a further purpose behind this investigation was to examine if this change in hormonal secretion was responsible for the behavioural changes.

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TABLE 1

HOUSING OF TALAPOIN MONKEYS DURING TREATMENTS

	Treatment received				
Pairs	Sulpiride	Naloxone	Naltrexone	Males Housed Singly	Naltrexone
♀2054-♀327	+	+	+	C1	+
♀22-♀6*		+	+	D	+
♂M-♀C1	+	+	+	340	+
♂S-♂I*		+	+	S	+
♂2-♀1	+	+	+	I	+
♂21-♀10	+	+	+	Du	+
♂13-♀W		+	+	M	+
♂D-♀5†		+	+		

*These pairs also received half and double the dose of naltrexone.
†Treatments were only given to 5 and no behavioural data were collected on this pair.
♀♀=castrate.

METHOD

The experimental animals were 18 adult talapoin monkeys which had been housed in the laboratory for at least 9 months prior to these experiments. Both males and females were used, intact and castrated (see Table 1), and they were housed either singly or in pairs in cages (0.8×0.8×0.5 m) in a colony room within sight, sound and smell of other talapoin monkeys. The animals were fed once daily in the morning with a diet of 41B pellets, mixed seeds and fresh fruit.

During experiments, samples of blood were taken under ketamine anaesthesia using femoral venipuncture to obtain 2–3 ml blood. Serum was separated the following day and stored at −20°C until assayed for testosterone, LH, cortisol and prolactin by radioimmunoassay techniques described previously [24].

Statistical analysis was carried out on the means of data collected for each individual during baseline, treatment and drug-withdrawal periods (for details see below). Hormonal data were analysed using *t*-tests, while behavioural data were analysed by means of Wilcoxon matched-pairs tests and Mann-Whitney U-tests. In all cases the tests were two-tailed.

Drug Studies on Pairs

A total of 16 animals were used: 8 females (of which 3 were ovariectomised and receiving no oestrogen replacement) and 8 males (one of which was castrated and not given testosterone) (Table 1). In each study, a drug treatment lasted for one week, during which injections (0.2 ml) were given twice daily at 10.00 and 16.00. This was preceded and followed by 1 week of saline injections (0.2 ml) given at the same time of day, these periods being called Baseline and Withdrawal respectively. Blood was taken on days 1, 3 and 6 of each period.

Sulpiride study. 1.5 mg/kg sulpiride (Dogmatil Lab. Delagrange) was given to 4 males and 4 females housed as two same sex and two mixed sex pairs (Table 1). Our previous study had shown opiate receptor blockade produced either increases or no change in prolactin, suggesting an antagonistic action on dopamine. Hence the choice of a dopamine antagonist to determine if dopamine changes were responsible for the behavioural effects.

Naltrexone/naloxone study. Since naltrexone, but not naloxone, has been reported to have behaviourally dysphoric effects in man [30], it was decided to compare the two opiate receptor blockers in monkeys:

(a) The same 8 monkeys housed as above plus four additional intact females (Table 1) were used: 0.5 mg/kg of either naltrexone or naloxone (Endo Labs. Inc.) was given blind, to half the pairs (n=6) and saline to the others (n=6) and the treatment subsequently reversed.

(b) Two intact males (S and I) and two intact females (22,6) were further treated after a four month interval with 0.25 mg/kg, and then after a 2 month interval with 1 mg/kg of naloxone. Three males used in the above (a) study (C, D, 340) were housed alone and also treated with the 0.5 mg/kg dose of naltrexone after a 6 month interval from any drug treatment.

In all these studies blood was taken 60 minutes after the p.m. injection. Behavioural data were collected by a check-sheet method, for 20 minutes, twice daily, by an observer seated in front of two pairs of monkeys. The experiments were preceded by a period of 2–4 weeks observations to habituate the monkeys to the procedures. Each session began 5 minutes after the drug or saline injection. All 4 monkeys were watched continuously. Just prior to observation, following injection, the monkeys were given half their food and at the end of the session the rest of the food and their fruit was given.

(c) In order to relate behavioural changes directly to endocrine effects of the drug, six males were serially bled on 2 separate occasions. Three were treated with naltrexone and three with saline, then the order of saline and naltrexone treatment was reversed. A blood sample was taken (t=0 min) and as soon as possible after these animals were injected with either saline (0.2 ml) or naltrexone (0.5 mg/kg in 0.2 ml saline). Fifteen minutes later a second blood sample was taken.

Behaviours Scored

Social behaviour—This consisted of the number of times an animal invited grooming, or groomed its partner.

Agressive Behaviour—The number of displaces, threats or attacks to its partner, or threats to monkeys in other cages (or to the observer) were scored.

Movement—to gain an estimate of general locomotor activity the number of times each individual moved from one half of the cage to the other was noted.

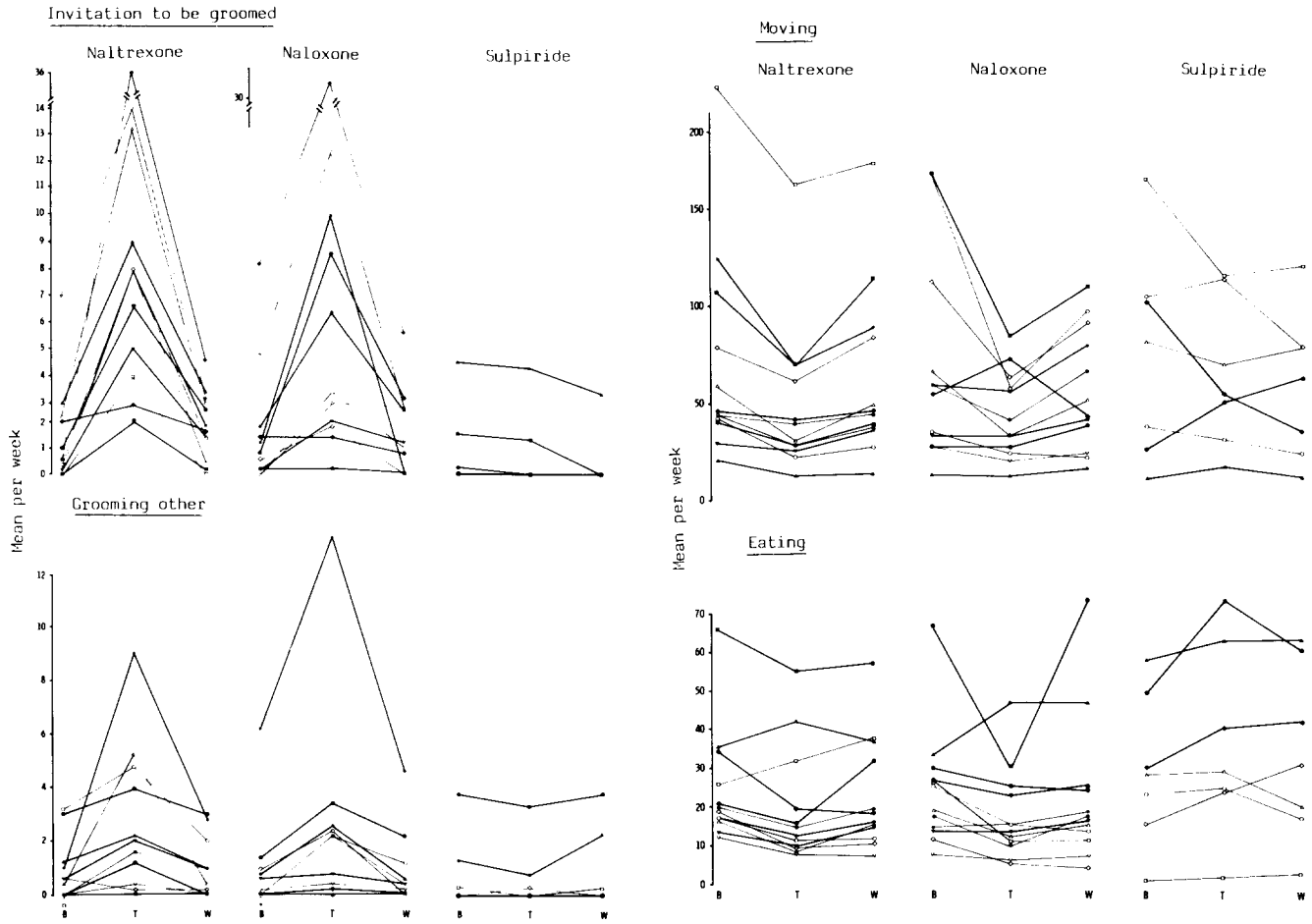

FIG. 1. The effect of naltrexone, naloxone and sulpiride on social behaviour in male and female talapoin monkeys. The mean for each week's observation is shown for each individual. The heaviest line at zero shows the overlapping score of more than one individual. The thin lines show the females. Naloxone and Naltrexone produced significant increases ($p<0.01$) in grooming and invitations to groom, and decreases in moving and eating ($p<0.05$). Sulpiride was without effect on grooming and moving, but increased eating ($p<0.02$). B=Baseline, T=Drug treatment, W=Withdrawal of drug.

Eating Behaviour—This was measured by scoring each occasion when an animal was seen to pick up or chew a piece of food. In addition, the monkey's response to the fresh fruit given at the end of the test was also recorded.

Self-grooming and Scratching—These behaviours were recorded whenever they were observed and are self-explanatory.

Any pattern of behaviour which looked unusual to the observer (i.e., had never been seen during Baseline) was also recorded.

RESULTS

Behavioural Data

The behavioural data from the three drug treatments are represented in Figs. 1 and 2. In order to validate the pooling of data across days a repeated means ANOVA was conducted across days. No significant differences were found across time for naloxone (grooming invitations $F=0.57$, $p>0.84$; grooming bouts $F=0.91$, $p>0.62$) or naltrexone (grooming invitations $F=0.21$, $p>0.99$; grooming bouts $F=0.32$, $p>0.97$).

Social Behaviour

As shown in Fig. 1, treatment with naltrexone led to a dramatic increase in both grooming ($t=2$, $p<0.01$) and invitations to be groomed ($t=0$, $p<0.002$). This increase in grooming was limited to the time of treatment, with levels falling to baseline on withdrawal of the drug. The increase in grooming invitations was more marked in the females ($t=0$, $p<0.02$) than in the males ($t=2$, $p<0.05$).

Treatment with naloxone had similar effects on both grooming and invitation behaviours ($t=0$, $p<0.01$), although the increase in invitations to be groomed was lower than that seen during naltrexone administration ($U=28$, $p<0.02$). Sulpiride clearly had no effect on grooming interactions (Fig. 1).

Self-grooming was unaffected, while levels of scratching actually fell during naltrexone treatment ($t=6$, $p<0.01$) and during naloxone treatment ($t=12$, $p<0.05$) when compared with baseline levels (Fig. 2).

Three males housed alone and treated with 0.5 mg/kg naltrexone (study b) showed no changes in self-grooming, scratching or eating and could not behaviourally be distinguished from when they received saline injections.

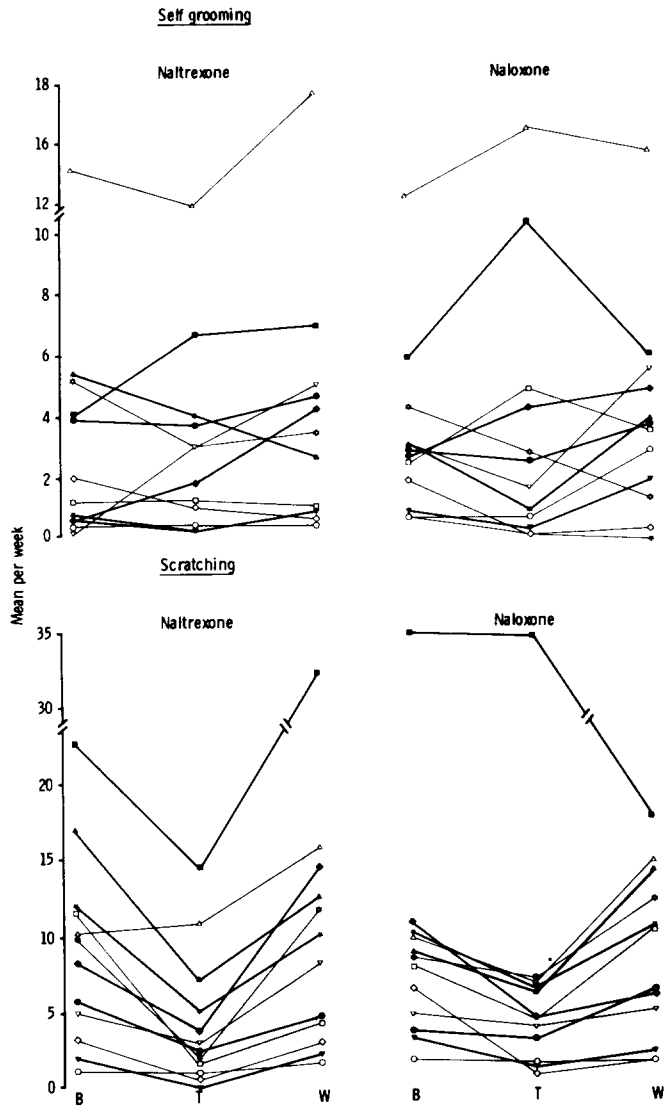

FIG. 2. The effect of naltrexone, naloxone in male and female talapoin monkeys. The mean for each week's observation is shown for each individual. Thin lines represent females and thick lines males. Scratching significantly decreased with Naloxone and Naltrexone ($p<0.05$). B=Baseline, T=Drug treatment, W=Withdrawal of drug.

Both naloxone and naltrexone drugs induced a stretching behaviour (arching of the back with a stiff leg gait lasting several seconds) in 7 of the 12 animals observed in pairs. This behaviour was seen frequently enough to represent a significant effect of these drugs ($U=6, p<0.01$). The animals did not however appear drowsy or unwell. Sulpiride never induced this behaviour, nor did it affect any of the other behaviours mentioned above.

General Behaviours

Moving. Both naltrexone and naloxone were associated with significant decreases in locomotor activity ($t=0, p<0.01$ and $t=5, p<0.05$, respectively), with no differences seen between the sexes or between the drugs (Fig. 1). Sulpiride had no effect on moving.

Eating. The general attitude of the monkeys to the food was unchanged during drug treatment, i.e., they grabbed the seed and pellets as soon as they were offered, and at the end of the test those individuals who had always rushed for their fruit continued to do so. However, opiate blockade was overall associated with a decrease in eating (Fig. 2): naltexone withdrawal led to a significant increase in eating ($t=13, p<0.05$), and naloxone treatment was associated with lower levels of eating than both during baseline ($t=10$, $p<0.05$) and withdrawal ($t=6, p<0.02$). There was no difference between male and female response or between the two drugs.

Sulpiride on the other hand, led to an increase in eating over baseline ($t=0$, $p<0.02$) but there was no change on withdrawal of the drug.

Other Behaviours

Treatment with opiate receptor blockers had no effect on any aggressive behaviours.

Hormonal Data

Neither naltrexone nor naloxone had a consistent effect on prolactin levels in either males or females (Table 2). In contrast, sulpiride led to a dramatic increase in this hormone in all individuals ($t=6.8$; $t=6.27$, $p<0.001$ with respect to either baseline or withdrawal). Both naltrexone and naloxone were associated with a significant increase in cortisol over baseline one hour after treatment ($t=2.3$, $p<0.05$ and $t=4.25, p<0.001$, respectively). Withdrawal of naloxone was associated with a significant decrease in this hormone ($t=6.64, p<0.001$). There was no difference in the response of males or females, nor between the effects of the two drugs (Table 2). Sulpiride also induced an increase in cortisol levels over baseline values ($t=3.61$, $p<0.01$), but there was no change in these levels on withdrawal of the drug.

Treatment with both naltrexone and naloxone led to a marked increase in testosterone in the 4 males ($t=3.3$, $p<0.03$ and $t=9.71$, $p<0.003$, respectively). Drug withdrawal was associated with a decrease in testosterone ($t=3.65, p<0.04$ and $t=7.56, p<0.001$). Sulpiride had no effect on testosterone in any of the males (Table 2).

There was a significant increase in LH when naltrexone, but not naloxone, was administered to males ($t=3.35$, $p<0.05$ and $t=2.99$, $p<0.05$). Drug withdrawal was associated with a decrease in LH in the case of naloxone ($t=2.99$, $p<0.05$) but not naltrexone ($p>0.225$). Sulpiride had no effect on LH levels in any male. None of the 3 treatments altered LH levels in the intact or ovariectomised females.

Study b. Two males and two females (all intact) were treated with different doses of naltrexone to compare with the 0.5 mg/kg dose. After a dose of 0.25 mg/kg the increase in grooming behaviour and grooming invitations was not observed. Indeed there was no change in any of the behaviour scored including eating, moving, self-grooming and scratching. Cortisol increased, as with other treatments and so too did testosterone in the males, but prolactin was unchanged. When the dose was increased to 1 mg/kg, grooming behaviour and grooming invitations increased as they did with the 0.5 mg treatment. Frequencies of other behaviours at this higher dose changed in accordance with those observed during the 0.5 mg/kg treatment, and again testosterone and cortisol increased significantly while prolactin was unchanged.

Study c. Plasma samples taken at 15 minutes after drug treatment did not show increases in testosterone, LH, cor-

tisol and prolactin levels (Fig. 3) and did not differ significantly from controls. This is in marked contrast to the increases found in the first three of these hormones in plasma taken 60 minutes after drug injection.

DISCUSSION

The most outstanding feature of these results was the increased grooming behaviour (grooming invitations, and mutual grooming) a form of social bonding, which opiate receptor blockade induced. This occurred in both males and females, intact or castrate, and with opiate receptor blockers, naloxone and naltrexone (0.5 mg/kg), but not with the DA antagonist, sulpiride (1.5 mg/kg). The stimulation of this behaviour was dose dependent and did not appear with the lower 0.25 mg/kg dose of naltrexone. Increased grooming and grooming invitations normally occur in pair bonding of primates during and following copulation [33]; in cementing social relations [19,36] particularly between mother and infant [21]; in maintaining peace and cohesion in primate societies [21,37], and following aggressive outbursts [25]. Grooming interactions form part of the normal behavioural repertoire of primates and although generalizable to different social situations, these have in common the provision of comfort and bonding to the participants.

The rapidity of onset of mutual grooming following opiate receptor blockade suggests a direct activation independent of any secondary hormonal changes since these hormonal changes were observed to occur with the lower dose of drug treatment, when the behavioural changes were absent. Moreover, the onset of social grooming occurred within 10 minutes of drug treatment and continued until the end of observations, and yet no significant endocrine changes could be detected, when plasma was taken 15 minutes after drug treatment (Study c). Nor was there any indication of this behaviour being due to a non-specific action of the drug pathologically influencing the well-being of the animal. Monkeys treated with naltrexone or naloxone appeared normal, moved normally, showed the same enthusiasm for their food and ate as usual. The decreases in total food consumption and moving were therefore probably secondary to the monkeys spending more increased time engrossed in grooming and being groomed. It is also unlikely that an increase in specific aspects of social interaction would occur if the well-being of animals were disturbed. Moreover, the increase in grooming behaviour that these studies show is not accompanied by any increase in self-grooming or scratching, suggesting it is not related to any local discomfort in the fur. This view was further supported by the fact that animals housed alone and treated with naltrexone failed to show increased self-grooming or scratching.

The drug induced changes in grooming and the seeking of close social contact (grooming invitations) is particularly interesting in view of the hypothesis put forward by Panksepp and colleagues [34] that the positive affect arising from social bonds may be mediated by cerebral endorphin containing systems. Panksepp, on the basis of observing separation distress in guinea pigs and puppies, concluded that brain endorphins may play an important role in mediating social attachment. Our own studies on monkeys support this view, but our interpretation would be that opiate receptor blockade enhances the need for social attachment. Thus, in a state of endogenous opiate withdrawal as induced by naloxone or naltrexone, the monkeys are induced to seek support and comfort in grooming behaviour. The mutual bombardment

TABLE 2

THE EFFECT OF NALTREXONE, NALOXONE AND SULPIRIDE ON PLASMA HORMONES IN MONKEYS (MEAN±S.D.)

Hormone	Naltrexone			Naloxone			Sulpiride		
	Baseline	Treatment	Withdrawal	Baseline	Treatment	Withdrawal	Baseline	Treatment	Withdrawal
Cortisol (mg/ml)	409 ±25	456 ±21*	364 ±26	408 ±25	500 ±28*	388 ±21	389 ±39	493 ±39	490 ±42
Prolactin (mIU/ml)	0.41± 0.04	0.44± 0.05	0.45± 0.07	0.40± 0.06	0.34± 0.05	0.36± 0.03	0.23± 0.05	1.01± 0.40*	0.26± 0.12
LH (mg/ml)	12.8 ±14.8	13.3 ±14.6	13.5 ±15.7	17.2 ±27.1	18.6 ±23.4	13.3 ±17.2	11.2 ± 9.1	11.1 ±10.4	11.8 ±11.2
Testosterone (mg/ml)	11.2 ± 4.3	19.6 ± 0.6*	9.5 ± 5.4	13.5 ± 4.3	21.2 ± 3.4*	10.9 ± 4.5	15.1 ± 2.5	11.1 ± 3.0	11.1 ± 3.9

*$p<0.01$. For subjects in each treatment see Table 1.

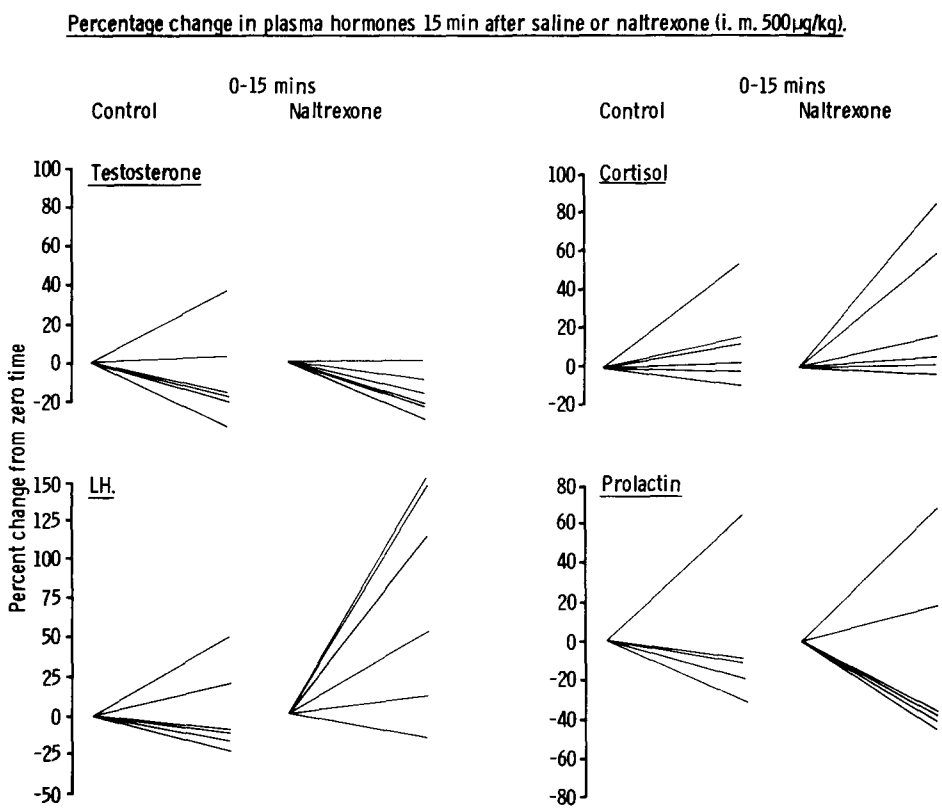

FIG. 3. The effects of naltrexone versus vehicle injection on changes in plasma testosterone, cortisol, LH and prolactin 15 minutes after drug injection. No significant increases were observed in any of the hormones at this time point. B=Baseline, T=Drug treatment, W=Withdrawal of drug.

with tactile stimulation which accompanies grooming may enhance the release of endogenous opiates. Such cutaneous stimulation may have a counterpart in acupuncture, a procedure known to stimulate endogenous opiates in man [10]. These studies together with the additional research on other behaviours and endocrine status enable us to be reasonably confident as to the specificity of endorphin withdrawal on this attachment behaviour.

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