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Comparison of Motor Depressant Effects of Caerulein and N-Propylnorapomorphine in Mice

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VASAR, E , M MAIMETS, A NURK, A SOOSAAR AND L ALLIKMETS *Comparison of motor depressant effects of caerulein and N-propylnorapomorphine in mice* PHARMACOL BIOCHEM BEHAV 24(3) 469–478, 1986 —The motor depressant effects of caerulein and N-propylnorapomorphine (NPA) were compared in male mice Caerulein (1–50 μg/kg SC) in a dose dependent manner depressed the exploratory activity, whereas NPA in lower doses (0 5–10 μg/kg SC) decreased the motor activity, but in higher doses (over 50 μg/kg) had stimulating effect on the exploratory behavior In mice selected according to their motor response after administration of 100 μg/kg NPA to weak and strong responders, the low dose of NPA (1 μg/kg) similarly suppressed motor activity in both selected groups, while the effect of caerulein (2 μg/kg) was apparently higher in weak responders Destruction of catecholaminergic terminals by 6-hydroxydopamine (60 μg ICV) reversed completely the motor depressant effect of NPA, whereas degeneration of serotoninergic terminals (5,7-dihydroxytryptamine 60 μg ICV or p-chloroamphetamine 2×15 mg/kg IP) enhanced the sedative effect of NPA The motor depressant effect of caerulein remained unchanged after lesions of monoaminergic terminals in forebrain Subchronic haloperidol (0 25 mg/kg IP, twice daily during 14 days) treatment, reducing significantly the density of high-affinity dopamine$_2$- and serotonin$_2$-receptors, decreased the motor depressant action of caerulein It is possible that motor depressant effect of caerulein, differently from the action of NPA, is mediated through the high-affinity dopamine$_2$-receptors and in lesser extent through the high-affinity serotonin$_2$-receptors

Exploratory activity Caerulein N-propylnorapomorphine Dopamine$_2$-receptors Serotonin$_2$-receptors

THE suppression of spontaneous locomotor activity by low doses of apomorphine in rodents is a widely studied behavioral phenomenon It is generally accepted that the sedative action of apomorphine and its more powerful analog N-propylnorapomorphine (NPA) is mediated through the stimulation of dopamine "autoreceptors," inhibiting the dopaminergic neurons activity [9, 10, 38, 45] This opinion is supported by various investigations The subcutaneous administration of apomorphine in low doses inhibited the firing rate of dopaminergic neurons in mesencephalon [2], decreased dopamine release and suppressed dopamine turnover in forebrain structures [32,44] Lesion of dopaminergic terminals by 6-hydroxydopamine and administration of different neuroleptic drugs in low doses reversed the inhibiting action of apomorphine on behavior and dopaminergic neurons activity [3, 42, 46] However, some recent investigations demonstrated a more complicated nature of apomorphine's action in low and moderate doses It was found [16] that haloperidol and sulpiride reversed the sedative effect of moderate dose (150 μg/kg) of apomorphine, whereas the action of low dose (25 μg/kg) of apomorphine was resistant to the antagonizing action of neuroleptic drugs The complicated nature of apomorphine's action in low doses was described also in chronic schizophrenic patients, evidently resistant to neuroleptic medication. The reduction of schizophrenic symptomatology was demonstrated in approximately 50% of patients, suffering mainly from paranoid schizophrenia [47,48] It was quite surprising that apomorphine possessed its beneficial activity when coadministered with neuroleptic drugs, but not alone [1, 21, 37]

Obviously similar suppression of animals' spontaneous behavior was found after systemic administration of cholecystokinin octapeptide (CCK-8) and caerulein in mice [56, 57, 58] CCK-8 and caerulein significantly potentiated apomorphine-induced inhibition of dopaminergic neurons in mesencephalon [30] There is strict evidence that CCK and dopamine coexist in some mesencephalic cells innervating forebrain limbic and cortical regions [31] In addition, CCK has been reported to decrease dopamine turnover in the discrete regions of caudate-putamen [24] However, CCK also decreased serotonin turnover [51], whereas apomorphine had the opposite effect on serotonin metabolism [26] Recently the rapid and long-lasting reduction of psychotic symptoms, mainly negative, in schizophrenic patients after administration of different CCK-related peptides was demonstrated [7, 39, 40]

The main task of the present investigation was to compare the mechanisms of inhibiting action of apomorphine and CCK on the animals' behavior The attention was drawn to the study of interaction of caerulein and NPA with dopamine- and

serotonınergıc mechanısms Caerulein and NPA were selected for the present ınvestigatıon as the most effective compounds among, respectıvely, CCK-8 and apomorphıne analogs [8, 55, 56]

GENERAL METHOD

Animals

Male albıno mice weighıng 25±3 g were used Mice were maıntaıned at 20±2°C and on 12 hr lıght, between 8 a m and 8 p m , wıth food and water allowed ad lıb

Measurement of Spontaneous Locomotor Activity

Spontaneous locomotor actıvıty was measured ın grouped albıno mice, 10 anımals ın each group, between 10 a m and 4 p m Immedıately after systemıc admınıstratıon of drugs a group of mice was placed ın the mıddle of an open-field cage The open-field consısted of a 1×1 m area surrounded by a 40 cm hıgh wall The locomotor actıvıty of anımals was counted by 5 ındependent photocells located ın walls Interruptıons of the lıght beams were recorded electromechanıcally and the level of locomotor actıvıty was expressed ın counts per 15 or 30 mın perıod The experıment was repeated wıth each drug combınatıon at least three tımes on dıfferent days and the data analyzed usıng Student's *t*-test

Selection of Mice According to Their Motor Response to Administration of NPA

There exısts the possıbılıty of selectıng rats accordıng to theır motor response after 50 μg/kg NPA treatment [15] A sımılar attempt was made for selectıon of mice In the present study the selectıon was performed wıth subcutaneous admınıstratıon of 100 μg/kg NPA ın 400 male mice The experıment was carrıed out ın ındıvıdual cages The cage for measurıng ındıvıdual locomotor actıvıty was a cylınder wıth an ınner dıameter 40 cm and 2 photocells for detectıon of locomotor actıvıty Locomotor actıvıty was counted between 15 and 30 mın after subcutaneous NPA (100 μg/kg) treatment

Lesions of Brain Monoaminergic Terminals

Monoamınergıc neurotoxıns 6-hydroxydopamıne (6-OHDA) and 5,7-dıhydroxytryptamıne (5,7-DHT) were dıssolved ın 0 1% solutıon of ascorbıc acıd 6-OHDA (60 μg ın 5 μl) and 5,7-DHT (60 μg ın 5 μl) were ınjected ınto the rıght lateral ventrıcle of mice under the ether anesthesıa The behavıoral and bındıng experıments were carrıed out 8 days after the ınjectıon of neurotoxıns Fınally, the ınjectıon sıtes were confırmed hıstologıcally to be located wıthın the rıght lateral ventrıcle p-Chloroamphetamıne ın neurotoxıc dose (2×15 mg/kg 8 and 7 days before the experıment) was also used for lesıonıng of serotonınergıc termınals [5] The effect of neurotoxıns on the content of monamınes and theır major metabolıtes ın brain structures was assessed bıochemıcally usıng fluorımetrıc assay [20]

In Vivo ^{3}H-Spiperone Binding

^{3}H-spıperone (5 μg/kg, 17 Cı/mmole, Amersham Internatıonal, U K) was ınjected subcutaneously ınto the dorsal part of mouse neck NPA (5 and 50 μg/kg) and caerulein (20–250 μg/kg) were used to ınhıbıt ^{3}H-spıperone bındıng Two doses of NPA wıth dıfferent actıon on rodent behavıor were selected because two sıtes wıth dıfferent affınıty for dopamıne and ıts agonısts exısted on dopamıne$_2$-receptors [18,27] Fıve μg/kg NPA ıs ED_{50} for suppressıon of exploratory actıvıty ın mice, whereas 50 μg/kg NPA ıs ED_{50} for motor excıtatıon ın rodents [8] NPA and caerulein were admınıstered 15 mın before ^{3}H-spıperone The anımals (6 mice per group) were sacrıfıced 20 mın after ^{3}H-spıperone treatment by cervıcal dıslocatıon The brains were rapıdly

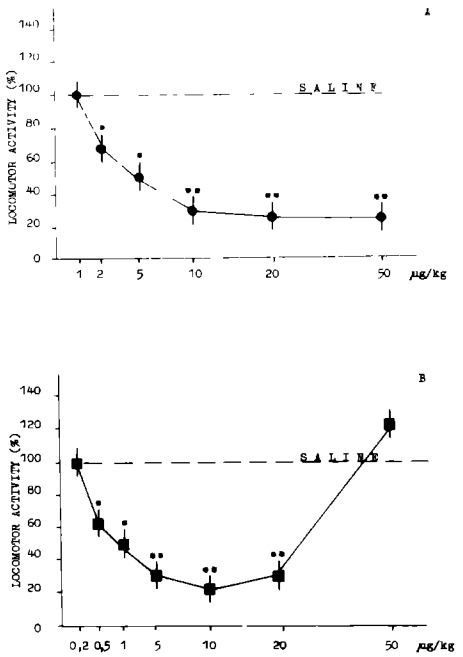

FIG 1 The effect of dıfferent doses of N-propylnorapomorphıne and caerulein on exploratory behavıor ın mice Each poınt ın the fıgure represents mean value of three ındependent studıes ın grouped mice (10 anımals ın group) Abscıssa—the dose of NPA or caerulein ın μg/kg Caerulein—A , NPA—B The mean value for salıne treated group was 1182±170 counts durıng 30 mın Statıstıcally evıdent dıfferences from salıne treated mice $*p<0.05$, $**p<0.01$ (Student's *t*-test)

TABLE 1

THE ACTION OF CONCOMITANT ADMINISTRATION OF CAERULEIN AND NPA ON MICE SPONTANEOUS LOCOMOTOR ACTIVITY

	Spontaneous locomotor actıvıty of mice			
	Counts durıng			
Drug/dose	15 mın	%	30 mın	%
Salıne	608 ± 58	100	1230 ± 162	100
NPA 0 5 μg/kg	380 ± 42*	63	780 ± 68*	63
Caerulein 2 μg/kg	352 ± 38*	58	746 ± 65*	61
NPA + Caerulein	170 ± 16†	28	276 ± 24†	22
NPA 10 μg/kg	158 ± 12†	26	240 ± 32†	20
Caerulein 1 μg/kg	560 ± 57	92	1080 ± 182	88
NPA + Caerulein	33 ± 4‡	5	61 ± 8‡	5

The mean values of four ındependent experıments on grouped mice (10 anımals ın group) are presented $*p<0.05$, $†p<0.01$, $‡p<0.001$ (Student's paıred *t*-test, ın relatıon to salıne treated anımals)

TABLE 2

THE EFFECT OF CAERULEIN AND NPA ON EXPLORATORY ACTIVITY AND ^{3}H-SPIPERONE IN VIVO BINDING IN MICE SELECTED WITH 100 μg/kg NPA

	Inhibition of locomotor activity to 100 μg/kg NPA			
	Weak Responders		Strong Responders	
	Motor activity counts during 30 min			
Drug/dose		%		%
Saline	1168 ± 98	100	1224 ± 115	100
NPA 1 μg/kg	550 ± 58	47	630 ± 52	52
Caerulein 2 μg/kg	292 ± 34*	25	690 ± 68	56

	Inhibition of ^{3}H-spiperone binding to 100 μg/kg NPA			
	Weak Responders		Strong Responders	
	cpm per gram tissue			
	Subcortex	Dorsal cortex	Subcortex	Dorsal cortex
NPA 5 μg/kg	+1600 ± 280†	+750 ± 200†	9900 ± 1020	10950 ± 1200
NPA (50–5) μg/kg	5180 ± 380*	3750 ± 280*	10200 ± 980	6900 ± 520
Caerulein 100 μg/kg	+1800 ± 360†	+1200 ± 300†	11840 ± 930	11150 ± 1060

The experiments were carried out 10–12 days after mice selection

The mean values of three independent experiments are advanced in table +—Stimulation of ^{3}H-spiperone binding *$p<0.05$, †$p<0.01$ (Student's paired t-test, compared to strong responding mice)

removed and dorsal cortex and subcortical forebrain structures (striata and limbic structures) were dissected on ice The dissected brain areas of each group were pooled and homogenized using a glass-teflon homogenizer by hand during 1 min The homogenization procedure was performed in ice-cold Tris-HCl buffer (50 mM, pH 7 4, 20°C) in the volume of 40 mg tissue per ml After homogenization 0 5 ml (20 mg tissue) of suspension was pippeted into 6 polypropylene tubes (1 5 ml) and centrifuged during 10 min at 9000×g The supernatant was carefully discarded and remaining pellet was washed and cut into vials Radioactivity of samples was counted after stabilization in Bray scintillation cocktail within 12 hours in Beckman LS 6800 with counting efficacy 43% The binding experiments were repeated at least three times and the data analyzed using Student's t-test

Drugs

Drugs used in the present investigation were caerulein (Ceruletide, Farmitalia Carlo Erba, Italy), haloperidol (Gedeon Richter, Hungary), N-propylnorapomorphine (Sterling-Winthrop, USA), p-chloroamphetamine, 6-hydroxydopamine, 5,7-dihydroxytryptamine (Sigma, USA) Caerulein, commercial solution of haloperidol and p-chloroamphetamine were dissolved in saline The injection solution of NPA was prepared in 0 001 N HCl Each injection was done in a volume of 0 1 ml/10 g body weight

EXPERIMENT 1 THE INVOLVEMENT OF DOPAMINERGIC MECHANISMS IN THE MOTOR DEPRESSANT ACTION OF CAERULEIN AND N-PROPYLNORAPOMORPHINE

The aim of experiment 1 was to study the role of dopaminergic mechanisms in the sedative effects of caerulein and NPA. The problems under examination were (1) the action of different doses of caerulein and NPA on exploratory activity in mice, (2) the effect of concomitant use of caerulein and NPA on locomotor activity in mice, (3) the action of caerulein and NPA on exploratory activity and ^{3}H-

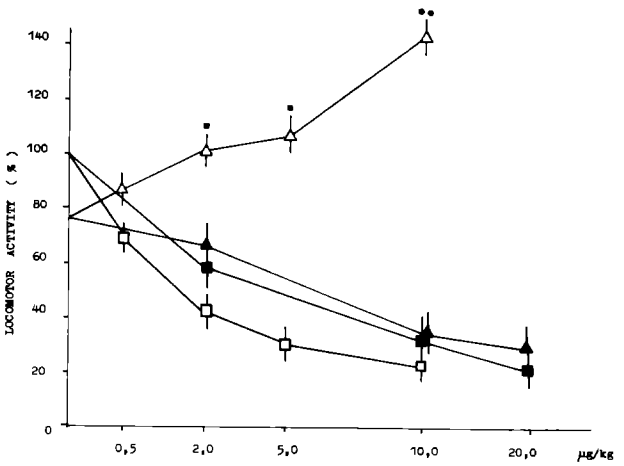

FIG 2 The changes in motor depressant effect of caerulein and N-propylnorapomorphine after intraventricular administration of 6-hydroxydopamine White signs—the action of NPA, black signs—caerulein Triangles—after administration of 6-OHDA, squares—after intraventricular injection of 0 1% ascorbic acid Abscissa—the dose of NPA or caerulein in μg/kg The mean value for saline medicated mouse was 1098±156 counts during 30 min in the case of 0 1% ascorbic acid and 780±78 in case of 6-OHDA Statistically evident differences from ascorbic acid pretreated group *$p<0.05$, **$p<0.01$ (Student's t-test)

TABLE 3

THE CHANGES IN ^{3}H-SPIPERONE BINDING AFTER INTRACEREBROVENTRICULAR ADMINISTRATION OF 6-HYDROXYDOPAMINE AND LONG-TERM ADMINISTRATION OF HALOPERIDOL AND P-CHLOROAMPHETAMINE

	Inhibition of ^{3}H-spiperone binding cpm per gram tissue					
	NPA 5 μg/kg		NPA (50–5) μg/kg		Caerulein 50 μg/kg	
Drug/dose	Subcortex	Dorsal cortex	Subcortex	Dorsal cortex	Subcortex	Dorsal cortex
Saline	7800 ± 580	6950 ± 620	5200 ± 640	4000 ± 480	5250 ± 420	4750 ± 390
6-OHDA 60 μg	14400 ± 930†	11800 ± 1060*	1020 ± 200†	2040 ± 240*	3000 ± 470*	2600 ± 320
PCA 2×15 mg/kg	4240 ± 560*	3320 ± 310†	5800 ± 670	3900 ± 350	3500 ± 430	3600 ± 410
Haloperidol 0 25 mg/kg	1100 ± 120†	2150 ± 380*	10400 ± 980†	6700 ± 530*	+3600 ± 320‡	+400 ± 120†

The binding of ^{3}H-spiperone after intraventricular administration of 0 1% ascorbic acid did not differ from the binding after long-term saline treatment +—Stimulation of ^{3}H-spiperone binding *$p<0$ 05, †$p<0$ 01, ‡$p<0$ 001, compared to saline treated mice (Student's t-test)

spiperone binding parameters in pharmacologically selected mice The animals were selected according to their motor response after administration of 100 μg/kg NPA into two groups—weak and strong responders The uneven motor reaction after NPA administration reflected the different density of postsynaptic dopamine$_2$-receptors in rodents [14, 15, 29], (4) the effects of caerulein and NPA on locomotor activity in mice and ^{3}H-spiperone binding parameters after destruction of presynaptic dopaminergic terminals by 6-hydroxydopamine

METHOD

The group of mice was placed into the center of an open-field cage immediately after subcutaneous injection of caerulein (1–50 μg/kg) or NPA (0 2–50 μg/kg) After selection of appropriate doses, giving marked suppression of spontaneous locomotor activity, the effect of concomitant use of caerulein and NPA was studied The action of NPA (1 μg/kg) and caerulein (2 μg/kg) was also examined in mice selected according to their motor response to the administration of NPA in a high dose (100 μg/kg) The groups of weak and strong responders to 100 μg/kg NPA were selected among 400 mice The motor activity was assessed in individual cages from 15 to 30 min after 100 μg/kg NPA injection The mean value of motor activity for the first group (weak responders) was 36±3 8 counts during 15 min and 216±15 2 for the second (strong responders) The response of these two groups to saline administration did not differ markedly It was 1168±98 counts during 30 min for weak responders and 1224±115 counts for strong responders. Simultaneously with behavioral investigations ^{3}H-spiperone in vivo binding studies were performed NPA (5 and 50 μg/kg) and caerulein (100 μg/kg) were used as displacing drugs. Two doses of NPA were administered to demonstrate two distinct binding sites for NPA on dopamine$_2$- and serotonin$_2$-receptors Inhibition of ^{3}H-spiperone binding by 5 μg/kg NPA expressed the amount of high-affinity sites for NPA, whereas the difference between the inhibiting action of 50 and 5 μg/kg NPA demonstrated the number of low-affinity sites Catecholaminergic neurotoxin 6-OHDA (60 μg) was injected into the right lateral cerebral ventricle in a volume of 5 μl during 3 min under ether anesthesia Seven days were allowed for recovery from intraventricular intervention After completion of behavioral experiments the site of microinjection was detected histologically

RESULTS

Effect of Caerulein and NPA on Exploratory Motor Activity

Caerulein in a dose dependent manner depressed the exploratory activity in male mice (Fig 1A) Two μg/kg caerulein caused the minimal significant reduction of motor activity and 20–50 μg/kg the maximal effect Low doses of NPA also reduced the animals' spontaneous locomotor activity 0 5 μg/kg NPA caused remarkable and 10 μg/kg NPA induced the maximal reduction of mice exploratory behavior (Fig 1B) The further elevation of NPA dose did not enhance the sedative action, but on the contrary 50 μg/kg NPA had a mild stimulating effect on motor activity of mice After coadministration of NPA and caerulein the reduction of motor activity was obviously higher compared to the treatment of both drugs alone (Table 1) One μg/kg caerulein, which did not significantly affect the mice behavior, potentiated the motor depressant effect of NPA (10 μg/kg) This combination of drugs caused nearly complete suppression of locomotor activity In mice, selected according to their motor response after administration of 100 μg/kg NPA, 1 μg/kg NPA in a similar manner suppressed exploratory activity in strong as well as in weak responders (Table 2) However, the sedative effect of caerulein (2 μg/kg) was dependent on the mice sensitivity to 100 μg/kg NPA In strong responders the sedative effect of caerulein was lower Significant differences were found also in ^{3}H-spiperone binding performed in "in vivo" conditions (Table 2). In weak responders caerulein (100 μg/kg) stimulated ^{3}H-spiperone binding in both brain regions studied, whereas in strong responders it had the opposite effect, inhibiting ^{3}H-spiperone binding (Table 2) Five μg/kg NPA also increased ^{3}H-spiperone binding in weak responders, while the displacing potency of 50 μg/kg NPA in weak responders was lower than the effect of 5 μg/kg NPA in strong responders

Effect of 6-OHDA on Locomotor Effects of Caerulein and NPA, and ^{3}H-Spiperone Binding

Intraventricular administration of 6-OHDA (60 μg) induced more than 60% reduction of dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) levels in striatal slices (dorsal cortex, striata and mesolimbic structures) of mice brain without changing markedly serotonin levels. Simultaneously the reduction of spontaneous locomotor activity was seen in mice after 6-OHDA treatment (Fig

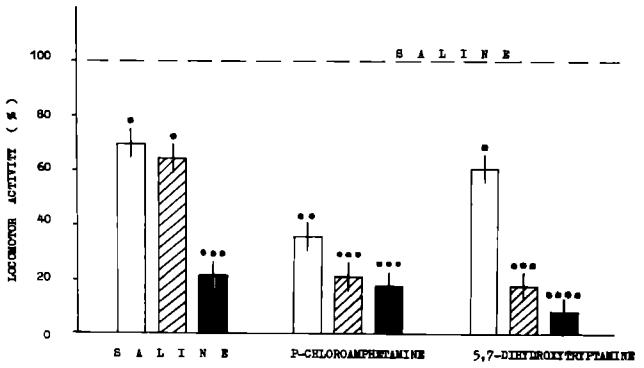

FIG 3 The influence of p-chloroamphetamine and 5,7-dihydroxytryptamine pretreatment on motor depressant effect of caerulein and N-propylnorapomorphine White bars—caerulein 2 μg/kg, striped bars—NPA 0 5 μg/kg and black bars—caerulein+NPA The mean value of motor activity for saline treated group was 1180±122 in case of long-term saline administration, 1020±140 in case of 5,7-DHT and 1270±178 counts during 30 min in case of PCA *$p<0$ 05, **$p<0$ 02, ***$p<0$ 01, ****$p<0$ 001, compared to saline pretreatment (Student's t-test)

TABLE 4

THE EFFECT OF HALOPERIDOL AND CAERULEIN ON MICE EXPLORATORY ACTIVITY AFTER 14 DAYS HALOPERIDOL TREATMENT

	Saline		Haloperidol	
	Motor activity counts during 30 min			
Drug/dose		%		%
Saline	1180 ± 188	100	1054 ± 143	100
Caerulein 2 μg/kg	680 ± 78*	58	920 ± 89	90
Haloperidol 50 μg/kg	880 ± 96	75	1280 ± 160	122
Caerulein + Haloperidol	620 ± 64*	53	520 ± 56†	49

The investigation was performed 72 hours after cessation of haloperidol or saline treatment The mean values of three independent studies are advanced *$p<0$ 05, †$p<0$ 01, compared to saline treated animals (Student's t-test)

2) NPA completely lost its sedative action and stimulated the mice exploratory activity after administration of 6-OHDA, while the action of caerulein remained unchanged (Fig 2) In binding experiments 6-OHDA caused a significant increase in displacing action of 5 μg/kg NPA, but reduced the potency of 50 μg/kg (Table 3) The inhibiting action of caerulein (50 μg/kg) on ^{3}H-spiperone binding was also somewhat lower after 6-OHDA treatment Administration of 6-OHDA altered ^{3}H-spiperone binding more relevantly in subcortical structures than in dorsal cortex

DISCUSSION

Caerulein and NPA in low doses caused similar suppression of exploratory activity of mice Coadministration of NPA and caerulein evidently potentiated their depressive action on behavior There is clear evidence for coexistence of dopamine and CCK-8 in the same mesencephalic dopaminergic neurons [31] It was demonstrated that CCK-8 and caerulein potentiated apomorphine-induced inhibition of dopaminergic neurons in mesencephalon [30]. Lesion of presynaptic dopaminergic terminals by 6-OHDA completely reversed the motor depressant action of NPA, demonstrating the prevalent role of presynaptic mechanisms in the action of NPA The motor depressant effect of caerulein was resistant to the administration of 6-OHDA The different action of caerulein in selected mice according to their response to 100 μg/kg NPA revealed that the sedative effect of caerulein was more probably related to postsynaptic dopamine receptors The sedative effect of caerulein was higher in weak NPA responders, which evidently had lower density of dopamine$_2$- and serotonin$_2$-receptors in forebrain structures It was established that dopamine$_2$-receptors had one high-affinity site for neuroleptic drugs, but two sites—low- and high-affinity—for dopamine, apomorphine and NPA [18,27]. In weak responders caerulein and 5 μg/kg NPA stimulated ^{3}H-spiperone binding, but inhibited it in strong responders. NPA had similar sedative action in both groups of selected mice, revealing that dopamine "autoreceptors" were not related to high-affinity dopamine$_2$-receptors [27] Costall [14] has found that in strong responding rats to NPA (50 μg/kg) the content of dopamine (in nucleus accumbens) was approximately twice higher than in weak responders. It appears that displacing potency of caerulein against ^{3}H-spiperone binding is dependent on dopamine content in brain structures and caerulein only modulates the interaction of endogenous dopamine with dopamine$_2$-receptors It is quite possible that these differences in the action of caerulein on ^{3}H-spiperone binding in two selected groups of mice are linked to the different sedative effects of caerulein in these animals.

In conclusion, experiment 1 evidences that the sedative effect of caerulein is related, differently from NPA action, to postsynaptic dopamine receptors Caerulein seems to act as a functional antagonist of behavior stimulating effect of dopamine

EXPERIMENT 2: THE EFFECT OF SEROTONINERGIC LESIONS AND LONG-TERM HALOPERIDOL TREATMENT ON MOTOR DEPRESSANT AND ^{3}H-SPIPERONE BINDING INHIBITING EFFECTS OF CAERULEIN AND N-PROPYLNORAPOMORPHINE

Experiment 1 suggested differences in the mechanism of sedative action of caerulein and NPA. The aim of experiment 2 was to study further the mechanisms of action of caerulein and NPA using serotoninergic lesions and long-term administration of haloperidol.

METHOD

Serotoninergic neurotoxin 5,7-DHT (60 μg) was injected into the right lateral ventricle in a volume of 5 μl during 3 min under ether anesthesia Seven days were allowed for recovery from intraventricular intervention After completion of behavioral experiments the site of microinjection was detected histologically. According to some authors [5, 28, 35], administration of p-chloroamphetamine (PCA) in high doses causes degeneration of serotoninergic terminals in forebrain structures PCA was injected twice in a dose of 15 mg/kg, 8 and 7 days before the behavioral and binding experiments The action of NPA and caerulein was also studied after 14 days

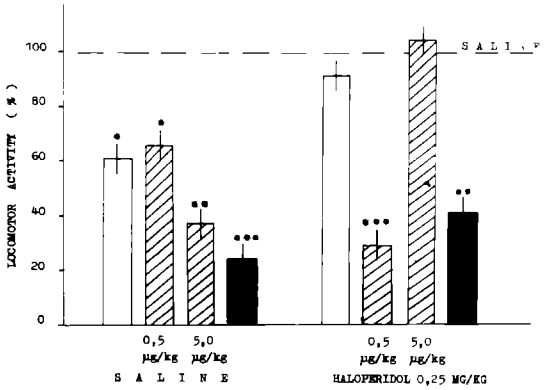

FIG 4 The changes in motor inhibiting action of N-propylnorapomorphine and caerulein after cessation of 14 days haloperidol medication White bars—caerulein 2 μg/kg, striped—NPA 0 5 and 5 0 μg/kg, black—the combination of caerulein and 0 5 μg/kg NPA The mean value of motor activity for saline treated group was 1180±147 counts during 30 min *$p<0$ 05, **$p<0$ 02, ***$p<0$ 01 (Student's t-test)

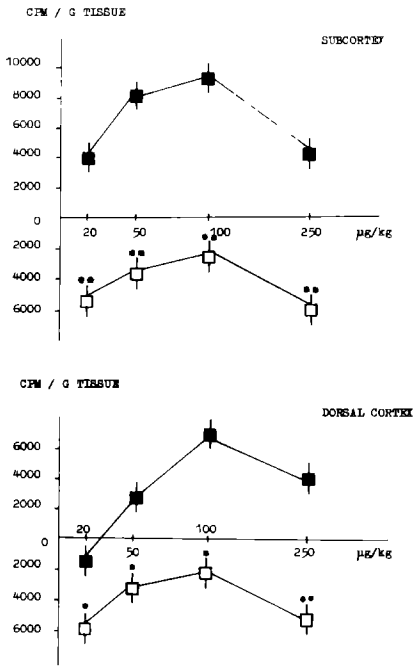

FIG 5 The action of caerulein on ^{3}H-spiperone binding after cessation of 14 days haloperidol treatment Black squares—the action of caerulein after saline pretreatment, white squares—after two weeks haloperidol administration Abscissa the dose of caerulein in μg/kg, ordinate radioactivity counts per gram tissue −—inhibition, and +—stimulation of ^{3}H-spiperone binding *$p<0$ 05, **$p<0$ 01 vs saline pretreated animals (Student's t-test)

administration of haloperidol (0 25 mg/kg, twice daily), increasing the sensitivity of pre- and postsynaptic dopamine receptors [11,53]. Seventy-two hours after cessation of two weeks haloperidol treatment the behavioral experiment with appropriate doses of caerulein, NPA and haloperidol was performed Simultaneously with the behavioral experiment the in vivo ^{3}H-spiperone binding studies were carried out after long-term administration of PCA and haloperidol After lesioning of serotoninergic terminals of brain by PCA and 5,7-DHT the spectrofluorimetric method was used for detection of dopamine, serotonin and their major metabolites [20]

RESULTS

Effect of PCA and 5,7-DHT on Locomotor Effect of Caerulein and NPA

The pretreatment with PCA and 5,7-DHT decreased obviously (50–60%) the levels of serotonin and its major metabolite 5-hydroxyindoleacetic acid in striatal slices, without changing dopamine concentrations. The administration of both serotoninergic neurotoxins evidently potentiated the motor inhibiting effect of NPA The action of simultaneous administration of NPA and caerulein was also augmented, whereas the sedative effect of caerulein in grouped mice was somewhat enhanced only after administration of PCA (Fig. 3) The pretreatment with PCA (2×15 mg/kg) inhibited the displacing potency of 5 μg/kg NPA and 50 μg/kg caerulein (Table 3), while the part of ^{3}H-spiperone binding displacable only by 50 μg/kg NPA remained unchanged

Effect of NPA and Caerulein on Locomotor Activity and ^{3}H-Spiperone Binding After Long-Term Haloperidol Treatment

The mild sedative effect of 50 μg/kg haloperidol was reversed to stimulation of exploratory activity after cessation of long-term haloperidol (0 25 mg/kg twice daily during two weeks) treatment (Table 4) Tolerance developed also to the motor depressant action of 2 μg/kg caerulein In saline pretreated mice the sedative action of simultaneous treatment of haloperidol and caerulein did not differ from the action of caerulein alone However, after withdrawal of long-term administration of haloperidol the concomitant treatment of caerulein and haloperidol completely reversed the tolerance to the action of both drugs (Table 4) The changes in motor depressant action of NPA were dependent on the dose of NPA 0 5 μg/kg NPA had more pronounced inhibiting effect after two weeks haloperidol medication (Fig 4), while the action of 5 μg/kg NPA was significantly reduced Two weeks haloperidol treatment also reduced the interaction between NPA and caerulein (Fig 4) Some animals became hyperexcitable after simultaneous administration of NPA and caerulein to haloperidol pretreated mice The diminution of 5 μg/kg NPA inhibiting action on ^{3}H-spiperone binding was seen after 14 days haloperidol medication (Table 3), whereas the action of 50 μg/kg NPA was evidently increased The inhibiting action of 50 μg/kg caerulein was turned to stimulation of ^{3}H-spiperone binding after cessation of long-term neuroleptic treatment (Table 3) More detailed analysis of caerulein inhibiting action revealed (Fig. 5) the more pronounced effect of caerulein on ^{3}H-spiperone binding in subcortical structures, with maximal inhibition after administration of 100 μg/kg caerulein After cessation of two weeks haloperidol treatment the inhibition curve of caerulein was shifted to stimulation of ^{3}H-spiperone binding (Fig 5)

DISCUSSION

Experiment 2 evidently supports our opinion that the sedative effects of caerulein and NPA are mediated through dissimilar mechanisms Lesions of serotoninergic terminals

by PCA and 5,7-DHT demonstrate the involvement of serotoninergic mechanisms in the inhibitory action of NPA This opinion was supported by our previous investigation [52], where the potentiation of apomorphine sedative effect by low dose of pirenperone, a selective antagonist of serotonin$_2$-receptors, was shown The sedative effect of caerulein was influenced only by pretreatment with PCA, but not by microinjection of 5,7-DHT The possible explanation for these differences may be the dissimilar action of 5,7-DHT and PCA on postsynaptic serotonin$_2$-receptors sensitivity It was found that 5,7-DHT caused behavioral hypersensitivity on serotonin receptors [6, 49, 50], while PCA induced subsensitivity to serotonin agonists [5] These findings may support the involvement of postsynaptic serotonin$_2$-receptors in the action of caerulein, but to a lesser extent than dopamine$_2$-receptors This opinion is in agreement with binding studies where higher doses of caerulein were needed for inhibition of ^{3}H-spiperone binding to serotonin$_2$-receptors in dorsal cortex than to dopamine$_2$-receptors in subcortical structures

Investigations performed after cessation of two weeks haloperidol treatment support the hypothesis of Protais [42] that the sedative effect of moderate doses of NPA is related to other types of dopamine receptors than the action of low doses Long-term haloperidol medication induced tolerance to the sedative effect of 5 μg/kg NPA, but increased the action of 0 5 μg/kg NPA In the binding experiments the reduction of displacing potency of 5 μg/kg NPA after withdrawal of 14 days haloperidol was also seen It is probable that NPA in moderate doses interacts with postsynaptic dopamine$_2$-receptors having high-affinity for dopamine agonists and not only with so-called dopamine "autoreceptors " Two weeks haloperidol treatment caused tolerance to both effects of caerulein—sedative and inhibition of ^{3}H-spiperone binding The interaction between NPA and caerulein was also decreased after 14 days neuroleptic administration, while coadministration of haloperidol and caerulein in low doses reversed the tolerance to the sedative effects of both drugs It is probable that the stimulation of ^{3}H-spiperone binding to dopamine$_2$- and serotonin$_2$-receptors after long-term neuroleptic medication plays a role in the antipsychotic action of neuroleptic drugs There was described the substantial dose dependent increase of CCK-8 content in subcortical forebrain structures after two weeks administration of different neuroleptic drugs (haloperidol, chlorpromazine, clozapine) [23] The density of CCK binding sites was also elevated after long-term neuroleptic medication [12]

In conclusion, experiment 2 supports the idea about the involvement of postsynaptic dopamine$_2$-receptors and to a lesser extent serotonin$_2$-receptors in the action of caerulein It is probable that the action of caerulein on animals behavior and ^{3}H-spiperone binding is related to the functional activity of dopamine$_2$- and serotonin$_2$-receptors, but also to the levels of endogenous neurotransmitters

GENERAL DISCUSSION

There are two opposite concepts existing about the site of action of CCK-8 and caerulein after systemic administration The first group of investigators [17,34] has demonstrated the relation of sedative effects of CCK-8 and caerulein to the afferent system of nervus vagus Vagotomy [34] or lesions of nucleus tractus solitarius [17], the central termination of vagal sensory fibers, abolished the depression of somatic function induced by CCK-8 or caeurlein However, the pharmacological experiments described by Zetler [56, 57, 58] suggest that CCK-like peptides possess marked effects in animal behavior models known to reliably reflect the efficacy of well-known centrally active drugs such as analgesics, neuroleptics and tranquilizers

The present investigation reveals that at least partly the central monoaminergic mechanisms are involved in the depressive action of caerulein on mice behavior This idea is supported by the following findings (1) Caerulein inhibits in vivo ^{3}H-spiperone binding in the brain, in lower doses to dopamine$_2$-receptors in subcortex and in somewhat higher doses to serotonin$_2$-receptors in dorsal cortex This finding is in agreement with the in vitro investigations [4] showing that 10 nM CCK-8 significantly modulates ^{3}H-spiperone binding to dopamine$_2$-receptors in striatum and moderatley to serotonin$_2$-receptors in dorsal cortex, (2) The sedative effect of caerulein was in negative correlation with reaction of mice to motor stimulating action of NPA (100 μg/kg) and density of ^{3}H-spiperone binding sites in forebrain structures, (3) Two weeks haloperidol administration induced the tolerance to the motor depressant effect of caerulein and reversed the inhibiting action of caerulein into stimulation of ^{3}H-spiperone binding

The potentiation of apomorphine-induced inhibition of dopamine neurons by CCK-8 and caerulein was demonstrated in mesencephalon [30] But, the present investigation indicates the differences in the mechanism of motor depressant action of NPA and caerulein It appears that NPA releases its inhibiting action of mice behavior through the presynaptic dopamine receptors, while caerulein mainly interacts with postsynaptic dopamine$_2$-receptors Intraventricular administration of 6-OHDA, destructing presynaptic dopaminergic terminals, shifted the sedative effect of NPA into stimulation of mice exploratory activity, whereas the action of caerulein remained unchanged In fact, the sedative effect of caerulein was in negative relation with the postsynaptic effect of NPA—to stimulation of locomotor activity Similar correlation was found between the behavioral effect of caerulein and density of ^{3}H-spiperone binding sites in forebrain These findings are in agreement with investigations [4,25] showing that CCK-8 more readily interacted with ^{3}H-spiperone than ^{3}H-NPA binding in "in vitro" conditions There was described [18,27] the existence of two binding sites for dopamine agonists on dopamine$_2$-receptors (high- and low-affinity) and only high-affinity site for neuroleptic drugs It was found [43] that these two sites for dopamine agonists had different localization in striatum—high-affinity sites were located predominantly on intrinsic neurons and low-affinity sites on corticostriatal fibers The high-affinity sites were regulated by guanine nucleotides GTP or its analogs significantly reduced the interaction of dopamine agonists with dopamine$_2$-receptors [27,43] It seems that caerulein more probably interacts with high-affinity binding sites for dopamine agonists on dopamine$_2$-receptors, antagonizing the stimulating action of dopamine and its analogs on animals' behavior Caerulein (75 μg/kg and higher doses) effectively reversed the motor stimulating action of dl-amphetamine (5 mg/kg), but did not affect quipazine (5 mg/kg), serotonin$_2$-receptors agonist, head-twitches (our unpublished data) and cage climbing behavior induced by higher doses of apomorphine in mice [57] The selection of mice according to their response after administration of 100 μg/kg NPA also support the involvement of high-affinity dopamine$_2$-receptors in the action of caerulein The clearcut

positive correlation between the content of dopamine in nucleus accumbens and the response to motor stimulating effect of NPA was discovered in rats [14] In strong responders the concentration of dopamine in nucleus accumbens was approximately two times higher compared to weak responders [14] In the present study, caerulein and 5 μg/kg NPA stimulated ^{3}H-spiperone binding in weak responding mice, while in strong responders both drugs had the opposite effect It appears that the action of caerulein on ^{3}H-spiperone binding is dependent on the levels of dopamine and affinity of dopamine$_2$-receptors to dopamine The long-term infusion of dopamine into nucleus accumbens caused the opposite changes in dopamine$_2$-receptors sensitivity in selected rats [15] In weak responders dopamine demonstrated dopamine receptor antagonist like properties, increasing the sensitivity of dopamine$_2$-receptors, while in strong responders it had the opposite effect, decreasing the affinity of dopamine receptors It is probable that NPA, similar to dopamine, has dopamine antagonist properties in weak responders in moderate dose (stimulation of ^{3}H-spiperone binding) and in high responders it acts as a receptor agonist (inhibition of ^{3}H-spiperone binding) The mixed agonist-antagonist properties of apomorphine and NPA seem to have the clinical relevance, because apomorphine reduces the psychotic symptomatology only in one subgroup of schizophrenic patients, suffering mainly from the paranoid schizophrenia, receiving neuroleptic medication, but not without neuroleptic drugs [1, 19, 21, 37, 47] Probably, this action of apomorphine is different from the sedative action of apomorphine, which was antagonized by neuroleptic drugs [13] It is possible that in these patients apomorphine caused the short-lasting stimulation of neuroleptics binding to dopamine$_2$- and serotonin$_2$-receptors

The differences in the action of NPA and caerulein also involve the serotoninergic mechanisms It seems that the inhibiting action of caerulein on mice behavior is mainly dependent on dopaminergic mechanisms, while NPA also interacts with serotonin receptors There was demonstrated the displacement of ^{3}H-ketanserin from serotonin$_2$-receptors by apomorphine [36] In the present study NPA inhibited similarly ^{3}H-spiperone binding in dorsal cortex (mainly serotonin$_2$-receptors) as well as in subcortical forebrain structures (prevailing dopamine$_2$-receptors) Caerulein in lower doses interacted with dopamine$_2$-receptors, whereas the higher doses were needed for interaction with serotonin$_2$-receptors It was found that to suppress dopamine turnover lower concentrations of CCK were needed than to inhibit serotonin turnover [51] Destruction of serotoninergic terminals by PCA and 5,7-DHT significantly increased the motor depressant effect of NPA, while only PCA, decreasing also serotonin$_2$-receptors sensitivity [5], moderately potentiated the action of caerulein The involvement of serotoninergic mechanisms in the behavioral effects of apomorphine was also stated by other authors The administration of different serotonin agonists into median raphe nuclei, innervating mesolimbic area, potentiated in rats the motor stimulation induced by apomorphine [22] Apomorphine in high doses (over 4 mg/kg) induced in cats behavioral effects similar to LSD, an agonist of serotonin$_2$-receptors [50] In the clinical studies [33], it was established that apomorphine had pronounced sedative action only in patients with enlarged cerebral ventricles In this subgroup of schizophrenic patients the decreased content of 5-hydroxyindoleacetic acid, the major metabolite of serotonin, in cerebrospinal fluid was described [41] These clinical observations are in agreement with our study showing the increased sedative effect of apomorphine and NPA in the case of deficiency of central serotoninergic mechanisms

Special attention was drawn to the interaction between haloperidol, the classical neuroleptic drug, and caerulein In the pharmacological experiments similarities were found in the behavioral effects of caerulein and haloperidol, but a positive interaction between these drugs was not found [55, 57, 58] Similar absence of interaction in intact animals was established in the present study The interaction between caerulein and haloperidol became evident after two weeks haloperidol administration Caerulein reversed the tolerance to the sedative effect of haloperidol and increased ^{3}H-spiperone binding after long-term neuroleptic medication The increased number of CCK binding sites was demonstrated after long-term haloperidol treatment [12] Different neuroleptic drugs (haloperidol, chlorpromazine, clozapine) induced dose dependent elevation of CCK-8 content in forebrain subcortical structures after two weeks administration [23] It is possible the mechanisms described above are involved in the beneficial action of CCK-like peptides in neuroleptic-resistant schizophrenic patients [39,40]

In conclusion, it is probable that apomorphine and NPA have at least three distinct levels of action (1) The stimulation of dopamine "autoreceptors" causes the sedative effect in animals and humans [37], (2) The interaction with high-affinity dopamine$_2$- and serotonin$_2$-receptors induces the stimulation of ^{3}H-spiperone binding in animals responding weakly to motor stimulant action of NPA The beneficial clinical effect of apomorphine and NPA [47,48] might be related to these monoaminergic mechanisms, (3) Through the stimulation of low affinity dopamine$_2$- and serotonin$_2$-receptors are mediated the typical behavioral effects of apomorphine and NPA in higher doses (stereotyped behavior, cage climbing behavior, aggressiveness, etc)

Caerulein, after systemic administration, more probably interacts with high-affinity dopamine$_2$-receptors and to a lesser extent with high-affinity serotonin$_2$-receptors, inhibiting the stimulating effect of dopamine and its analogs on animals' behavior

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