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Nociceptin inhibits acquisition of amphetamine-induced place preference and sensitization to stereotypy in rats

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Abstract

Nociceptin (also called orphanin FQ), a 17-amino-acid peptide, is the natural ligand of the nociceptin opioid peptide (NOP) receptor. This peptide shows similarities, in its structure, to opioid peptides, mainly to dynorphin A. However, unlike opioid peptides, it does not produce a conditioned place preference or aversion but inhibits rewarding effect of drugs of abuse. The present study was designed to examine the ability of nociceptin to block the acquisition of amphetamine-induced place preference, and the development of amphetamine-induced sensitization to stereotypy in rats. Our experiments indicated that repeated administration of nociceptin at increasing doses during conditioning significantly attenuated the reinforcing effect of amphetamine in conditioned place preference paradigm. Nociceptin did not change the acute effect of amphetamine-induced stereotypy but prevented the development of sensitization to stereotypy measured on the challenge day. Our results suggest the involvement of nociceptin in long-lasting neuronal adaptation after repeated amphetamine treatment.

Keywords: Nociceptin; Amphetamine; Conditioned place preference; Sensitization; Stereotypy; (Rat)

1. Introduction

Repeated administration of psychostimulants (e.g. cocaine, amphetamine) results in a progressive augmentation of their stimulatory effects, a phenomenon referred to as sensitization (Kalivas and Stewart, 1991). This phenomenon, which can persist for weeks or months following the cessation of drug treatment, has been implicated in drug-craving and reinstatement of compulsive drug-seeking behavior (Robinson and Berridge, 1993). Rewarding effect of drug is thought to be associated with a feeling of "euphoria" that may also lead to compulsive drug-seeking and taking in humans. Conditioned place preference paradigm is an animal model for evaluation of the reward produced by drugs of abuse (Tzschentke, 1998; Schechter and Calcagnetti, 1993, 1998; Carr et al., 1989). Both these animal models underlay many aspects of drug addiction and craving in humans.

The rewarding and psychomotor-stimulating effects of cocaine and amphetamine seem to be associated with the increase in dopaminergic and glutamatergic transmission in mesolimbic corticostriatal pathways (Wolf, 1998; Pierce and Kalivas, 1997). These neurotransmitters are also involved in the development of increased sensitivity to psychostimulants after repeated exposure to the drug (e.g. behavioral sensitization) (Karler et al., 1994, 1995).

Our previous studies have demonstrated a suppressive effect of centrally administered nociceptin, the natural ligand of the G-protein-coupled NOP receptor on the expression of cocaine-induced conditioned place preference in rats (Kotlinska et al., 2002). Nociceptin, despite the structural similarity with dynorphin A (Meunier et al., 1995; Reinscheid et al., 1995), does not bind to the opioid receptors, and its pharmacological effects are not sensitive to naloxone treatment (Jenck et al., 2000). However, in contrast to opioids, nociceptin elicits hyperalgesia rather than analgesia when administered at a supraspinal site and,

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furthermore, it affects feeding, learning, and memory, anxiety, and vegetative functions (for review, see Mogil and Pasternak, 2001). One aspect in which the classical opioid and NOP receptors resemble each other is that they occur presynaptically on a variety of neurons where they cause inhibition of release of a respective neurotransmitter (Schlicker and Morari, 2000).

The NOP receptors (Mollereau et al., 1994) and nociceptin-like immunoreactivity are widely distributed in the brain (Anton et al., 1996; Peluso et al., 1998), particularly in areas involved in motivational and emotional behaviors. Unlike opioid peptides, nociceptin does not produce a conditioned place preference or aversion (Devine et al., 1996a) but inhibits rewarding effect of drugs of abuse (Ciccocioppo et al., 2000a,b). The aim of present study was to investigate the influence of nociceptin on the acquisition of amphetamine-induced place preference and the acquisition of amphetamine-induced sensitization to stereotypy in rats.

2. Materials and methods

2.1. Subjects and surgery

Male Wistar rats (220–250 g, Gorzkowska, Warszawa, Poland) were chosen as the strain sensitive to rewarding effects of drugs (Bardo et al., 1995). The animals were housed six per cage with standard food (Bacutil-Motycz, Poland) and water ad libitum. The animals were kept under a 12:12-h light–dark cycle and were adapted to the laboratory conditions for at least 1 week. The rats were handled once a day for 5 days before the beginning of the experiment. At least 5 days before the experiments, the animals were prepared for intracerebroventricular (i.c.v.) injections with the aid of a stereotaxic apparatus, under pentobarbital (30 mg/kg, i.p.) anesthesia. As cannula patency was achieved in our previous experiments based on the atlas König and Klippel (1963), in the present study, the skull was exposed and a guide cannula (internal diameter 0.39 mm; outside diameter 0.71 mm, Milanowek, Poland) was implanted into the right lateral ventricle, using the following coordinates: 1.5 mm lateral, 1.0 mm caudal, and 3.5 mm ventral from bregma. The correctness of the i.c.v. injections was verified histologically after experiments using cresyl violet. The results obtained from rats with incorrect cannula placements were rejected. The experiments were carried out according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals, and to the European Community Council Directive for Care and Use of Laboratory Animals.

2.2. The conditioned place preference procedure

The conditioned place preference procedure (biased design) was similar to those used in previous experiments (Kotlinska et al., 2002) and carried out according to the method described by Bespalov et al. (1994) and Del Pozo et al. (1996). The biased design is still one of the procedures commonly used by other authors alternatively to unbiased (Zarrindast et al., 2003; Ren et al., 2002; Tzschentke, 1998).

The apparatus to carry out the conditioned place preference procedure consists of six rectangular boxes (60 × 35 × 30 cm), each one divided into three compartments (25 × 35 cm) separated by removable guillotine doors from a small central gray area (10 × 10 cm). The walls of the two large compartments differed in color, one having black walls, while the walls of the other one were painted white. The boxes were kept in a soundproof room with a neutral masking noise and with a dim 40 lx illumination.

The conditioned place preference schedule consisted of a pre-testing phase (1 day), a conditioning phase (4 days) and testing phase (1 day). During the pre-testing phase, the baseline preference of rats was determined. Each rat was placed in the central gray area, the guillotine doors were raised and each rat was allowed to move freely for 15 min between three compartments of the boxes. The time spent by each animal in the two large compartments was recorded. Preliminary data from our laboratory indicated that naïve rats spend more time in the black compartment than in the white one, when given free-choice access to the entire apparatus for 15 min. Thus, to establish conditioning, we paired amphetamine (1 mg/kg) with the initially nonpreferred white compartment (drug-associated). Control rats received an i.c.v. and an intraperitoneal (i.p.) injection of saline before their exposure to the white or black compartment. Nociceptin was given i.c.v. immediately before i.p. injection of amphetamine during conditioning phase. The doses of nociceptin were chosen on the base of our previous experiments (Kotlinska et al., 2002) and were doubled every day (5, 10, 20 and 40 nmol) for 4 days of the conditioning phase, according to the generally accepted procedure used by Lutfy et al. (2002). This was performed because of the developing tolerance to nociceptin (Lutfy et al., 1999; Devine et al., 1996b). During this phase, the rats were injected with saline or nociceptin and confined to the black (preferred) compartment for 30 min. After at least 6 h, the rats received nociceptin and amphetamine and were placed in the white (drug-associated) compartment for 30 min. This conditioning period consisted of two 30-min sessions daily for 4 consecutive days. Changes in place preference were measured drug-free on day 5 (testing phase). During this phase, the guillotine doors were raised. Rats were placed in the tunnel in the central part of the apparatus, and the time spent by each animal in the white compartment was recorded for 15 min.

2.3. Procedure of sensitization to stereotypy

The influence of nociceptin on the acquisition of sensitization to stereotyped behaviors induced by systemic, subcutaneous (s.c.) injection of amphetamine (5 mg/kg)

was investigated. The sensitization was developed during 5 consecutive days. Every day, animals received one injection of nociceptin or saline (i.c.v.) prior to amphetamine (5 mg/kg, s.c.) or saline alone (control group). The dose of nociceptin (5, 10, 20, 30 and 40 nmol) was increased every day during the development of sensitization. To detect the effect of sensitization, all groups of rats (saline–saline; saline–amphetamine; nociceptin–amphetamine and nociceptin–saline) were challenged with amphetamine (5 mg/kg, s.c.) 7 days after the last injection (i.e. on 12th day). Stereotyped behavior was evaluated (in special cages) for each rat on the 1st and 12th days of experiment, according to the four-point scale of Costall et al. (1972):

1. Discontinuous sniffing, periodic exploratory behavior,
2. Continuous sniffing, periodic exploratory behavior,
3. Continuous sniffing, discontinuous biting, gnawing or licking,
4. Continuous biting, gnawing or licking, no exploratory behavior.

Stereotypy ratings were started immediately after the amphetamine injection and recorded in 15-min epochs for 1 h by two independent experimenters who were unaware of a treatment that an animal received.

2.4. Locomotor activity

Locomotor activity of individual rats was recorded using a photocell apparatus (square cages, 40 cm a side, Opto-Varimex-3, Columbus Instruments, Columbus, USA). The animals were placed individually into Plexiglas boxes, which were situated in a sound-attenuated room equipped with two rows of 15 infrared light-sensitive photocells each, located 45 and 100 mm above the floor. Before the test, the rats were injected with nociceptin (10 or 30 nmol, i.c.v.) or saline, prior to amphetamine (1 mg/kg, s.c.) or saline (controls) and then they were placed in the Plexiglas boxes. The horizontal activity was recorded for a total period of 60 min. A few days before experiment, the rats were prepared for i.c.v. injection according to the method described above (for place preference or sensitization).

2.5. Drugs

D-Amphetamine sulfate (Sigma, St. Louis, MO, USA) was dissolved in saline and injected i.p. Nociceptin (1–17) was synthesized by the Fmoc (9-fluorenylmethoxycarbonyl) chemistry on a solid-phase support. The purity of the peptide was greater than 98% and was tested by high-pressure liquid chromatography and electrospray ionization mass spectrometry. The peptide was dissolved in physiological saline (0.9% NaCl) and injected in a volume of 5 μl/rat, i.c.v. The volume was injected for 30 s using the Hamilton syringe (10 μl) and 30 cm catheter that enabled free movements of animals while the substance was injected. Pentobarbital (Vetbutal) was obtained from Biowet (Pulawy, Poland).

2.6. Data analysis

The statistical significance of drug effects in conditioned place preference paradigm and locomotor activity were assessed by the analysis of variance (one-way ANOVA), and the significance of a difference between individual groups was determined by a Tukey–Kramer test. Stereotypy data were analyzed using Kruskal–Wallis test at each time of observation to determine when a significant difference was observed. Mann–Whitney *U*-test was used to determine which group differed from others. The rationale for the application of both these tests was based on the data obtained in similar experiments by Abekawa et al. (2002). Data are expressed as means (± S.E.M.).

3. Results

3.1. Effect of nociceptin on the acquisition of conditioned place preference induced by amphetamine

On the pre-conditioning test day, the rats spent significantly more time in the black compartment (>480 s) than in the white compartment (<60 s). The side preference was not statistically different between groups. The natural preferences of rats were not changed by saline injection during conditioning sessions.

The data were expressed as a score, i.e. testing minus pre-testing time (in seconds) spent in a drug-associated (white) compartment. One-way ANOVA revealed significant differences between groups [$F(3,23)=6.29$, $P<0.01$] in the conditioned place preference paradigm during the testing phase. Post hoc analysis showed that chronic administration of amphetamine during conditioning phase induced a significant place preference in the testing phase ($P<0.01$, comparing saline–saline vs. saline–amphetamine groups). Nociceptin administration at increasing doses (started at the dose of 5 nmol and doubled on day 2 and again on days 3 and 4 of conditioning phase) significantly attenuated the reinforcing effect of amphetamine ($P<0.05$, comparing nociceptin–amphetamine vs. saline–amphetamine groups). Nociceptin given alone at increasing doses during conditioning phase did not change the time spent by rats in the drug-associated compartment during the test day, in comparison with control (saline–saline) animals (Fig. 1).

3.2. Effect of nociceptin on the acquisition of sensitization to stereotypy induced by amphetamine

Visual observation of stereotypy was conducted by two observers, one of them was unaware of the treatment

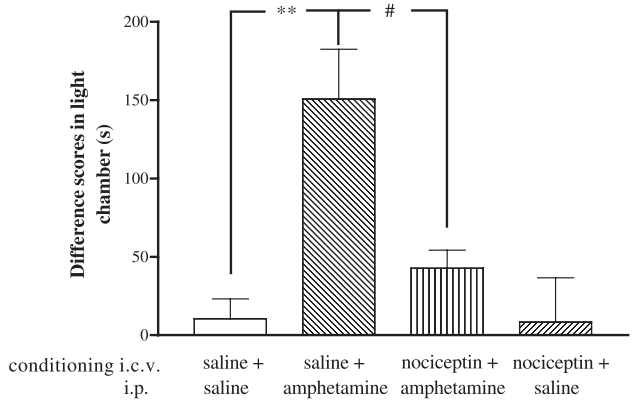

Fig. 1. Effect of nociceptin on the acquisition of amphetamine-induced conditioned place preference. Changes in place preference were measured drug-free on day 5. Scores were calculated as a difference (in seconds) between testing and pre-testing time spent in the drug-associated compartment. Results were analyzed using one-way analysis of variance (ANOVA); post hoc individual comparisons were made using Tukey–Kramer test. $^{**}P<0.01$ vs. saline-treated group; $^{\#}P<0.05$ vs. amphetamine-treated group; $n=8$.

conditions. In most cases, the two observers gave the same score (correlation ratio $r>0.9$). Each animal was assigned, every 15 min, a rating score of 0–4, according to the scale mentioned above.

Fig. 2 shows the stereotypy rating scores induced by a single (1st day) systemic injection of amphetamine (5 mg/kg, sc) given immediately after the i.c.v. pretreatment with nociceptin (5 nmol) or saline. Kruskal–Wallis test indicates significant differences between the groups between 15th and 60th min of observation ($P<0.01$). Mann–Whitney *U*-test revealed that there were no significant differences between nociceptin–amphetamine and saline–amphetamine groups.

Day 12 shows stereotypy rating score induced by a challenge injection of amphetamine (5 mg/kg) on 7th day (12th day of experiment), after the last amphetamine treatment (5 mg/kg, once daily, for 5 days). Kruskal–Wallis test indicated a significant difference between 30th and 45th min ($P<0.05$). Mann–Whitney *U*-test revealed that rating score of stereotypy of the amphetamine–saline group was higher than the control (saline–saline) between 30th and 45th min ($P<0.05$). The stereotypy of amphetamine–saline group was also higher on the 12th day than on the 1st day of experiment ($P<0.05$). I.c.v. pretreatment with nociceptin (at increasing doses from 5 to 40 nmol, for 5 days) significantly attenuated the acquisition of amphetamine-induced sensitization to stereotypy ($P<0.01$). Chronic injection of nociceptin alone at increasing doses (5–40 nmol) for 5 days did not change the score of the amphetamine-induced stereotypy (5 mg/kg) on the challenge day, as compared to saline group (Fig. 2).

3.3. Effect of nociceptin on the amphetamine-induced hyperlocomotor activity in rats

Locomotor activity of rats was measured as horizontal activity, and is shown in Fig. 3 as mean ± S.E.M. One-way ANOVA revealed a significant difference between groups [$F(3, 24)=23.36$, $P<0.001$]. Amphetamine, at a dose of 1 mg/kg, s.c., produced a significant increase of horizontal activity (Fig. 3, $P<0.001$). Previous acute injection of nociceptin at the doses of 10 or 30 nmol did not change

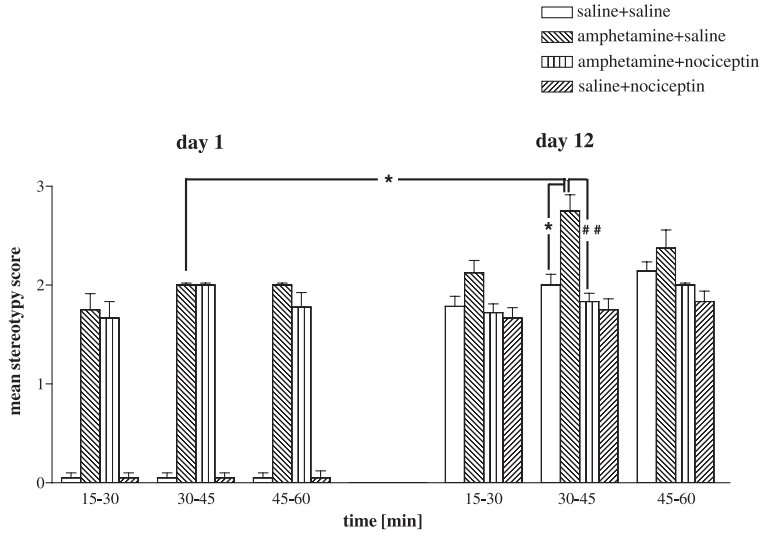

Fig. 2. Effect of nociceptin on the acquisition of amphetamine-induced sensitization to stereotypy in rats. Kruskal–Wallis test indicated a significant difference from 15 to 60 min ($P<0.01$) on the day 1 of experiment. There were no significant differences between nociceptin–amphetamin and saline–amphetamine group (Mann–Whitney *U*-test). On day 12, Kruskal–Wallis test revealed significant differences from 30 to 45 min ($P<0.05$). $^{*}P<0.5$ vs. saline–saline group (on days 12 and 1) and $^{\#\#}P<0.01$ vs. amphetamine–saline group (Mann–Whitney *U*-test). Data are expressed as the mean ± S.E.M.; $n=10$.

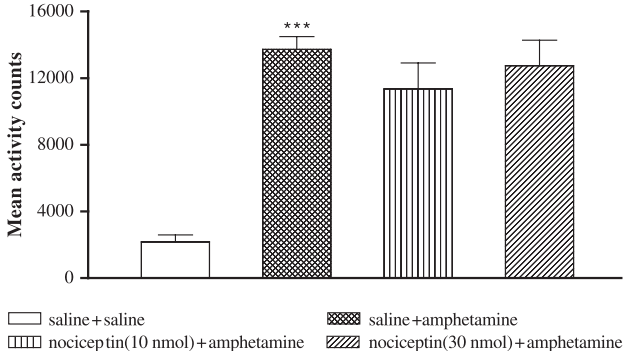

Fig. 3. Effect of nociceptin on the hyperlocomotor activity induced by amphetamine. Locomotor activity was recorded for 60 min. Each value represents mean ± S.E.M. ***$P<0.001$ vs. control group (revealed by the post hoc Tukey–Kramer test); $n=8$.

the hyperlocomotor activity induced by a single amphetamine injection (Fig. 3).

4. Discussion

The main finding of the present study is that the increasing doses of nociceptin given i.c.v. prior to systemic amphetamine administration during conditioned phase of place preference paradigm block the acquisition of amphetamine-induced place preference. Furthermore, chronic injection of nociceptin at the increasing doses, prior to the amphetamine injection, blocks amphetamine sensitization to stereotypy. Single injection of nociceptin (i.e. 5 nmol) does not change the acute amphetamine-induced stereotypy.

A variety of drugs of abuse appear to exert their rewarding effect via activation of a common neuronal substrate (Di Chiara and Imperato, 1988; Koob and Bloom, 1988). In particular, the mesolimbic dopamine system has been implicated in drug-induced reward because drug administration activates this system, and its destruction disrupts the rewarding effect of opiates and stimulants (Smith et al., 1985; Spyraki et al., 1982).

Nociceptin seems to reduce the rewarding properties of drugs such as ethanol (Kuzmin et al., 2003; Ciccocioppo et al., 1999) or morphine in the conditioned place preference paradigm (Ciccocioppo et al., 2000b; Murphy et al., 1999) which was manifested as a significant reduction of the increase of time spent in the drug-paired compartment after conditioning. It has been suggested that nociceptin attenuated place preference to morphine probably by inhibiting its stimulatory effect on mesolimbic dopamine system (Murphy et al., 1999). In fact, i.c.v. injection of nociceptin effectively inhibits dopamine release, (as verified by microdialysis study) in the nucleus accumbens of the rat stimulated by systemically injected morphine (Di Giannuario et al., 1999).

The ability of nociceptin to modulate dopaminergic (Maidment et al., 2002; Norton et al., 2002) and glutamatergic (Meis and Pape, 2001; Nicol et al., 1996) neurotransmission in the central nervous system is well established. The recent data indicate that NOP receptors are expressed in dopamine (Maidment et al., 2002; Norton et al., 2002) cells located in the ventral tegmental area and in the substantia nigra compacta. Moreover, nociceptin mRNA was found largely in nondopaminergic (i.e. γ-aminobutyric acid) neurons (Norton et al., 2002). Our experiments indicated, for the first time, that nociceptin may also attenuate amphetamine-induced conditioned place preference (Fig. 1). Because the rewarding effect of amphetamine is also dependent on stimulation of dopaminergic (Di Chiara and Imperato, 1988) and glutamatergic (Tzschentke and Schmidt, 1998) transmission in mesolimbic structures and because nociceptin not only inhibits the release of dopamine in nucleus accumbens but also inhibits the effects of dopaminergic agonists via postsynaptic action (Lutfy et al., 2001), the mechanism of nociceptin on amphetamine-induced conditioned place preference remains to be clarified.

There are only a few data that nociceptin influence on the development of drug-induced sensitization. Lutfy et al. (2002) indicated that nociceptin blocks the development of sensitization to cocaine-induced locomotor activity in rats. Our study demonstrated, for the first time, that nociceptin is able to inhibit the development of amphetamine-induced sensitization to stereotypy in rats. The dopaminergic stimulus in the striatum is considered to induce stereotypy (Creese and Iverson, 1974). Most studies indicated that stereotypic effect of amphetamine requires not only a functional dopaminergic, but also glutamatergic and γ-aminobutyric acid systems (Karler et al., 1994, 1995), and all three systems are necessary for both the induction and expression of sensitization to stereotypy. Sensitization by the local application of amphetamine or other psychostimulants has only been reported for the ventral tegmental area and the substantia nigra (Vezina and Stewart, 1990; Kalivas and Weber, 1988), but sensitization appears to involve not a site but rather a circuit because the local application of CPP, the NMDA antagonist, or sulpiride, the dopamine antagonist, in either the striatum (Bedingfield et al., 1997) or the cortex can block systemically induced sensitization. In our study, the acute injection of nociceptin (5 nmol) did not affect stereotypy induced by a single injection of amphetamine. The obtained results (Fig. 3) also indicated that an acute injection of nociceptin (10 and 30 nmol) did not change the hyperlocomotion induced by single amphetamine injection in rats. However, nociceptin given prior to amphetamine for 5 days at the daily increased dose (5, 10, 20, 30 and 40 nmol) during the development of sensitization, significantly attenuated the induction of sensitization on the challenge dose of amphetamine. Reports of nociceptin-induced inhibition of glutamate release in the cortex (Nicol et al., 1996), lateral amygdala (Meis and Pape, 2001), and inhibition of dopamine release in the striatum (Flau et al., 2002) are therefore interesting in relation to our findings

and can explain inhibitory effect of nociceptin on the development of amphetamine sensitization.

The results of these experiments may also be interpreted in terms of a learning impairment or a retrieval deficit. In fact, nociceptin has been found to impair hippocampal-dependent spatial learning in mice (Higgins et al., 2002) and rats (Sandin et al., 1997). In vitro studies showed that it inhibits synaptic transmission and long-term potentiation in rat hippocampal slices (Yu and Xie, 1998; Yu et al., 1997). NOP receptor knockout mice show greater learning ability and have better memory retention than the wild-type mice (Noda et al., 2000). Thus, it seems possible that nociceptin can block formation of the learned association between the effects of ethanol (Kuzmin et al., 2003) or amphetamine (as in present study) and environmental cues. This effect may interfere with our results obtained in our experiments.

Taken together, our results suggest the involvement of nociceptin in the mechanism of long-lasting neuronal adaptation after repeated amphetamine treatment. This effect may implicate neuroadaptive changes in brain structures, and functions that ultimately lead to addiction.

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