Delayed Suppressive Effect of a Low Dose of Caerulein on the Grooming Behavior Induced by the D1-Receptor Agonist SKF 38393

Yoshikatsu Masuda, Shigeo Mural, Hiroko Saito, Eiichi Abe and Tadanobu Itoh

Department of Pharmacology, School of Dentistry, Iwate Medical University, 19-1, Uchimaru, Morioka 020, Japan

Received May 6, 1992 Accepted August 8, 1992

ABSTRACT—Caerulein (CLN, 0.8–80 μg/kg, s.c.) was administered to male rats 10 min or 24 hr before the injection of SKF 38393 (3 mg/kg, i.p.). The increased mouth movement and grooming behavior by SKF 38393 were suppressed dose-dependently by CLN 10 min before the SKF 38393. CLN at the dose of 0.8 μg/kg, given 24 hr before the SKF 38393, suppressed the grooming behavior by SKF 38393. These findings suggest that a low dose of CLN, but not a high dose, had a delayed suppressive effect on the grooming behavior induced by an excess of D1-activity.

Keywords: Caerulein, SKF 38393, Grooming behavior

Long-term administration of a neuroleptic to schizophrenic patients can often result in involuntary dyskinetic disorders such as tardive dyskinesia, which is thought to be mediated by an increased dopaminergic activity in the striatum. Chronic treatment of rats with neuroleptics cause an increase in mouth movements. The increased mouth movements are used as an animal model of tardive dyskinesia (1, 2). The increase in mouth movements is also induced by a single administration of the selective dopamine D1-agonist SKF 38393 (3, 4). The increased mouth movements of the rat induced by the long-term administration of neuroleptics and that induced by the administration of the selective D1-agonist SKF 38393 resemble each other in the aspect that both are characterized by a relative excess of D1-activity (3, 4). Cholecystokinin octapeptide (CCK-8) suppresses both SKF 38393-induced behavior and chronic neuroleptic-induced involuntary dyskinetic disorders (2, 5). This suggests that CCK-8 may be of use against involuntary dyskinetic disorders. These studies were carried out with an emphasis on analyzing the immediate effect of CCK-8.

Caerulein (CLN), an analogue of CCK-8, has a long lasting effect on the monoamine level in rat brain regions (6). Behavioral studies showed the long-lasting effect of CLN (7, 8). For example, Ogawa et al. (8) reported long-lasting effect of CLN on permanent motor behavioral abnormalities induced by the neurotoxin iminodipropionitrile. Moreover, CLN produced biphasic and long-lasting improvement in a schizophrenic patient with bucco-lingual dyskinesia (9). These reports suggest that CLN has a continuous or delayed suppressive effect on involuntary movements. In this study, we determined if CLN has a delayed suppressive effect on the mouth movements and grooming behavior induced by SKF 38393.

Eighty male Sprague-Dawley rats (Nihon SLC, Shizuoka, Japan), initially weighing 250–300 g, were housed three per cage on a 12-hr light–12-hr dark cycle and allowed standard food pellets and water ad libitum for one week before the experiment.

To test the immediate effect of CLN, five rats were placed individually in transparent boxes (18 × 26 × 28 cm) and left there for one hour to acclimate them. Then CLN (ceruletide diethylamine, synthesized at the Shionogi Research Pharmaceuticals Laboratories) was subcutaneously administered in doses of 0.8, 8 and 80 μg/kg to the 1st, 2nd, and 3rd rat, respectively, and saline was administered to the 4th and 5th rat. Ten minutes after the injection, SKF 38393 ((±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride, Smith, Kline and French Laboratories) at the dose of 3 mg/kg was administered intraperitoneally to all the rats except for the 5th rat. The 5th rat was administered saline as a control. From ten min after the injection of SKF 38393, mouth movements, grooming be-
bavior and the level of awakening were observed for 1 min every 10 min and rated. The level of awakening was observed to evaluate the sedative effect of CLN (10). Five rats were monitored at one time by staggered observation. The observation was carried out 6 times, and each score was summed. The same procedure was repeated 8 times using 40 rats.

The delayed effect of CLN was tested by administration of CLN (0.8 µg/kg–80 µg/kg) or saline as in the experiments to determine the immediate effect and then they were returned to the animal room. Twenty four hours after the injection of CLN, they were placed individually in transparent boxes and left for one hour. Then the same procedure as used to examine the immediate effect was carried out.

The following acts of behavior were observed: mouth movements, consisting of vacuous chewing and tongue protrusion, and grooming behavior, consisting of vibration of the forepaws, face washing, body grooming, paw licking and genital grooming. The acts of behavior were rated as follows: for mouth movements and grooming behavior: score of 1 for discontinuous behavior, a score of 2 for continuous behavior; for the level of awakening: a score of 0 for sleepy rat, a score of 1 for drowsy rat, a score of 2 for awake rat and a score of 3 for the rat manifesting movement. Data on the five groups were assessed according to the method of Kruskal-Wallis followed by the non parametric Williams’ test using statistic soft ware (MUSCUT, Yukms Corp.)

The upper panel of Fig. 1 shows the immediate effect of CLN. The saline + SKF 38393 group shows a significant increase in mouth movements (left) and grooming behavior (middle) compared to the saline + saline group. CLN, which was given 10 min before SKF 38393, suppresses SKF 38393 induced behavior dose-dependently. CLN 80 µg/kg significantly suppresses mouth movements and grooming behavior, and simultaneously decreases the level of awakening (right) compared to all other groups.

The lower panel shows the delayed effect of CLN. The saline + SKF 38393 group shows a significant increase in mouth movements (left) and grooming behavior (middle) compared to the saline + saline group. CLN, which was given 24 hr before SKF 38393, had no effect on SKF 38393-induced mouth movements, but...
had an effect on SKF 38393-induced grooming behavior. The low dose of CLN (0.8 μg/kg) suppressed SKF 38393-induced grooming behavior significantly. CLN had no effect on the level of awakening (right).

The finding showed that SKF 38393-induced behavior was suppressed by the immediate effect of CLN as already reported for CCK-8 (5). CLN at the dose of 80 μg/kg suppressed powerfully both SKF 38393-induced behavior and the level of awakening. CLN has a neuroleptic like effect (11). A neuroleptic such as haloperidol acutely suppressed the behavior induced by a dopamine agonist, but there was a rebound increase (12). It appears that the immediate effect of CLN may be based on the neuroleptic-like property of CLN.

The experiment on the delayed effect showed that a low dose of CLN (0.8 μg/kg) had a delayed effect on SKF 38393-induced grooming behavior. In rodents, grooming behavior occurs under conditions of extreme arousal. The enhancement of grooming behavior is considered a displacement activity, which may be essential in restoring homeostasis (13). Thus, an impairment of the homeostasis mechanism may explain the greater grooming behavior observed in rats pretreated with SKF 38393, and a low dose of CLN may decrease the impairment of homeostasis. Nishikawa et al. (9) reported the biphasic and long-lasting effect of a single dose of CLN (0.8 μg/kg) on tardive dyskinesia. Our results showed a similar phenomenon, but failed to suppress mouth movements. The result of the delayed effect of CLN provide two interesting findings: 1) CLN (0.8 μg/kg) was effective for suppressing grooming behavior and ineffective for suppressing mouth movements. 2) Only a low dose of CLN (0.8 μg/kg) was effective, and 80 mg/kg of CLN was ineffective. There is no apparent explanation for these results. Several reports indicate that D₁ and D₂ receptor systems functionally interact to regulate the full expression of dopamine mediated behaviors; one is a co-operative interaction, as in the regulation of grooming (14), and the other is oppositional, as in the regulation of vacuous chewing (3). Both grooming behavior and mouth movements are induced by the stimulation of D₁-receptors, but the mouth movements were suppressed by a D₂-agonist, while on the other hand, the grooming behavior was suppressed by a D₁-agonist. We assume that this difference of D₁/D₂ interaction for the grooming behavior and mouth movements appeared as the difference of a delayed effect of CLN for two behaviors. Although the mechanism for the delayed effect of a low dose CLN (0.8 μg/kg) is not clear, a possible explanation may be that CLN modulates dopamine release through an interaction between presynaptic cholecystokinin receptors and dopamine autoreceptors (15), and the haloperidol-like effect (rebound increase) of a high dose of CLN (80 μg/kg) may mask the delayed suppressive effect.

In conclusion, a low dose of CLN (0.8 μg/kg but not 8 mg/kg and 80 μg/kg) has a delayed suppressive effect on grooming behavior. However, the result also provides little support for the ability of CLN (0.8-80 μmg/kg) to produce a delayed antagonism of D₁-agonist-induced mouth movements.

Acknowledgments

We thank Ms. M. Miyata for skillful technical assistance. Caerulein was generously supplied by Shionogi Pharmaceutical Company.

REFERENCES

1. Waddington, J.L., Youssef, H.A., O’Boyle, K.M. and Mo- lloy, A.G.: A reappraisal of abnormal involuntary movements (tardive dyskinesia) in schizophrenia and other disorders: animal models and alternative hypotheses. In The Neurobiology of Dopamine Systems, Edited by Winlow, W. and Markstein, R., p. 266–286, Manchester University Press, Manchester (1986)

2. Stoessl, A.J., Dourish, C.T. and Iversen, S.D.: Chronic neuroleptic-induced mouth movement in the rat: suppression by CCK and selective dopamine D₁ and D₂ receptor antagonists. Psychopharmacology (Berlin) 98, 372–379 (1989)

3. Johansson, P., Levin, E., Gunne, L. and Ellison, G.: Opposite effects of a D₁ and D₂ agonist on oral movements in rats. Eur. J. Pharmacol. 134, 83–88 (1987)

4. Rosengarten, H., Schweitzer, J.W. and Friedhoff, A.J.: Induction of oral dyskinesias in naive rats by D₁ stimulation. Life Sci 33, 2479–2482 (1983)

5. Dourish, C.T., Hutson, P.H., Kitchener, S.J., O’Neil, M.J. and Suman-Chauhan, N.: Behavioral and neurochemical evidence for an interaction of CCK with D₁ dopamine receptors. In Multiple Cholecystokinin Receptors in the Central Nervous System, Edited by Dourish, C.T., Cooper, S.J., Iversen, S.D. and Iversen, L.L., p. 189 –192, Oxford University Press, Oxford (1992)

6. Kuroki, T., Matsumoto, T., Hirano, M., Kagoshima, H., Yao, H., Uchimaru, H., Nakamura, K. and Nakahara, T.: Long-lasting effect of systemically administered caerulein on monoaminergic neuronal pathways in rat brain. Neuropeptides 9, 169–176 (1987)

7. Matsubara, K. and Matsushita, A.: Analysis of the long-last- ing antagonistic effect of caerulein on amphetamine hyperactivity in rats. Japan. J. Pharmacol. 38, 381–390 (1985)

8. Ogawa, N., Haba, K., Asanuma, M. and Mori, M.: Long-lasting effect of ceruleotide on dyskinesia and monoaminergic neuronal pathways in rats treated with inominodipropionicitrile. Brain Res. 556, 271–279 (1991)

9. Nishikawa, T., Tanaka, M., Koga, I. and Uchida, Y.: Biphasic and long-lasting effect of ceruleotide on tardive dyskinesia. Psychopharmacology (Berlin) 86, 43–44 (1985)

10. Zettler, G.: Behavioral pharmacology of CCK and analogues. Psychopharmacol. Bull. 19, 347–351 (1983)
11 Van Ree, J.M., Gaffori, O. and De Wied, D.: In rats, the behavioral profiles of CCK-8 related peptides resembles that of antipsychotic agents. Eur. J. Pharmacol. 93, 63–68 (1983)

12 Gunne, L.M., Anderson, U., Bondesson, U. and Johansson, P.: Spontaneous chewing movements in rats during acute and chronic antipsychotic drug administration. Pharmacol. Biochem. Behav. 25, 897–901 (1986)

13 Continella, G., Drago, F., Auditore, S. and Scapagnini U.: Quantitative alteration of grooming behavior in aged male rats. Pharmacol. Biochem. Behav. 35, 839–841 (1985)

14 Waddington, J.L.: Functional interaction between D-1 and D-2 dopamine receptor system: their role in the regulation of psychomotor behavior, putative mechanisms, and clinical relevance. J. Psychopharmacol. 3, 1–10 (1989)

15 Tanganelli, S., Fuxe, K., von Euler, G., Agasti, L.F., Ferraro, L. and Ungerstedt, U.: Involvement of cholecystokinin receptors in the control of striatal dopamine autoreceptors. Naunyn Schmiedebergs Arch. Pharmacol. 342, 300–304 (1990)