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Opposite Actions of Oxytocin and Vasopressin in the Development of Cocaine-Induced Behavioral Sensitization in Mice

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SARNYAI, Z., G. SZABÓ, G. L. KOVÁCS, AND G. TELEGDY. *Opposite actions of oxytocin and vasopressin in the development of cocaine-induced behavioral sensitization in mice.* PHARMACOL BIOCHEM BEHAV 43(2) 491–494, 1992. – Subchronic administration of cocaine induces behavioral sensitization (increasing hypermotility) to a challenge dose of the drug administered 72 h after the cessation of treatment. The effects of repeated administration of the neurohypophyseal hormones oxytocin (OXT) and arginine[8]-vasopressin (AVP) on the development of behavioral sensitization induced by subchronic treatment with cocaine were investigated in mice. Repeated treatment of OXT and AVP did not modify the locomotor stimulatory effect of the challenge dose of cocaine in cocaine-naive control animals. OXT in a dose of 0.5 μg (sc) augmented the cocaine-induced behavioral sensitization. In contrast, AVP (0.005–0.5 μg/mouse, sc) dose dependently attenuated the development of sensitization to the hypermotility-inducing effect of cocaine. The results suggest that the behavioral sensitization induced by cocaine can be modulated in opposite directions by neurohypophyseal hormones.

Cocaine Behavioral sensitization Oxytocin Vasopressin Hypermotility

IT has recently been demonstrated that some of the effects of the widely used psychostimulant drug cocaine could be modified by neurohypophyseal hormones arginine[8]-vasopressin (AVP) and oxytocin (OXT) in experimental animals. AVP and related peptides inhibit the acquisition of intravenous self-administration of cocaine in rats (27). Cocaine-induced locomotor hyperactivity could be decreased by the pretreatment of OXT but not by AVP in mice (8,22). The effect of OXT and the possible role of basal forebrain OXTergic binding sites were demonstrated in the inhibition of cocaine-induced stereotyped sniffing behavior (21). OXT impairs the development of behavioral tolerance to cocaine in rats (20). Both acute and repeated treatment of cocaine modify the levels of neurohypophyseal hormones in the hypothalamus and in different limbic-forebrain structures in rats (23).

Repeated, intermittent administration of cocaine produces an enduring enhancement in the behavioral response (e.g., stereotyped behavior, locomotor hyperactivity) elicited by subsequent exposure to cocaine (6,17). This phenomenon is known as behavioral sensitization, which is thought to be a useful animal model for studying certain aspects of the progressive pathology of a number of psychiatric disorders, including manic depressive disorder and schizophrenia (19).

Only one data was available for the role of AVP in cocaine-induced behavioral sensitization in rats (15). However, in the present study we aimed to investigate the effects of neurohypophyseal hormones on the development of behavioral sensitization induced by cocaine in mice.

METHOD

Male mice of an inbred CFLP strain (LATI, Gödöllö, Hungary) weighing 25–30 g were used. Food and water were provided ad lib. Animals were maintained on a 12 L : 12 D cycle, the light phase beginning at 7:00 a.m. Experiments were performed between 10:00 a.m. and 4:00 p.m. Mice were treated subchronically with either saline (sal) or cocaine (coc) (7.5 mg/kg, SC) twice a day for 5 days. Animals were tested for locomotor activity with a challenge dose of cocaine (7.5 mg/kg, SC) 3 days after cessation of the subchronic treatment. OXT, AVP, and saline were administered 1 h prior to cocaine or saline injections, except on the test day. The following groups were used throughout the experiment: The sal + sal + sal group received a subchronic treatment of saline, saline pretreatment 60 min prior to each repeated saline treatment, and a challenge dose of saline administered on the test day (drug-naive control); sal + sal + coc-treated animals (cocaine control) received a pretreatment of saline prior to

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subchronic saline treatment and then cocaine on the test day; sal + coc + coc-treated mice (sensitized control) were administered saline pretreatment 60 min prior to subchronic treatment of cocaine and a challenge dose of cocaine on the test day; OXT/AVP + sal + sal and OXT/AVP + sal + coc groups received peptide pretreatment 60 min prior to subchronic saline treatment and were administered saline or cocaine on the test day; OXT/AVP + coc + coc-treated animals received a peptide pretreatment prior to subchronic cocaine administration and the challenge dose of cocaine was injected on the test day. Locomotor hyperactivity was evaluated in an open-field situation. On the test day, animals were placed into an open-field box (35 × 35 × 50 cm, divided into 49 identical squares). After a 5-min habituation period, an initial testing session was undertaken, which lasted for 1 min and provided data on the baseline open-field crossing activity prior to administration of a challenge dose of cocaine. Ten minutes after injection of a test dose of cocaine (7.5 mg/kg, SC), animals were returned to the box for another 5-min period and the number of total crossings was registered visually for 1 min. Counts of locomotor activity were made each time the animal entered a new square with more than half the body length. Locomotor activity was expressed as a percentage of baseline open-field activity. The investigator was not aware of the sequence of treatment at the time of the open-field study.

Data were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's studentized range test for paired comparison. A probability level of 0.05 was accepted as indicating significant differences.

Cocaine HCl (E. Merck, Darmstadt, Germany) was dissolved in physiological saline and injected in a dose of 7.5 mg/kg. Synthetic OXT and AVP (Sigma Chemical Co., St. Louis, MO) were dissolved in saline and injected in doses of 0.005, 0.05, or 0.5 μg/mouse SC. Control animals received an equivalent amount of saline.

RESULTS

The effect of OXT on the development of behavioral sensitization to cocaine is shown in Table 1. A single dose of cocaine (7.5 mg/kg) caused a significant, $F(8, 149) = 18.33$, $p < 0.0001$, locomotor hyperactivity as compared to the saline (sal + sal + sal) group (Tables 1 and 2). In animals subjected to previous subchronic cocaine injections, a challenge dose of cocaine induced locomotor hyperactivity as compared to the sal + sal + coc group ($p < 0.05$), indicating the development of behavioral sensitization to cocaine (Tables 1 and 2). Repeated treatment with different doses of OXT (OXT + sal + coc) did not interfere with the effect of the test dose of cocaine (sal + sal + coc) ($p > 0.05$). The cocaine-induced sensitization was facilitated only by the highest dose (0.5 μg/mouse) of OXT ($p < 0.05$).

TABLE 1

EFFECT OF OXT ON THE DEVELOPMENT OF BEHAVIORAL SENSITIZATION INDUCED BY COCAINE IN MICE

Treatment	No. of Animals	Locomotor Activity*
sal + sal + sal	25	65.4 ± 3.7
sal + sal + coc	27	158.6 ± 12.9†
sal + coc + coc	31	220.4 ± 14.3‡
0.005 μg OXT + sal + coc	10	192.5 ± 15.1
0.05 μg OXT + sal + coc	14	171.4 ± 10.5
0.5 μg OXT + sal + coc	9	206.4 ± 11.6
0.005 μg OXT + coc + coc	10	232.4 ± 33.8
0.05 μg OXT + coc + coc	20	236.1 ± 14.8
0.5 μg OXT + coc + coc	10	309.4 ± 38.9§

Statistical analysis was performed by ANOVA, followed by Tukey's test. $F(8, 149) = 18.33$, $p < 0.0001$, sal, 0.9% NaCl; coc, 7.5 mg/kg cocaine SC.

*Mean ± SEM number of crossings as a percentage of the baseline activity.

†$p < 0.05$ v. sal + sal + sal group.

‡$p < 0.05$ v. sal + sal + coc group.

§$p < 0.05$ v. sal + coc + coc group.

TABLE 2

EFFECT OF AVP ON THE DEVELOPMENT OF BEHAVIORAL SENSITIZATION INDUCED BY COCAINE IN MICE

Treatment	No. of Animals	Locomotor Activity*
sal + sal + sal	28	62.4 ± 3.1
sal + sal + coc	21	155.2 ± 17.8†
sal + coc + coc	17	221.4 ± 23.6‡
0.005 μg AVP + sal + coc	13	150.9 ± 13.3
0.05 μg AVP + sal + coc	12	126.6 ± 17.1
0.5 μg AVP + sal + coc	15	196.9 ± 12.6
0.005 μg AVP + coc + coc	17	138.3 ± 16.9§
0.05 μg AVP + coc + coc	16	154.8 ± 18.8§
0.5 μg AVP + coc + coc	16	152.6 ± 19.3§

Abbreviations: see Table 1. $F(8, 146) = 10.23$, $p < 0.0001$.

*Mean ± SEM number of crossings as a percentage of the baseline activity.

†$p < 0.05$ vs. sal + sal + sal group.

‡$p < 0.05$ vs. sal + sal + coc group.

§$p < 0.05$ vs. sal + coc + coc group.

Table 2 shows the effect of AVP on cocaine-induced sensitization, $F(8, 146) = 10.30$, $p < 0.0001$. None of the AVP doses (AVP + sal + coc) affected the motor-activating effect of a single, challenge dose of cocaine ($p > 0.05$). All investigated doses of AVP (0.005, 0.05, and 0.5 μg/mouse) inhibited the behavioral sensitization induced by repeated administration of cocaine.

DISCUSSION

Repeated, intermittent administration of cocaine induced the development of behavioral sensitization 72 h after the cessation of subchronic treatment. Repeated pretreatments with OXT facilitated the cocaine-induced sensitization. Different doses of AVP administered under the same conditions inhibited the development of sensitization.

The experimental model for the induction of behavioral hypersensitivity to cocaine was used according to Riffee et al. (17) and we also demonstrated the development of sensitization to a challenge dose of cocaine. It might be assumed that the behavioral changes registered on the test day simply reflect the withdrawal state of animals. For the exclusion of withdrawal signs, the basal locomotor activity was measured before the treatment with the test dose of cocaine. We found no difference in the basal open-field crossing activity between mice treated subchronically with saline and cocaine (data not shown). During cocaine withdrawal, locomotor hypoactivity was observed in rats (4).

Repeated administration of different doses of OXT (OXT

+ sal + sal) or AVP (AVP + sal + sal) did not itself affect the spontaneous locomotor activity (data not shown) or hyperactivity induced by a single dose of cocaine (Tables 1 and 2) 72 h after the last injection of neurohypophyseal peptide. OXT in all doses investigated displayed a tendency to augment the behavioral sensitization, but only the effect of the highest dose of OXT proved statistically significant. In contrast, all doses of AVP blocked the behavioral sensitization induced by cocaine. The dissociation in the behavioral effects of these two structurally related neuropeptides has been extensively demonstrated in other experimental paradigms. AVP facilitated, whereas OXT inhibited, learning and memory processes in rats (11) and humans (7). OXT and AVP exhibited opposite effects on the hippocampal theta rhythm (3) and on narcotic tolerance and dependence (9). Similar differences were registered in the present study. Our results of the inhibitory action of AVP in cocaine-induced behavioral sensitization seems to be opposite to the data of Post et al. (15), who demonstrated an impaired behavioral sensitization to cocaine in homozygote vasopressin-deficient Brattleboro rats compared to heterozygote litter-mate controls. In our present study, mice with normal vasopressin secretion were used and the pharmacological doses of AVP were administered in a different treatment schedule, which might explain the contradiction in these results. In addition, as Post and coworkers (15) hypothesized, "... it cannot be completely ruled out that vasopressin replacement also normalizes the associated biochemical abnormalities which could be involved in the sensitization process."

An understanding of the mechanisms involved in the mediation of the effects of OXT and AVP on cocaine-induced sensitization requires further experiments. AVP increased the disappearance of dopamine in the nucleus accumbens in α-MPT-treated rats (10,26,28). In contrast, OXT decreased the utilization of dopamine in the striatum (25) and nucleus accumbens (22). OXT potentiated the behavioral hypoactivity induced by a low dose of apomorphine, suggesting that the peptide interferes with specific dopaminergic receptor systems, presumably located presynaptically in the nucleus accumbens area (29). On the other hand, it is well known that the behavioral effects of cocaine are manifested through the stimulation of dopaminergic neurotransmission in the mesolimbic and nigrostriatal dopaminergic terminal regions by inhibition of dopamine uptake (18) and dopamine release processes (24). It has also been shown that the effect of cocaine on mesolimbic dopamine system is collerated with reinforcement (5,14). Missale et al. (13) reported that subchronic treatment with cocaine induces an increase in accumbens cocaine binding sites linked to the dopamine uptake system. Dopamine binding in the striatum was increased after repeated injections of cocaine (12). Akimoto et al. (1) demonstrated that an elevated striatal dopamine efflux is responsible for the cross-sensitization between cocaine and methamphetamine. Both the increased sensitivity of postsynaptic binding sites for dopamine (6) and presynaptic dopamine-autoreceptor desensitization (2) have been postulated as putative mechanisms of the development of psychomotor stimulant-induced behavioral sensitization.

The above results suggest that the effects of OXT and AVP on the development of sensitization to cocaine may be based upon the modulation of the dopaminergic neurotransmission (22), which was altered during the repeated cocaine treatment. The direct interaction between neurohypophyseal hormones and cocaine binding sites cannot be excluded.

In conclusion, our data show that the neurohypophyseal hormones OXT and AVP act in opposite ways on the development of behavioral sensitization induced by repeated administrations of cocaine. These data extend previous reports on the role of OXT and AVP in adaptive neuronal changes, which may be the biologic basis of drug addiction processes.

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