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Pharmacological Properties of Ceruletide in the Vertical and Horizontal Locomotor Activities of Mice

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ITOH, T., S. MURAI, Y. MASUDA, E. ABE, N. OHKUBO, O. ITSUKAICHI AND S. SHOJI. *Pharmacological properties of ceruletide in the vertical and horizontal locomotor activities of mice.* PHARMACOL BIOCHEM BEHAV 43(2) 571–576, 1992.—To clarify the pharmacological properties of ceruletide (CER) and cholecystokinin-octapeptide (CCK-8) with respect to vertical (VLA) and horizontal (HLA) locomotor activities of mice, effects of pretreatment with CER (0.5, 5, and 50 μg/kg, IP) and CCK-8 (5, 50, and 500 μg/kg, IP) on apomorphine (0.1 mg/kg, SC)- and clonidine (0.1 mg/kg, SC)-induced hypo-VLA and -HLA and on apomorphine (1 mg/kg, SC)-induced hyper-VLA and -HLA were examined. CER and CCK-8 had a dose-dependent inhibitory effect on VLA and HLA in intact mice. Pretreatment with CER had a biphasic effect (increase and decrease) on apomorphine- and clonidine-induced hypo-VLA, as well as an effect on apomorphine-induced hypo-HLA, a decreased effect on clonidine-induced hypo-HLA, and a decreased effect on apomorphine-induced hyper-VLA and -HLA. On the other hand, pretreatment with CCK-8 had no effect on apomorphine- and clonidine-induced hypo-VLA and -HLA and a decreased effect on apomorphine-induced hyper-HLA but not on hyper-VLA. These results suggest that for apomorphine- and clonidine-induced locomotion in mice CER has pharmacological properties different from those of CCK-8.

Vertical and horizontal locomotion Ceruletide CCK-8 Mouse

CHOLECYSTOKININ-octapeptide (CCK-8), related to the gut hormone, has been demonstrated to be widely distributed in mammalian brains (5,10,14,28,36). Recently, it was determined that CCK-8 coexists with dopamine (DA) in the dopaminergic neuron of the mesolimbic areas (6,7,31,32,39) but not in the striatum (15), and that CCK-8 modulates the activity of DA (6,32,34) regardless of the existence of the DA/CCK coexisting neurons (12).

On the other hand, ceruletide (CER), a decapeptide homologous to CCK-8, originally extracted from the skin of the frog, *Hyla caerulea* (2), is known to produce decreased locomotor activity (40,41), palpebral ptosis, and analgesia (41,42), with a reduction in the levels of homovanillic acid and 3,4-dihydroxyacetic acid in the rat brain (24). Furthermore, it was found that in the clinic CER has the long-lasting improvement effect in patients with various chronic schizophrenic symptoms (4,25,26,37) and symptoms of involuntary movement disorders (3,21,27), such as dyskinesia and chorea-like movement.

In general, it is useful in the clinic to clarify the target effect of a drug on the cardinal symptom in a disease because it offers important information for discovering the cardinal symptom in a disease from the mode of reactivity and the availability of the drug. In the present study, with the aim to elucidate the pharmacological properties of CER in locomotor activity the effects of CER on the ambulatory and rearing activities modulated with drugs exerting influence on the dopaminergic and adrenergic nervous systems were examined using mice and compared with those of CCK-8.

METHOD

Animals

Six-week-old male ddY strain mice with weights ranging from 25–28 g, purchased from the Shizuoka Laboratory Animal Center (Japan), were used. Mice were housed in groups of 10 per plastic cage (43.5 × 28.5 × 19.5 cm) in a room with a controlled temperature of 24 ± 2°C, a humidity of 60 ± 5%, and a 12 L:12 D cycle (light 0700–1900 h, dark 1900–0700 h), with free access to standardized food and water. Experiments were conducted between 0900 and 1300 h and mice were used only once in each experiment.

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Drugs

Chemicals were obtained from the following sources: CER was a gift from the Shionogi Research Laboratories (Osaka, Japan). Clonidine HCl was obtained from Japan Boehringer Ingelheim (Kawanishi, Japan), CCK-8 from Peptide Laboratory (Minoo, Japan), and opomorphine HCl from Sigma Chemical Co. (St. Louis, MO). All drugs were dissolved in a sterile saline solution and then injected IP or SC with a volume of 5 ml/kg. An extremely low dose of ascorbic acid was added to an apomorphine solution to prevent its oxidation.

The amount of drugs used was as follows: CER at 0.5, 5, and 50 μg/kg IP; CCK-8 at 5, 50, and 500 μg/kg IP; apomorphine at 0.1 and 1 mg/kg SC; clonidine at 0.1 mg/kg SC.

Measurement of Locomotor Activity

Measurement of locomotor activity in mice was carried out between 0900 and 1300 h using 10 sets of apparatus developed by Itoh et al. (17). The apparatus can divide the activities of each mouse into vertical locomotor activity (VLA) for rearing activity and horizontal locomotor activity (HLA) for ambulatory activity and measure the activities of many mice at the same time. The apparatus consists of a plastic box (16 × 29 × 30 cm), an infrared photo-coupler mounted at a height of 1.8 cm to measure HLA, and nine infrared photo-couplers mounted at a height of 6.5 cm to measure VLA.

Measurement of VLA and HLA was performed during a 20-min period in mice pretreated with an IP injection of CER or CCK-8 30 min prior to SC injection of apomorphine or clonidine. The control group was injected with a sterile saline solution of the same volume as the drug.

Statistics

Data was analyzed by a single-factor analysis of variance (ANOVA) and subsequently with Newman-Keuls method for individual groups.

In all statistical evaluations, $p < 0.05$ was used as the criterion for statistical significance.

RESULTS

Effects of CER and CCK-8 on VLA and HLA

As shown in Fig. 1, CER and CCK-8 dose dependently inhibited both VLA and HLA.

Effects of Pretreatment With CER and CCK-8 on Apomorphine-Induced Hypo-VLA and -HLA.

A low dose (0.1 mg/kg, SC) of apomorphine significantly inhibited both VLA and HLA. For low-dose apomorphine-induced hypo-VLA and -HLA, as shown in Fig. 2, pretreatment with CER showed a significantly increased effect at a dosage of 5 μg/kg and a tendency toward decreased effect at a dosage of 50 μg/kg. On the other hand, pretreatment with CCK-8 exerted no influence on low-dose apomorphine-induced hypo-VLA and -HLA.

Effects of Pretreatment With CER and CCK-8 on Apomorphine-Induced Hyper-VLA and -HLA

A high dose (1 mg/kg, SC) of apomorphine markedly increased both VLA and HLA. For high-dose apomorphine-induced hyper-VLA, as shown in Fig. 3, pretreatment with CER at all dosages showed a decreased effect, while for high-dose apomorphine-induced hyper-HLA pretreatment with CER at 5 μg/kg showed a decreased effect but not at 0.5 and 50 μg/kg. On the other hand, for high-dose apomorphine-induced hyper-HLA pretreatment with CCK-8 at 50 and 500 μg/kg showed a decreased effect, while for high-dose apomorphine-induced hyper-VLA pretreatment with CCK-8 at all doses had no effect.

Effects of Pretreatment With CER and CCK-8 on Clonidine-Induced Hypo-VLA and -HLA

Clonidine (0.1 mg/kg, SC) markedly inhibited both VLA and HLA. For clonidine-induced hypo-VLA, as shown in Fig. 4, pretreatment with CER showed a tendency toward decreased effect at a dosage of 0.5 μg/kg and a significantly

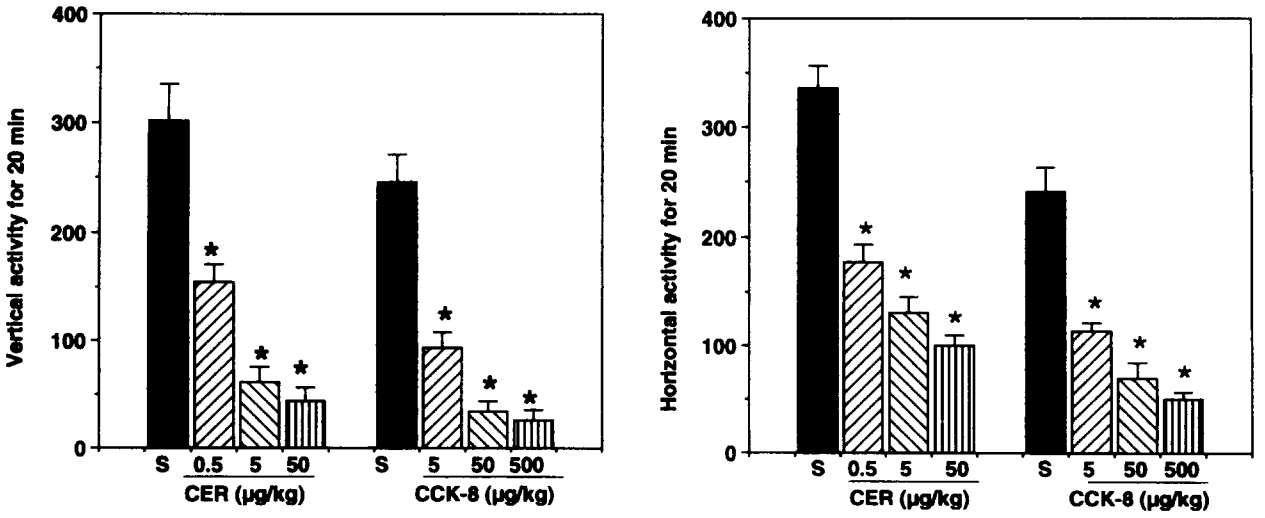

FIG. 1. Effects of CER and CCK-8 on vertical and horizontal locomotor activities in mice. Vertical and horizontal locomotor activities were recorded during a 20-min period 30 min after IP injection of CER and CCK-8. Shown are the means ± SEM ($n = 10$). S, saline. *$p < 0.05$ vs. saline.

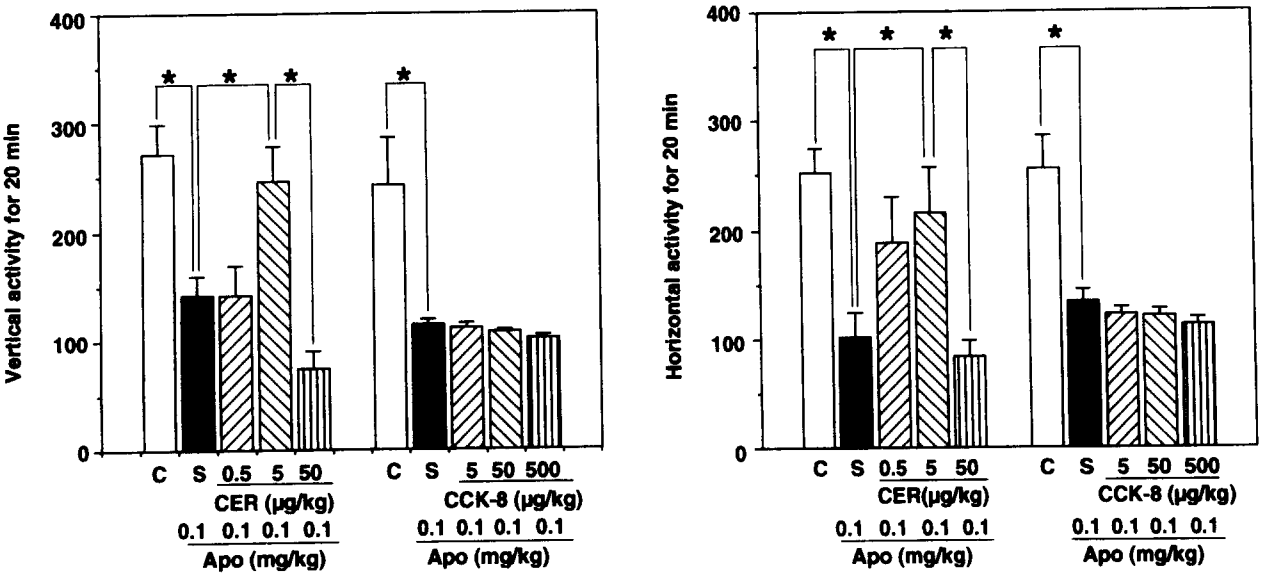

FIG. 2. Effects of CER and CCK-8 on apomorphine-induced hypoactivity in mice. Vertical and horizontal locomotor activities were recorded during a 20-min period immediately after SC injection of 0.1 mg/kg apomorphine. CER and CCK-8 were IP injected 30 min before administration of apomorphine. Shown were the means ± SEM (n = 10). C, control; S, saline; Apo, apomorphine.
*$p < 0.05$ vs. saline-apomorphine group, and between 5 and 50 μg/kg of ceruletide-apomorphine group.

increased effect at a dosage of 5 μg/kg but no effect at 50 μg/kg. For clonidine-induced hypo-HLA, pretreatment with CER showed no effect, as well as for clonidine-induced hypo-VLA. On the other hand, pretreatment with CCK-8 at all dosages had no effect.

DISCUSSION

Recently, it was suggested that CER, a decapeptide homologous to CCK-8, has a central action similar to that of CCK-8 (40,41), especially for neuroleptic-like effects (37). Furthermore, it has been reported that in the clinic there are some cases where CER was effective against symptoms in patients with involuntary-movement disorders, such as tardive dyskinesia and chorea-like movement (3,21,27). Therefore, it is considered important to clarify the pharmacological properties in the behavioral activity of CER, which may have an antidyskinetic action.

In the present study, CER and CCK-8 significantly inhibited both VLA and HLA in intact mice. These results seem to

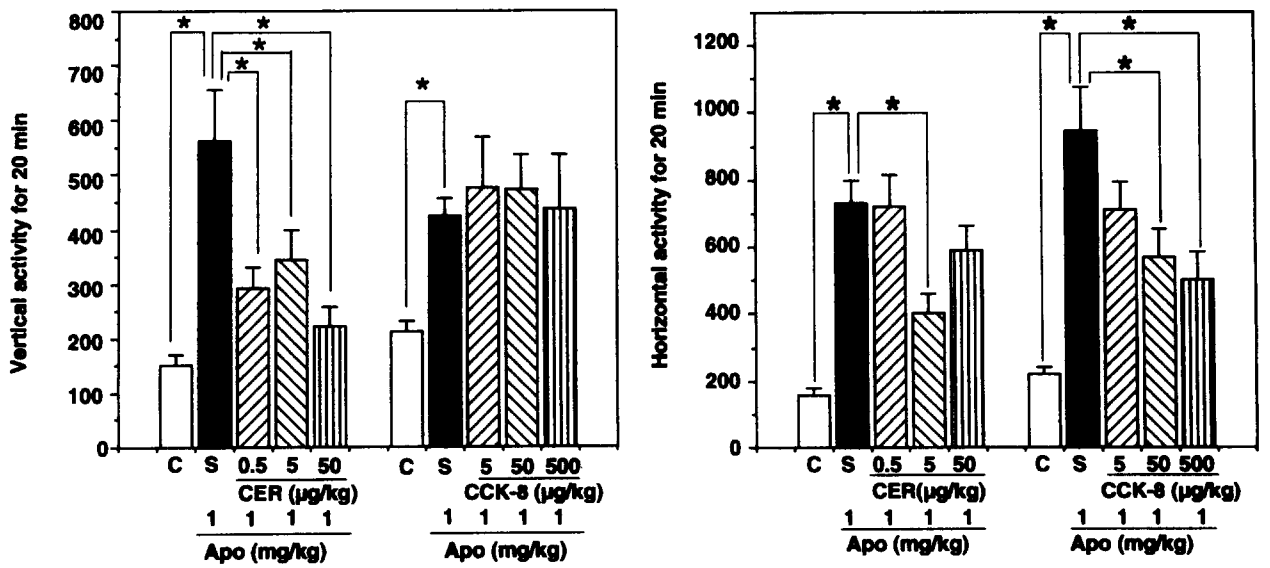

FIG. 3. Effects of CER and CCK-8 on apomorphine-induced hyperactivity in mice. Vertical and horizontal locomotor activities were recorded during a 20-min period immediately after SC injection of 1 mg/kg apomorphine. CER and CCK-8 were IP injected 30 min before administration of apomorphine. Shown are the means ± SEM (n = 10). C, control; S, saline; Apo, apomorphine.
*$p < 0.05$ vs. saline-apomorphine group.

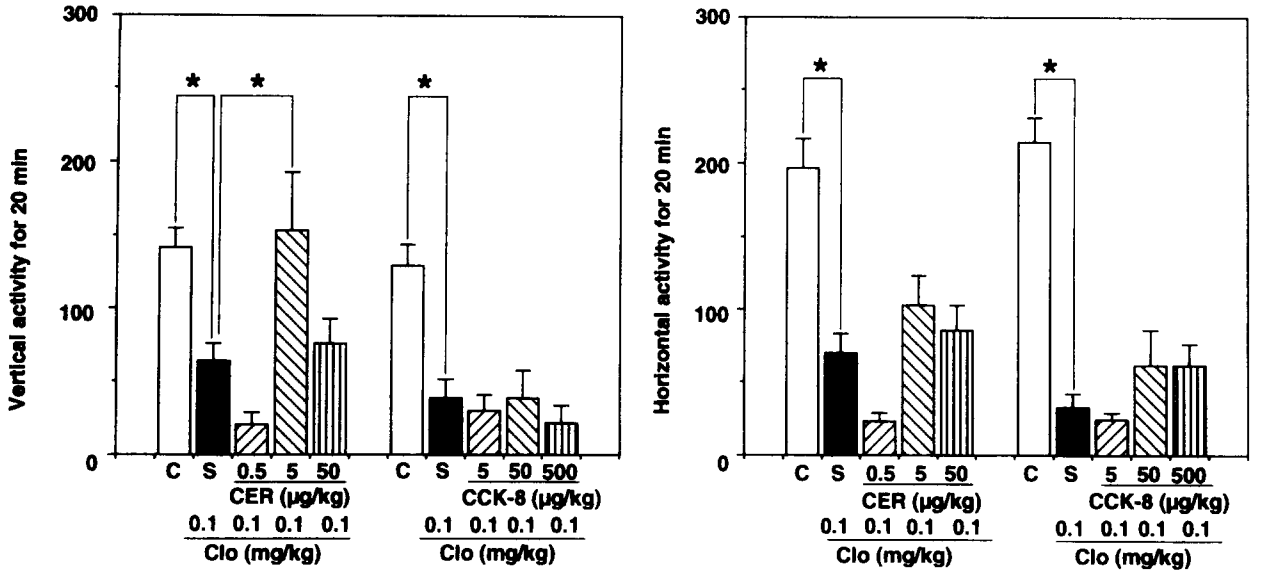

FIG. 4. Effects of CER and CCK-8 on clonidine-induced hypoactivity in mice. Vertical and horizontal locomotor activities were recorded during a 20-min period immediately after SC injection of 0.1 mg/kg clonidine. CER and CCK-8 were IP injected 30 min before administration of clonidine. Shown are the means ± SEM (n = 10). C, control; S, saline; Clo, clonidine.
*$p < 0.05$ vs. saline-clonidine group.

be similar to the inhibited rearing and ambulatory activities observed in mice receiving CER as reported by Hagino et al. (13) and Zetler (40) and in rats receiving CCK-8 as reported by Itoh and Katsuura (16), Katsuura et al. (19), and Weiss et al. (38).

A low dosage (0.1 mg/kg, SC) of apomorphine significantly inhibited both VLA and HLA in intact mice and a high dosage (1 mg/kg, SC) stimulated both. This is in agreement with the results of Di Chiara et al. (9), who demonstrated that low-dose apomorphine-induced hypoactivity is caused by activation of the presynaptic DA receptors in the central dopaminergic neurons and that high-dose apomorphine-induced hyperactivity is caused by activation of the postsynaptic DA receptors. In the present study, the fact that pretreatment with CER (5 μg/kg, IP) had an increased action on low-dose apomorphine-induced hypo-VLA and -HLA in mice is considered the result of the fact that CER exerted a direct and/or indirect influence on the presynaptic DA receptors that were activated with a low dose of apomorphine because it is reported that IP or ICV administration of CCK increased the number of D_2 receptors in the rat striatum and nucleus accumbens (11). Also, administration of CER to the rat nucleus accumbens inhibited low-dose apomorphine-induced hypoactivity (37), whereas pretreatment with CER at 50 μg/kg showed a tendency to decrease low-dose apomorphine-induced hypo-VLA and -HLA. However, it is not clear whether the mechanism for further reduction of low-dose apomorphine-induced hypo-VLA with CER at 50 μg/kg is due to an inhibition of the postsynaptic DA receptors or not. On the other hand, in the present study pretreatment with CCK-8 exerted no influence on low-dose apomorphine-induced hypo-VLA and -HLA in mice, although Studler et al. (35) reported that CCK-8 inhibited the activity of DA-sensitive adenylate cyclase in the presynaptic receptors of the rat nucleus accumbens and accelerated its activity in the postsynaptic receptors.

Subsequently, the fact that pretreatment with CER produced an inhibition to high-dose apomorphine-induced hyper-VLA and -HLA in mice is considered the result of the fact that CER exerted a direct and/or indirect influence on the postsynaptic receptors that were activated with a high dosage of apomorphine. However, this result is not in agreement with the results of Van Ree et al. (37), who demonstrated that administration of CER to the rat nucleus accumbens exerted no influence on high-dose apomorphine-induced hyperactivity. On the other hand, pretreatment with CCK-8 inhibited high-dose apomorphine-induced hyper-HLA but not hyper-VLA. This inhibitory effect of CCK-8 on hyper-HLA is considered the result of the fact that CCK-8 exerted a direct and/or indirect influence on the postsynaptic DA receptors that were activated with a high dosage of apomorphine.

In the present study, clonidine (0.1 mg/kg, SC) inhibited both VLA and HLA in intact mice. This is in agreement with the results of Delini-Stula et al. (8) and Maj et al. (22), who demonstrated that clonidine stimulates the presynaptic α_2-receptors in the central adrenergic neurons, inhibits a release of noradrenaline from the presynaptics, and suppresses locomotor activity in mice. Pretreatment with CER at 5 μg/kg significantly increased clonidine-induced hypo-VLA and increased rearing activity. This is thought to be the result of the fact that CER exerted influence on the presynaptic α_2-receptors that were activated with clonidine, whereas pretreatment with CER at 0.5 μg/kg showed a tendency to decrease both clonidine-induced hypo-VLA and -HLA in mice. This inhibition might be induced by pretreatment with a low dose of CER, which also had a direct and/or indirect effect on clonidine-activated presynaptic α_2-receptors, although influence of CER on the postsynaptic α_1-receptors also cannot be absolutely denied. Thus, it can be surmised that CER also may have a biphasic effect on the activity of the central adrenergic neurons. On the other hand, pretreatment with CCK-8 exerted no influence on clonidine-induced hypo-VLA and -HLA. Thus, although CER and CCK-8 cause an inhibitory effect on VLA and HLA in intact mice the two peptides displayed different pharmacological properties on apomorphine- and

clonidine-induced locomotor activities in mice: CER had some effect on both apomorphine- and clonidine-induced VLA and HLA, while CCK-8 affected only high-dose apomorphine-induced HLA.

In addition, it has been recently demonstrated that CCK coexists with DA in the dopaminergic neuron of the mesolimbic system but not in the striatum (6,7,31,32,39) and may act as a neurotransmitter or neuromodulator in the CNS (6,7, 32,38,39), and that the central action of CCK varies according to the sensitive changes of DA receptors regardless of the existence of the DA/CCK coexisting neurons (12). Therefore, it is suspected that CER, which bears resemblance to the central action of CCK, may have something to do with the DA receptors. Although it is known that the antipsychotic effect of neuroleptics is related to blocking of the DA receptors (20,33,34), CER has attracted special interest as having an antipsychotic effect with pharmacological properties different from that of neuroleptic profiles (37,41).

Furthermore, it was recently suggested that in the dopaminergic neurons an increase in the number of DA receptors and a supersensitivity to the DA receptors may promote the production of involuntary movements, such as oral dyskinesia and chorea-like movement (1,18,29,30). Especially, Kobayashi et al. (20) reported that supersensitivity to the D_1 and D_2 receptors may be closely related to the production of dyskinesia-like movement. Thus, because CER is suggested to possess antidyskinetic action in the clinical study (3,21,23,27) the connection between CER and DA receptors has attracted special attention (in our unpublished observation, we found that CER changed the levels of monoamine metabolites in mouse striatum and nucleus accumbens).

In the behavioral study of mice, it became clear that CER has pharmacological properties different from those of CCK-8, having an effect on activation of the pre- and postsynaptic DA receptors in the dopaminergic neuron, as well as an effect on the activation of the presynaptic α_2-receptors in the adrenergic neuron.

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