Pharmacology Biochemistry & Behavior, Vol. 35, pp. 855–859. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Similar Behavioral and Biochemical Effects of Long-Term Haloperidol and Caerulein Treatment in Albino Mice

EERO VASAR, LEMBIT ALLIKMETS, ANDRES SOOSAAR AND AVO LANG

Laboratory of Psychopharmacology, Institute of General & Molecular Pathology
Tartu University, 34 Veski Street, 202400 Tartu, Estonia, USSR

Received 6 June 1988

VASAR, E., L. ALLIKMETS, A. SOOSAAR AND A. LANG. *Similar behavioral and biochemical effects of long-term haloperidol and caerulein treatment in albino mice.* PHARMACOL BIOCHEM BEHAV **35**(4) 855–859, 1990.—Behavioral and biochemical experiments on male albino mice have revealed similar effects after the cessation of repeated (15 days) haloperidol (0.5 mg/kg daily IP) and caerulein (0.1 mg/kg daily SC) treatment. Tolerance developed to the action of muscimol (a GABA-A agonist, 1 mg/kg IP), caerulein (a CCK-8 agonist, 15 μg/kg SC) and flumazenil (a benzodiazepine antagonist, 10 mg/kg IP). Muscimol and caerulein were not able to suppress the motor activity of mice after 15 days treatment with haloperidol and caerulein. Flumazenil, which increased motor activity in saline-treated animals, also failed to affect activity after extended haloperidol or caerulein treatment. In contrast, the motor excitation induced by amphetamine (an indirect dopamine agonist, 3 mg/kg IP) was increased after haloperidol or caerulein administration. In radioligand binding studies the density of dopamine-2-receptors in striatum, opioid receptors in mesolimbic structures, and benzodiazepine and GABA-A receptors in brainstem was significantly elevated after long-term haloperidol or caerulein treatment. Simultaneously, the number of CCK-8, benzodiazepine and GABA-A receptors in cerebral cortex was decreased. It is probable that CCK-8-ergic mechanisms are involved closely in the action of repeated haloperidol treatment. CCK-8 seems to modulate the action of haloperidol through altering the sensitivity of dopamine, opioid, GABA-A and benzodiazepine receptors.

Long-term treatment Haloperidol Caerulein Exploratory activity Radioligand binding

IT is generally accepted that the antipsychotic potency of neuroleptic drugs is correlated with their affinity to dopamine-2-receptors in striatum (21,22). However, long-term treatment with neuroleptic drugs causes significant changes not only in dopamine receptors, but also in receptors for the other neurotransmitters. For example, the administration of haloperidol for 15 days increases the number of glutamate receptors in striatum (26), but decreases the density of GABA-A and benzodiazepine receptors in forebrain structures of rat (1,2). Recently, the involvement of cholecystokinin octapeptide (CCK-8) in the action of neuroleptic drugs has been established. Repeated administration, but not acute treatment, of different neuroleptic drugs (clozapine, chlorpromazine and haloperidol) evidently increases the amount of CCK-8 in striatum and mesolimbic structures (11). Chang *et al.* (6) have shown that long-term treatment with haloperidol increases the density of CCK-8 receptors in cortical and limbic structures of mice. In addition, Bunney *et al.* (3, 4, 7) have demonstrated that repeated, but not acute, administration of different neuroleptic drugs (haloperidol, chlorpromazine, clozapine, etc.) induces depolarization and subsequent inactivation of dopamine neurons in midbrain. Acute treatment with CCK-8 causes the same effect and proglumide, an antagonist of CCK-8, reverses completely the effect of neuroleptic drugs (4). The above studies support the idea that CCK-8 is playing an obvious role in the mediation of biochemical and behavioral effects of neuroleptic treatment. The aim of the present study was a further clarification of the involvement of CCK-8 in the action of neuroleptic drugs. To study this problem the behavioral and biochemical effects of long-term haloperidol and caerulein, an agonist of CCK-8 receptors, treatment were compared. The changes in dopamine-2-, opioid, GABA-A, benzodiazepine and CCK-8 receptors were studied in both behavioral and radioligand experiments. Carlsson (5) has suggested that neuroleptic drugs cause their antipsychotic effect by blocking mesolimbic dopamine receptors. Other investigators have reported that GABA- and CCK-8-ergic systems have dense morphofunctional connections with dopaminergic system in mesolimbic structures (12,14). Because the normal functioning of the mesolimbic dopamine system appears to be critical for the regulation of locomotor activity in rodents (8) we used the exploratory locomotor activity of mice to determine the long-term behavioural effects of haloperidol and caerulein. Haloperidol was chosen as the neuroleptic for investigation in this study, because it is a potent and widely used antipsychotic drug. It is also noteworthy that in drug discrimination experiments there is substantial generalization between haloperidol and CCK-8 (9). Caerulein was selected for investigation because it is most effective among the available CCK-8 analogs.

METHOD

Animals

Male albino mice unknown strain, weighing 25 ± 3 g, were used. Mice were maintained at 20 ± 2°C and on 12-hr light, between 8 a.m. and 8 p.m. with food and water ad lib.

Determination of Exploratory Activity

Exploratory activity was measured in individual cages. The cage for registration of exploratory activity was a cylinder with an inner diameter 40 cm and 2 photocells (located in walls) for detection of motor activity. Exploratory activity was counted between 15 and 45 min after intraperitoneal administration of amphetamine (an indirect dopamine agonist, 3 mg/kg), muscimol (a GABA-A agonist, 1 mg/kg) and flumazenil (a benzodiazepine antagonist Ro 15-1788, 10 mg/kg), or between 0 and 30 min in the case of subcutaneous treatment of caerulein (a CCK-8 agonist, 15 μg/kg). The doses of amphetamine, caerulein, muscimol and flumazenil were chosen according to results of our previous studies. These doses cause only moderate, but statistically evident, changes in exploratory activity. Thus, an increase or decrease in activity due to the action of these drugs can be detected after repeated treatment with haloperidol or caerulein.

Preparation of Brain Membranes for Radioligand Studies

Following decapitation (between 10 and 12 a.m.) the whole brain was rapidly removed from skull. The different brain regions (cerebral cortex, striata, mesolimbic structures/nucleus accumbens and tuberculum olfactorium/and brainstem) were dissected on ice. Freehand method was used for dissection of brainstem, whereas the other structures were dissected according to the method of Glowinski and Iversen (13). Brain regions from ten mice were pooled and homogenized in 10 volumes of ice-cold 50 mM Tris HCl, pH 7.4 at 4°C, using motor-driven Teflon-glass homogenizer for 12 strokes. The homogenate was centrifuged at 40000 × g for 15 min, resuspended in the same volume of buffer and again centrifuged for 15 min. The membrane preparation for all radioligand studies was the same, except for [^{3}H]-etorphine binding. In this case the homogenate of the mesolimbic structures was incubated for 45 min at 37°C between two centrifugations (for elimination of endogenous opioid peptides). In the case of [^{3}H]-muscimol binding the membranes were washed (centrifuged) 7 times at 40000 × g for 15 min.

Radioligand Binding Studies

Different incubation mixtures were used for the radioligand binding experiments. The binding of [^{3}H]-etorphine (36 Ci/mmole, Amersham International, U.K.), [^{3}H]-flunitrazepam (81 Ci/mmole, Amersham International, U.K.) and [^{3}H]-muscimol (19 Ci/mmole, Amersham International, U.K.) were performed in 50 mM Tris HCl (pH 7.4 at 4°C). [^{3}H]-Spiroperidol (77 Ci/mmole, Amersham International, U.K.) binding was determined in an incubation buffer consisting of the following: 50 mM Tris HCl (pH 7.4 at 4°C), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 1 mM $EDTANa_2$, 50 μM pargyline and 0.1% ascorbic acid. [^{3}H]-Pentagastrin (81 Ci/mmole, NEN-Dupont, USA) binding was studied in the following incubation medium: 10 mM HEPES-KOH (pH 6.8 at 4°C), 5 mM $MgCl_2$, 1 mM $EDTANa_2$, 0.2% bovine serum albumin.

For the binding experiments each polypropylene tube (1.5 ml) received 50 μl of [^{3}H]-ligand, 50 μl of incubation medium or displacing compound and 400 μl of brain membrane homogenate (1–4 mg of original tissue wet weight). [^{3}H]-Flunitrazepam was added in concentrations from 0.6 to 16 nM. The nonspecific binding was determined by using 1 μM flunitrazepam. The membranes of cerebral cortex and brainstem were incubated at 0°C for 60 min. [^{3}H]-Muscimol was used in concentrations from 1 to 80 nM. The nonspecific binding was measured by 100 μM muscimol. The membranes of cerebral cortex and brainstem were incubated for 10 min at 0°C. [^{3}H]-Etorphine was added in concentrations from 0.05 to 3 nM, the nonspecific binding was detected by adding naloxone (10 μM). The incubation of mesolimbic membranes was performed at 25°C for 45 min. [^{3}H]-Spiroperidol was used in concentrations from 0.1 to 2 nM and the nonspecific binding was measured by adding 1 μM spiroperidol. The membranes of murine striata were incubated for 30 min at 37°C. [^{3}H]-Pentagastrin was added to the incubation medium in concentrations from 0.1 to 20 nM, nonspecific binding was detected with 1 μM caerulein. Incubation of [^{3}H]-pentagastrin was performed for 75 min at 25°C.

In all cases the binding experiment was stopped by rapid centrifugation (Beckman microfuge model 12) for 3 min at 11000 × g. The supernatant was carefully discarded and remaining pellet was washed with ice-cold incubation buffer and the tips of polypropylene tubes were cut into counting vials. Radioactivity of samples was counted after stabilization in scintillation cocktail within 24 hours using a Beckman LS 6800 (counting efficacy 50–54%). The binding experiments were repeated at least three times and the data analyzed using the Scatchard method (19).

Drugs and Their Administration

The drugs used in the present investigation are caerulein (Ceruletide, Farmitalia Carlo Erba, Italy), haloperidol (Gedeon Richter, Hungary), spiroperidol (Janssen Pharmaceutica, Belgium), naloxone (Dupont, USA), flunitrazepam and flumazenil (Ro 15-1788) (Hoffmann-La Roche, Switzerland), muscimol (Serva, FRG), pargyline (Sigma, USA), amphetamine (USSR). Caerulein, muscimol, amphetamine and commercial solution of haloperidol were prepared in saline. The injection solution of flumazenil was made soluble in saline by adding some drops of Tween-80. Each injection was done in a volume of 0.1 ml/10 g body weight. Haloperidol (0.5 mg/kg IP) and caerulein (0.1 mg/kg SC) were injected once daily for 15 days. The doses of haloperidol and caerulein were chosen according to our previous studies. Acute administration of haloperidol (0.5 mg/kg) and caerulein (0.1 mg/kg) caused significant neuroleptic effects in mice (catalepsy and the reversal of the behavioral effects of dopamine agonists). The behavioral and radioligand experiments were performed 72 hours after the cessation of haloperidol and caerulein treatment.

Statistics

The results of the binding studies were evaluated by the Student's *t*-test. The results of the behavioral experiments were analyzed by the Mann-Whitney U-test.

RESULTS

According to our preliminary experiments the cessation of long-term administration of haloperidol and caerulein did not cause significant signs of withdrawal. The basal motor activity of mice was unaltered 72 hours after the last injection of repeated treatment with saline and haloperidol as well as caerulein (Table 1). In addition, we found that quinolinic acid- and picrotoxin-induced seizures were identical after the withdrawal of long-term saline, haloperidol or caerulein administration. The behavioral effects of ketamine (motor excitation, stereotyped behavior) remained unchanged after the withdrawal of haloperidol and caerulein (data not presented). In addition, there were no significant differences in the binding values of [^{3}H]-spiroperidol, [^{3}H]-flunitrazepam and [^{3}H]-pentagastrin if the tissues were obtained 2 or 72 hours after the last injection of haloperidol and caerulein. Consequently, the changes in mice behavior and radioligand binding described below were not caused by the withdrawal of haloperidol and caerulein, but rather were induced by the repeated administration of both drugs.

TABLE 1

THE EFFECT OF CAERULEIN, AMPHETAMINE, MUSCIMOL AND FLUMAZENIL ON EXPLORATORY ACTIVITY AFTER 15-DAY HALOPERIDOL OR CAERULEIN TREATMENT IN MICE

	Long-Term Treatment					
	Saline		Haloperidol		Caerulein	
	Motor Activity Counts During 30 Min					
Drug/dose		%		%		%
Saline	171 ± 15	100	188 ± 14	110	184 ± 18	108
Caerulein 15 μg/kg	104 ± 10	100	172 ± 15*	165	190 ± 15*	183
Amphetamine 3 mg/kg	409 ± 30	100	598 ± 45*	146	704 ± 62*	172
Muscimol 1 mg/kg	89 ± 10	100	203 ± 36*	228	170 ± 28*	191
Flumazenil 10 mg/kg	261 ± 17	100	162 ± 15*	62	193 ± 16*	74

The study was performed 72 hours after the cessation of haloperidol, caerulein or saline treatment. The mean values ± S.E.M. are shown. *$p<0.05$ (U-test Mann-Whitney, compared to mice, receiving saline injections for 15 days).

Seventy-two hours after the cessation of 15 days of haloperidol (0.5 mg/kg daily) and caerulein (0.1 mg/kg daily) treatment the effects of different drugs on mice motor activity were changed. The motor excitation induced by amphetamine (3 mg/kg) was evidently increased after haloperidol or caerulein treatment (Table 1). However, tolerance developed to the action of muscimol (1 mg/kg), caerulein (15 μg/kg) and flumazenil (10 mg/kg). Muscimol and caerulein were not able to suppress the motor activity of mice after haloperidol or caerulein administration (Table 1). Flumazenil, which increased the motor activity in saline-treated animals, failed to affect activity after 15 days of haloperidol or caerulein treatment.

The prolonged haloperidol and caerulein treatment also affected the binding of different radioligands to washed brain membranes in a similar way. They changed mainly the number of binding sites of different radioligands, but failed to affect the affinity of the radioligands for their sites. The density of [^{3}H]-spiroperidol binding sites in striatum (mainly dopamine-2-receptors) was significantly increased after the administration of both drugs (Table 2). Similar increase of [^{3}H]-etorphine (labelling mu-, delta- and kappa-opioid receptors) binding sites was detected in mesolimbic structures. Differently from [^{3}H]-spiroperidol and [^{3}H]-etorphine binding the number of [^{3}H]-pentagastrin (a ligand interacting with central CCK-8 receptors) binding sites was evidently decreased in cerebral cortex. The changes in [^{3}H]-flunitrazepam and [^{3}H]-muscimol binding were dependent on the brain region studied. In cerebral cortex their number was reduced, whereas in brainstem the density of [^{3}H]-flunitrazepam and [^{3}H]-muscimol binding sites was increased after 15-day treatment of haloperidol and caerulein (Table 2).

DISCUSSION

Zetler (27) has shown in his experiments on mice that caerulein causes haloperidol-like behavioral effects, but the further pharmacological analysis revealed marked differences in the action of haloperidol and caerulein. Haloperidol, the potent antipsychotic drug, preferentially blocks dopamine-2-receptors (18), whereas

TABLE 2

THE EFFECT OF 15 DAYS OF HALOPERIDOL OR CAERULEIN ADMINISTRATION ON PARAMETERS OF DOPAMINE-2-, BENZODIAZEPINE, $GABA_A$, OPIOID AND CCK-8 RECEPTORS IN MOUSE BRAIN

	K_d (nM)			B_{max} (pmoles/g tissue)		
Radioligand, Brain Structure	Saline	Haloperidol	Caerulein	Saline	Haloperidol	Caerulein
[^{3}H]-spiroperidol, striatum	0.47 ± 0.05	0.62 ± 0.05	0.63 ± 0.05	34.8 ± 3.0	45.0 ± 2.5*	49.2 ± 3.2*
[^{3}H]-flunitrazepam, cerebral cortex	1.70 ± 0.25	1.60 ± 0.25	1.50 ± 0.18	198 ± 12	144 ± 15*	138 ± 14*
[^{3}H]-flunitrazepam, brainstem	2.42 ± 0.20	1.92 ± 0.18	2.62 ± 0.17	103 ± 8	125 ± 12	142 ± 16*
[^{3}H]-muscimol, cerebral cortex	9.6 ± 1.6	10.2 ± 1.8	11.0 ± 1.2	91 ± 8	64 ± 5*	63 ± 6*
[^{3}H]-muscimol, brainstem	12.6 ± 1.3	13.2 ± 1.3	14.3 ± 1.3	38 ± 4	51 ± 4	50 ± 5
[^{3}H]-etorphine, mesolimbic area	0.62 ± 0.05	0.61 ± 0.05	0.77 ± 0.05	33 ± 2.4	42 ± 2.5*	46 ± 3.2*
[^{3}H]-pentagastrin, cerebral cortex	3.50 ± 0.40	3.20 ± 0.30	3.20 ± 0.32	5 ± 0.4	3.5 ± 0.3*	3.2 ± 0.3*

The study was performed 72 hours after the cessation of haloperidol, caerulein or saline treatment. The mean values of three independent experiments are shown. Statistically evident differences from saline-treated mice: *$p<0.05$ (Student's t-test). K_d: constant of dissociation (nM); B_{max}: apparent number of binding sites (pmoles/g wet weight tissue).

caerulein stimulates CCK-8 receptors (27). Despite the significant differences in the molecular action of the two drugs, long-term treatment with haloperidol and caerulein has a similar effect on behavior and causes similar changes in radioligand binding to washed brain membranes. Our data suggest that both compounds increase the number of dopamine-2-receptors in striatum and opioid receptors in mesolimbic structures. The increased sensitivity of mice to motor stimulating effect of amphetamine, a compound that increases the release of dopamine, probably reflects the enhancement of dopamine-2-receptors density after haloperidol or caerulein treatment. Some authors have demonstrated (17,23) that opioid receptors in limbic structures play an important role in the regulation of dopamine receptors' sensitivity. The prolonged administration of different neuroleptic drugs (haloperidol, sulpiride, flupenthixol, etc.) leads to the hypersensitivity not only of dopamine receptors, but also of opioid receptors in mesolimbic structures (20,23). It seems probable that the increased sensitivity of opioid receptors is obligatory for the development of hypersensitivity in dopamine receptors in mesolimbic area.

After 15 days of haloperidol and caerulein administration a marked decrease in CCK-8 receptors density in cerebral cortex is found. The significant reduction of motor depressant effect of caerulein after haloperidol or caerulein treatment is probably related to the decrease of CCK-8 receptor number in brain. Consequently, haloperidol and caerulein treatment cause a subsensitivity of CCK-8 receptors. A similar subsensitivity (decrease of [^{3}H]-CCK-8 binding sites in mouse and rat brain, tolerance or inversion of caerulein's behavioral effects) of CCK-8 receptors was found after long-term haloperidol treatment in our previous experiments (25). Many behavioral studies now support the idea that CCK-8 acts as a functional antagonist of dopamine and endogenous opioid peptides in brain (10, 16, 27). Accordingly, the subsensitivity of CCK-8 receptors seems to be necessary for the development of hypersensitivity of dopamine and opioid receptors. However, Chang *et al.* (6) have shown the opposite effect, the increase of the number of CCK-8 receptors, after repeated haloperidol treatment in mice. They have used [^{125}I]-CCK-33 for labelling of CCK-8 receptors and they have administered significantly higher dose of haloperidol (2–3 mg/kg) to mice. These factors may explain the differences between our study and that of Chang *et al.* (6). Despite the discrepancy the above-mentioned results would support the idea that CCK-8-ergic mechanisms play a crucial role in the mediation of the effects of prolonged neuroleptic treatment.

The changes in benzodiazepine and GABA-A receptors differ from those of the other neurotransmitter receptors after long-term haloperidol or caerulein administration. In frontal cortex the density of benzodiazepine and GABA-A receptors is reduced and it is parallel to the reduction of CCK-8 receptors. The number of benzodiazepine and GABA-A receptors in brainstem, on the contrary, is increased after haloperidol or caerulein treatment. The similar alteration of CCK-8 and benzodiazepine-GABA-A receptors in cerebral cortex may be linked to the finding that CCK-8 and GABA are co-mediators in the same neurons of cerebral cortex and hippocampus (15). The molecular changes in benzodiazepine and GABA-A receptors are probably associated with tolerance of behavioral effects of GABA-A agonist muscimol and benzodiazepine antagonist flumazenil. Muscimol did not suppress and flumazenil did not increase the motor activity of mice after long-term treatment of haloperidol and caerulein. The possible explanation for these changes may consist of the existence of functionally different benzodiazepine and GABA-A receptors in forebrain and brainstem structures (24). The results of present study show that CCK-8 may have, through CCK-8 receptors indeed, a modulating action on the sensitivity of GABA-A-benzodiazepine, opioid and dopamine receptors. This opinion is supported not only by present study, but also by other investigators. CCK-8 and caerulein inhibit not only the action of amphetamine and methylphenidate, interacting with presynaptic dopaminergic mechanisms, but also the effects of apomorphine, a direct agonist of dopamine receptors (27).

In conclusion, the similar actions of haloperidol and caerulein after long-term treatment seem to be related to the fact that the effects of haloperidol are effected not only through dopaminergic, but also via CCK-8-ergic mechanisms. The effect of CCK-8 seems to be related to the modulation (through CCK-8 receptors) of the sensitivity of different neurotransmitter receptors (dopamine, endogenous opioid peptides and GABA).

ACKNOWLEDGEMENTS

We would like to thank Farmitalia Carlo Erba, Janssen Pharmaceutica, Hoffmann-La Roche and Dupont for the generous gifts of drugs.

REFERENCES

1. Allikmets, L. H.; Zarkovsky, A. M.; Nurk, A. M.; Vasar, E. E.; Maimets, M. O.; Rago, L. K. Effect of prolonged administration of neuroleptics on CNS receptors plasticity. Proc. Med. Acad. Sci. USSR 11:37–42; 1984.
2. Allikmets, L. H.; Vasar, E. E.; Nurk, A. M.; Maimets, M. O. Adaptive changes on GABA and benzodiazepine receptors after prolonged treatment with haloperidol. In: Babkov, J. G., ed. Pharmacological regulation of desadaptation. Moscow: Institute of Pharmacology Press; 1986:36–43 (in Russian).
3. Bunney, B. S.; Grace, A. A. Acute and chronic haloperidol treatment: comparison of effects on nigral dopaminergic cell activity. Life Sci. 23:1715–1728; 1978.
4. Bunney, B. S.; Chodo, L. A.; Freeman, A. S. Further studies on the specificity of proglumide as a selective cholecystokinin antagonist in the central nervous system. Ann. NY Acad. Sci. 448:345–351; 1985.
5. Carlsson, A. Antipsychotic drugs, neurotransmitters and schizophrenia. Am. J. Psychiatry 135:164–173; 1978.
6. Chang, R. S. L.; Lotti, V. S.; Martin, G. E.; Chen, T. B. Increase in brain [^{125}I]-cholecystokinin (CCK) receptor binding following chronic haloperidol treatment, intracisternal 6-hydroxydopamine and ventral tegmental lesions. Life Sci. 32:871–878; 1983.
7. Chiodo, L. A.; Bunney, B. S. Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminegic neurons. J. Neurosci. 3:1607–1609; 1983.
8. Costall, B.; Domeney, A. M.; Naylor, R. J. The continuity of dopamine receptors antagonism can dictate the long-term behavioral consequences of a mesolimbic infusion of dopamine. Neuropharmacology 24:193–197; 1985.
9. De Witte, P.; Swanet, E.; Gewiss, M.; Goldman, S.; Roques, E.; Vanderhaeghen, J.-J. Psychopharmacological profile of cholecystokinin using the self-stimulation and the drug-discrimination paradigms. Ann. NY Acad. Sci. 448:470–487; 1985.
10. Faris, P. L.; Komisaruk, B. R.; Watkins, L. R.; Mayer, D. J. Evidence for the neuropeptide cholecystokinin as an antagonist of opiate analgesia. Science 219:310–312; 1983.
11. Frey, P. Cholecystokinin octapeptide levels in rat brain are changed after subchronic neuroleptic treatment. Eur. J. Pharmacol. 95:87–92; 1983.
12. Garbutt, J. C.; VanKammen, D. P. The interaction between GABA and dopamine: implications for schizophrenia. Schizophr. Bull. 9: 336–353; 1983.
13. Glowinski, J.; Iversen, L. L. Regional studies of catecholamines in rat brain. J. Neurochem. 13:655–664; 1966.
14. Hokfelt, T.; Rehfeld, J. F.; Skirboll, L.; Ivemark, B.; Goldstein, M.; Markey, K. Evidence for coexistence of dopamine and CCK in mesolimbic neurons. Nature 285:476–478; 1980.

15. Kosaka, T.; Kosaka, K.; Tateishi, K.; Hamaoka, Y.; Yanaihara, N.; Wu, J.-Y.; Hama, K. GABAergic neurons containing CCK-8-like or VIP-like immunoreactivities in the rat hippocampus and dentate gyrus. J. Comp. Neurol. 239:420–430; 1985.
16. Matsubara, K.; Matsushita, A. Long-lasting reduction of amphetamine induced hyperactivity in rats after combined coadministration of caerulein with haloperidol. Eur. J. Pharmacol. 101:157–158; 1984.
17. Matsubara, K.; Matsushita, A. β-endorphine involvement in the antidopaminergic effect of caerulein. Jpn. J. Pharmacol. 40:417–422; 1986.
18. Ortmann, R.; Bischoff, S.; Radeke, E.; Buech, O.; Delini-Stula, A. Correlations between different measures of antiserotonin activity of drugs: study with neuroleptics and serotonin blockers. Naunyn Schmiedebergs Arch. Pharmacol. 321:265–270; 1982.
19. Scatchard, G. The attraction of protein for small molecules and ions. Ann. NY Acad. Sci. 51:660–672; 1949.
20. Seeger, T. F.; Nazzaro, J. M.; Gardner, E. L. Selective inhibition of mesolimbic behavioral supersensitivity by naloxone. Eur. J. Pharmacol. 65:435–438; 1980.
21. Seeman, P.; Lee, T.; Chau-Wong, M.; Wong, K. Antipsychotic drug doses and dopamine/neuroleptic receptors. Nature 261:717–719; 1976.
22. Seeman, P. Brain dopamine receptors. Pharmacol. Rev. 32:229–313; 1980.
23. Stinus, L.; Nadaud, D.; Jauregui, J.; Kelley, A. E. Chronic treatment with five different neuroleptics elicits behavioral supersensitivity to opiate infusion into nucleus accumbens. Biol. Psychiatry 21:34–48; 1986.
24. Vasar, E. E.; Soosaar, A. H.; Nurk, A. M.; Maimets, M. O.; Allikmets, L. H. Distinct effect of long-term haloperidol treatment on GABA-A and benzodiazepine receptors in different brain areas. Bull. Exp. Biol. Med. 101:433–435; 1986.
25. Vasar, E. E.; Soosaar, A. H.; Maimets, M. O.; Allikmets, L. H. Reduced sensitivity of the brain cholecystokinin receptor after the prolonged treatment with haloperidol. Bull. Exp. Biol. Med. 101: 583–585; 1986.
26. Zarkovsky, A. M.; Allikmets, L. H. The action of acute and repeated administration of neuroleptics on CNS receptors. In: Abstracts of All-Union Symposium 'Chemistry, Pharmacology and Clinical Use of Neuroleptics,' Tartu: Tartu University Press; 1986:47–49 (in Russian).
27. Zetler, G. Neuropharmacological profile of cholecystokinin-like peptides. Ann. NY Acad. Sci. 448:448–469; 1985.