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Catecholamines and Endogenous Opioids in Ventral Tegmental Self-Stimulation Reward

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VAN WOLFSWINKEL, L., W. F. SEIFERT AND J. M. VAN REE. *Catecholamines and endogenous opioids in ventral tegmental self-stimulation reward.* PHARMACOL BIOCHEM BEHAV 30(3) 589–595, 1988.—Midbrain dopaminergic pathways and opioid receptor systems have been implicated in the reward experienced in electrical intracranial self-stimulation behavior. In the present experiment, the influence of graded doses of the dopamine antagonist haloperidol and of the agonist cocaine were investigated on electrical self-stimulation reward, elicited by electrodes located in the ventral tegmental area. A threshold method, which is rather insensitive for aspecific motor effects, was applied to determine the reward of self-stimulation. The method allowed to determine simultaneously the rate of lever pressing for self-stimulation. All doses of haloperidol and cocaine were administered with and without the opioid antagonist naloxone, in order to investigate the interaction between dopaminergic and opioid modulation of reward. Haloperidol lowered and cocaine tended to increase the response rate, whereas cocaine but also haloperidol lowered the self-stimulation threshold. The effects appear to be dose-dependent. Naloxone did not interact with the effect of the drugs on threshold and it lowered the response rate, but in the haloperidol-treated rats only. It is concluded that dopamine is involved in the reward of electrical self-stimulation elicited from the ventral tegmental area and that this involvement is independent of endorphin systems, suggesting the existence of separate catecholamine and opioid mechanisms modulating brain reward.

Cocaine Endogenous opioids Haloperidol Naloxone Reward Self-stimulation

INTRACRANIAL electrical self-stimulation (ICSS) can be used to investigate the neuronal systems involved in brain reward processes. Although ICSS has several unique features, similarities exist between ICSS and the reinforcing action of abused drugs and of 'natural' rewards like those related to feeding, reproduction and social interaction [47]. Much work has been performed to characterize a substrate for the reward of brain stimulation, and thereby probably also for other rewards. Whereas early investigations focussed on the involvement of noradrenaline systems in ICSS, subsequent evidence pointed to dopamine as the critical transmitter in neuronal systems supporting ICSS [12]. Anatomically, the sites supporting ICSS are closely related to dopamine systems, especially to the meso(cortico)limbic dopamine system. This system has its cell bodies in the ventral tegmental area and the axons run along the medial forebrain bundle to the nucleus accumbens and also to cortical sites, particularly the prefrontal cortex [22]. Most if not all sites in the mesocorticolimbic system have been shown to support self-stimulation [6,30]. The critical function of dopamine in ICSS is also supported by pharmacological experiments. The rate of lever pressing for electrical stimulation is decreased after administration of dopamine antagonists (neuroleptics). However, the doses of neuroleptics that decrease response rate are quite high and just below or in the range that produces marked motor impairment in rats [48]. They are much higher than the dose that, e.g., facilitates extinction of active avoidance behavior [4,21]. The possibility has therefore been raised that neuroleptics affect ICSS by induction of fatigue or by other nonreward related motor effects. Carefully conducted studies, designed to control for rate-depressant effects of dopamine antagonists, have however suggested that blockade of postsynaptic dopamine receptors may indeed be related to a reward reduction [13,14]. There is evidence that the dopamine neuronal system is indirectly activated by electrical stimulation; the electrophysiological properties of the unmyelinated dopamine fibers appear to be different from those of the activated system, which has properties of thick, fast conducting myelinated fibers. This latter system supposedly influences the mesolimbic dopamine system transsynaptically at the level of the ventral tegmental area [15,48].

The involvement of endogenous opioid systems in reward and ICSS has been studied because opiates and opioid peptides have strong rewarding and dependence-creating properties [39,41]. Stimulation of opioid receptor systems by morphine has been shown to dose-dependently increase the reward of ICSS, at least when determined with a response rate-insensitive threshold determination [8, 23, 42]. The opioid antagonist naloxone may decrease the reward of ICSS

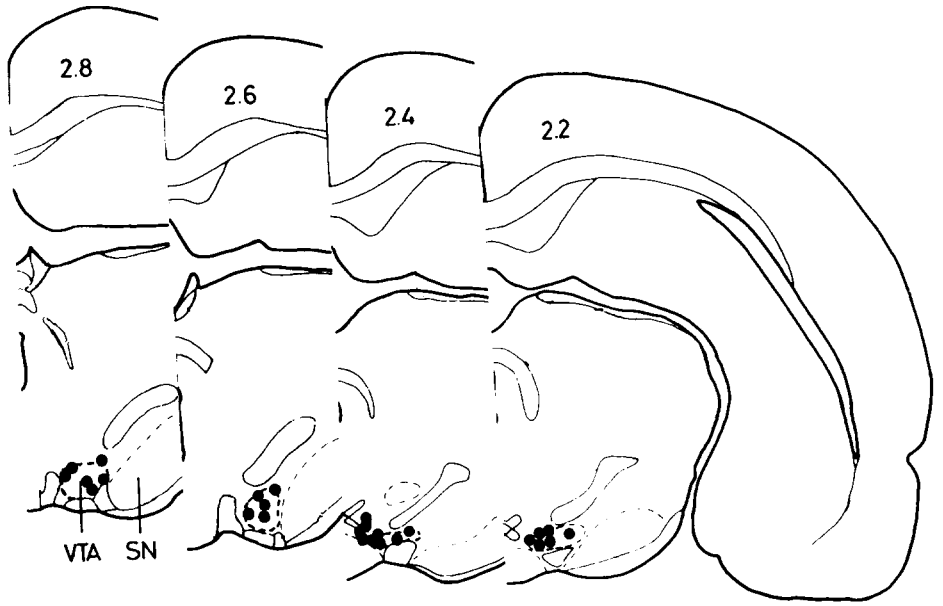

FIG. 1. Location of the tips of the electrodes as assessed by histological examination of thionin-stained sections of the brains of the experimental rats. Sections have been redrawn after Pellegrino *et al.* [28].

due to its interaction with endogenous opioid systems, although the available data are not consistent in this respect [3, 35, 42]. Esposito *et al.* [10], who found no influence of naloxone on ICSS behavior, observed that this drug potentiated the increase of threshold observed after the administration of the neuroleptic chlorpromazine (1–2 mg/kg) in rats. This interaction between opioid and dopamine systems with respect to reward is supported by physiological and anatomical data. Opioid receptors and their endogenous ligands are found both in the ventral tegmental area and in the nucleus accumbens [18,29]. Opiates have rewarding properties when administered into the ventral tegmental area [5,40] and influence dopaminergic neuronal activity when applied locally [26,37]. However, to some extent dopamine and opioid reward mechanisms may be separate, as opiate, but not cocaine, self-administration is blocked by naloxone, while neuroleptics hardly influence opiate self-administration in doses that completely abolish responding for cocaine [11,28].

The present experiments were performed to investigate the effects of the neuroleptic haloperidol and of cocaine on ICSS reward. Haloperidol is a potent dopamine receptor antagonist with affinity for pre- as well as for postsynaptic receptors and with marked depressant effects on motor behavior. Cocaine is a drug with strong addictive properties in animals and in man [38]. It blocks the re-uptake of noradrenaline and dopamine in vitro and it enhances the release of catecholamines in vivo. This latter mechanism is probably responsible for its stimulant and addictive properties [25]. In the present experiments the interaction of haloperidol and cocaine with endogenous opioids in ICSS was studied by combined treatment with the opioid antagonist naloxone. Naloxone was administered in a dose of 10 mg/kg in order to block the different types of opioid receptors completely [49]. The ICSS threshold was determined in rats with a response rate-insensitive procedure [42]. This threshold has been shown to be more indicative for reward than response rate. The procedure allows to determine separately the effect of the drugs on response rate. The electrode was placed in the lateral part of the ventral tegmental area. This site was selected because this region with dopamine cell bodies supports ICSS at high response rates and it is thought to be involved in the rewarding effects of opiates [47].

METHOD

Forty male Wistar rats (TNO, Zeist, The Netherlands) weighing 200–250 g, from our own breeding stock, were kept in single transparent cages with free access to tap water and laboratory food. They were implanted with twisted bipolar stainless steel electrodes of 200 μm thickness, insulated except at the cross section at the tip. These were aimed at the ventral tegmental area (coordinates A: 2.6, D: −3.7, L: 1.0, according to De Groot, see [27]), using standard stereotaxic procedures. The rats were trained to press a lever for response contingent intracranial electrical stimulation in a standard Skinner box (Campden Instruments Ltd., UK), equipped with two side by side levers, 14 cm apart. Stimulus trains of 0.5 sec duration were delivered by a digital stimulator (type ST, Janssen Scientific Instruments, Beerse, Belgium) through a spring shielded lead connected to the electrode. Bipolar rectangular pulses with a frequency of 100 Hz were given. Pulse duration and interval between the positive and the negative pulse were 0.5 msec. Experimental control was by standard 24 V relay equipment and a DEC PDP8 computer for data collection. Response acquisition training was given in daily 10 min training sessions, and rats that made at least 20 responses in the 4th training session were used for the experiments. Subsequently, 25 rats were trained to perform a two-lever stimulation rewarded task, in

which a response on one lever, the stimulation lever, was rewarded with a highly rewarding stimulus train (maximal current). After each response the current was decreased by 1% of the maximal current. A response on the other lever, the reset lever, set the current back to maximal. Any time during the session when the stimulation current was lowered, the rat could make a reset response. The stimulation current at the time of reset was recorded and the mean of these reset currents during the 25 min self-stimulation session was calculated and considered as the threshold current of that session. Threshold currents were expressed as percentage of the maximal current for each rat. Maximal currents were adjusted to obtain thresholds of about 80% without treatment and kept constant throughout the experiments. The response rate was calculated from those interresponse intervals at the stimulation lever in which no response on the reset lever was made.

After a stable performance was reached, testing of drugs started. During the tests the weight of the rats was between 350 and 450 g. The rats were given one session a day during 5 consecutive days (Monday to Friday). The first day no injection was given, and no data were recorded. This session was performed to obtain a stable baseline performance on the following test days. On those 4 days (day 2–5) all rats were injected subcutaneously twice, 1 hr and 5 min before the session, respectively. The first injection (1 ml/kg) was either saline (0.9% NaCl) or haloperidol, from a commercially available solution (Haldol, Janssen Pharmaceutica, Beerse, Belgium), diluted with saline to 5, 10, or 15 μg/ml. The next injection (1 ml/kg) was saline or naloxone (Endo Labs), dissolved in saline, 10 mg/ml. On day 2 the animals received saline twice, on day 3 haloperidol and either saline or naloxone, on day 4 twice saline and on day 5 haloperidol in the same dose as on day 3, with either naloxone or saline. Thus, in one week the animals were tested with one dose of haloperidol with and without naloxone, administered in random order and each haloperidol test day was preceded by a day on which two saline injections were administered, to which comparisons were made. At least 4 weeks after the haloperidol experiments, the animals and also some drug naive rats were tested with the combination of cocaine and naloxone, using the same experimental procedure. Cocaine was administered in doses of 5, 10 and 30 mg/kg, the dose of 5 mg/kg subcutaneously, 10 and 30 mg/kg intraperitoneally as the subcutaneous injection of this drug appeared to produce vasoconstriction, leading to local necrosis, skin irritation and possibly slow or incomplete absorption of cocaine.

Histology

After the experiment the rats were decapitated, their brains quickly removed and stored in 10% formalin. The location of the electrode tracts was assessed in frozen sections of 100 μm thickness, stained with thionin.

Data and Statistical Analysis

The threshold data were transformed by an arcsine transformation before statistical testing, to obtain a normal distribution of the results. The effects of drugs on threshold and on response rate were analysed separately by analysis of variance for repeated measures over the 4 days on which data were collected (SPSS MANOVA program). Consecutive tests with different doses of haloperidol or cocaine administered to a rat were considered as separate cases. Pearsons correlation coefficients were calculated for the relation between drug-induced changes of response rate and of threshold within rats. Differences were regarded as significant when the p-value was 0.05 or less.

RESULTS

Histological verification of the electrode sites showed that all electrodes were in the lateral part of the ventral tegmental area, or at the border of the medial forebrain bundle. The location of the electrode sites is shown in Fig. 1. The rats readily learned the self-stimulation procedure and showed a reliable performance after 4 weeks of daily training sessions. The intensity of the stimulation current ranged from 80 to 220 μA and was kept constant for each rat during the experiments.

After saline treatment of rats used in the haloperidol experiment, the mean threshold (±SEM) was 84.1±1.3% of maximal current and the mean response rate was 58.3±2.2/min. The number of animals tested with the different doses were 3, 11 and 9, for 5, 10 and 15 μg/kg of haloperidol, respectively. The threshold and the response rate on the day after drug administration was not different from those on the day before treatment. The data after drug treatment are shown in Fig. 2A and 2B for threshold and response rate, respectively. Analysis of variance showed that haloperidol caused a significant decrease of threshold, $F(1,18)=146.3$, $p<0.001$. The effect of haloperidol was dose-dependent, $F(2,18)=12.8$, $p=0.001$. No significant effect of naloxone was observed, $F(1,18)=1.5$, $p>0.2$, and also no interaction with the dose of haloperidol, $F(2,18)=2.0$, $p>0.1$. The response rate was significantly and dose-dependently decreased after haloperidol, $F(1,18)=65.5$, $p<0.001$ and $F(2,18)=7.0$, $p<0.01$, respectively. Naloxone caused a further decrease of the response rate in the haloperidol-treated rats, $F(1,18)=10.5$, $p<0.01$, but there was no interaction with the dose of haloperidol, $F(2,18)=0.3$, $p>0.5$.

The relation between changes of response rate and threshold in individual rats after drug treatment was analysed. A positive correlation was found after haloperidol treatment compared to the previous saline session, both without naloxone administration ($r=0.51$, $p<0.02$) and in combination with naloxone ($r=0.36$, $p<0.05$). There was also a positive correlation between the effect of naloxone on response rate and on threshold in individual haloperidol-treated rats ($r=0.50$, $p<0.05$).

In the rats treated with cocaine the threshold (±SEM) was 80.8±1.1% of the maximal current under saline conditions, the mean response rate was 56.1±3.2/min. The threshold and the response rate on the day after the administration of cocaine were comparable to that on the day before treatment. The performance of the rats after cocaine and naloxone treatment, expressed as % change in threshold and response rate, are depicted in Fig. 3A and B, respectively. The number of animals tested with the different doses of cocaine were 9, 15 and 15, for 5, 10 and 15 mg/kg, respectively. Cocaine induced a statistically significant decrease of threshold, $F(1,28)=10.5$, $p<0.005$, and this effect was dose-dependent, $F(2,28)=5.0$, $p<0.05$. Although naloxone tended to decrease the effect of cocaine on threshold, no significant effect of naloxone was observed, $F(1,28)=1.2$, $p>0.2$, and also no interaction with the dose of cocaine, $F(2,28)=0.04$, $p>0.5$. The increase of response rate after cocaine was small and just not significant, $F(1,28)=3.72$, $p=0.06$. No interaction with the dose of cocaine was observed, $F(2,28)=0.9$,

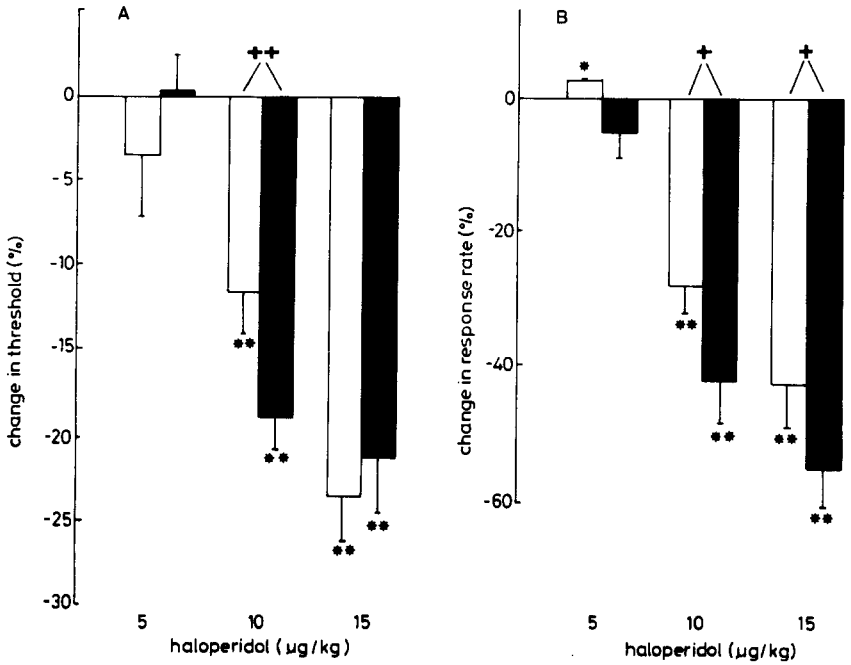

FIG. 2. Performance of rats in the response rate-insensitive threshold determination procedure, after treatment with haloperidol (5, 10 and 15 µg/kg), combined with saline (open column) or naloxone, 10 mg/kg (closed column). Data shown as % change (±SEM) in threshold (A) or response rate (B), as compared to the control session on the previous day, on which vehicle was administered. *=$p<0.05$, **=$p<0.01$, Student's t-test for paired samples, as compared to the control day. +=$p<0.05$, ++=$p<0.02$, as compared to the session without administration of naloxone.

$p>0.4$. In this experiment no effect of naloxone was found on response rate, $F(1,28)=2.0$, $p>0.1$, and also no interaction with the dose of cocaine, $F(2,28)=0.6$, $p>0.5$. Correlations of response rate and threshold within rats after cocaine and naloxone treatment were calculated analogous to the haloperidol experiment. These correlations were not statistically significant.

DISCUSSION

The behavioral threshold procedure applied in the present study allows to determine threshold and response rate separately and concurrently in the same self-stimulation session. In a previous study in which the effect of morphine on self-stimulation was investigated using this procedure, we found that the threshold was dose-dependently lowered, whereas the response rate was also decreased dose-dependently [42]. The threshold change probably reflects the rewarding and facilitatory effects on self-stimulation, while the decrease of response rate reflects the motor depression which is observed in the first hours after the injection of morphine in rats [19,32]. In the present cocaine experiment the rewarding effect of cocaine is reflected in the dose-dependent decrease of threshold. In contrast to morphine, cocaine has stimulatory effects on motor behavior, which is reflected in the increased response rate over control levels. This cocaine effect confirms that in this procedure the threshold reflects the changes in reward, while performance effects of drugs are reflected in response rate.

The dose-dependent effect of haloperidol on response rate in this study confirms other reports on the inhibitory action of neuroleptics on ICSS rate [33, 36, 44, 45]. However, the threshold for ICSS was lowered after haloperidol, indicating an increased reward of the electrical stimulation. This decrease of threshold has not been observed by others who administered neuroleptics in other rate-insensitive experimental procedures [9,50], but instead threshold increases were reported. These contrasting results may be caused by procedural differences [9], or by using pimozide instead of haloperidol [50]. While it cannot be excluded that the threshold changes are an effect of the present procedure, e.g., by perseveration on the stimulation lever, the threshold decrease may be due to blockade of presynaptic dopamine receptors. The doses of haloperidol were quite low and, as haloperidol has both pre- and postsynaptic receptor blocking activity, in the present dose range presynaptic inhibition resulting in an increased dopamine release may have influenced the behavior of the rats more than postsynaptic receptor blockade [1]. Accordingly, intra-accumbal treatment with haloperidol antagonized the hypoactivity induced by low doses and the hyperactivity from high doses of apomorphine—effects probably mediated by pre- and postsynaptically located dopamine receptors, respectively—with ED_{50} values of about 3 and 10 pg, respectively (Van Ree *et al.*, unpublished data). After subcutaneous administration of haloperidol an increased locomotion in some rats was reported [7]. This might explain the observed decrease of self-stimulation threshold after low doses of haloperidol.

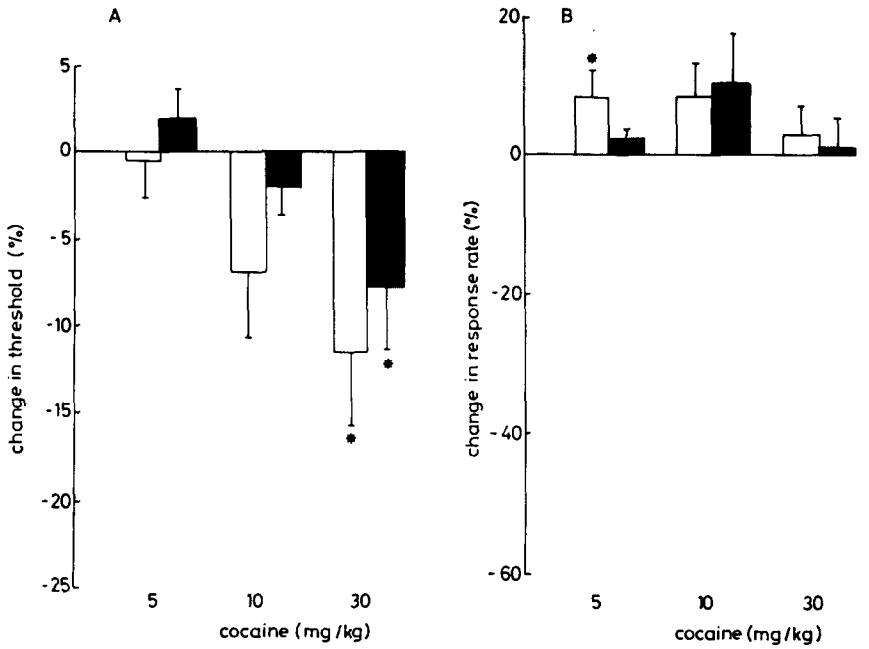

FIG. 3. Performance of rats in the response rate-insensitive threshold determination procedure, after treatment with cocaine (5, 10 and 15 mg/kg), combined with saline (open column) or naloxone, 10 mg/kg (closed column). Data shown as % change (±SEM) in threshold (A) or response rate (B), as compared to the control session on the previous day, on which vehicle was administered. *=$p<0.05$, Student's t-test for paired samples, as compared to the control day.

Also, a small increase of self-stimulation rate was found only after small doses of haloperidol, but not after some other neuroleptics [24]. Such a balance between pre- and postsynaptic inhibition of dopamine receptors may also underly the finding that rats do self-administer haloperidol but only in a narrow dose range (1–2 μg/injection) [16]. Others, however, could not reproduce the latter finding in their strains of rat [48]. The highest dose of haloperidol, 15 μg/kg in the present experiment, clearly disturbed motor behavior and as an almost complete block of motor behavior was observed when higher doses were tested in pilot experiments, these could not be investigated in this procedure. The rats used in our experiment apparently are very sensitive to the motor depression induced by haloperidol.

In the haloperidol-treated rats there was a significant correlation between the decrease of response rate and the increase of reward, as measured by threshold changes. Thus, although animals differ individually in their response to haloperidol, those that are more sensitive for the rate decrease also show more decrease of threshold after haloperidol. This suggests that response rate is in a comparable way sensitive for haloperidol as the mechanism that causes an increase of reward as shown by the decrease of threshold. It may be that the threshold changes in rats determined with the present procedure are caused by changes in responding, because the behavioral threshold method is not completely independent of response rate. However, the lack of correlation between changes in response rate and in threshold in the cocaine experiment does not support this suggestion.

Cocaine dose-dependently lowered the threshold for ICSS and, although not significantly, increased the response rate. Because the response rate in the present procedure is high— about half of the total session time the stimulator is active—rate increasing effects can hardly be detected. The lowered threshold indicates that the stimulation current is perceived as more rewarding by the rats after the treatment with cocaine. These effects agree with other data on the rewarding effects of cocaine. Self-administration and place preference studies and procedures of self-stimulation that differ from the present study showed that cocaine has strong rewarding and motor stimulant effects [31,34]. Rewarding effects of cocaine can be blocked specifically by neuroleptics and are most likely due to interaction with dopamine systems in the brain [2].

The response rate of the haloperidol-treated rats was reduced by naloxone. Since this effect was independent of the dose of haloperidol, it is likely caused by naloxone per se, as observed in a previous experiment without haloperidol treatment [42]. The threshold tended to be lower after treatment with naloxone, especially after 10 μg/kg of haloperidol (Fig. 2), but this effect was not statistically significant when tested using analysis of variance for all doses. No effect of naloxone on the response rate of cocaine-treated rats was observed. While naloxone has been reported to reduce the threshold decrease after the administration of cocaine or amphetamine to rats [20], this was not confirmed in the present study. From other experiments it appeared that naloxone has quite complex influences on responding for ICSS [46]. We have previously observed that naloxone affects self-stimulation in unexperienced animals, especially during acquisition of ICSS behavior, more than that in experienced rats [43]. This mechanism might have influenced the differ-

ence in effects of naloxone in haloperidol and in cocaine-treated rats. It is more likely, however, that an effect of naloxone on response rate is present in combination with haloperidol and not in combination with cocaine because rats with a depressed response rate after haloperidol are more affected in their performance by naloxone than rats receiving cocaine, where performance may be stimulated to a ceiling level. This bias might be misinterpreted as an interaction between naloxone and neuroleptics at the level of central reward mechanisms [10].

From the present experiments we conclude that there is no interaction between the changes in reward by cocaine or haloperidol and the blockade of endogenous opioid receptors by naloxone. Thus, at least in our rats having experience with ICSS, the catecholamine-related reward is probably independent of endorphin systems. Separate mechanisms of opioid and catecholamine reward may therefore exist, although a modulation of dopamine reward mechanisms by opioids can not yet be excluded.

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