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Cysteamine Blocks Amphetamine-Induced Deficits in Sensorimotor Gating

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FEIFEL, D. AND K. L. MINOR. *Cysteamine blocks amphetamine-induced deficits in sensorimotor gating.* PHARMACOL BIOCHEM BEHAV **58**(3) 689–693, 1997.—Somatostatin is a neuropeptide that has been shown to interact with dopamine. Low concentrations of cysteamine selectively depletes somatostatin and has been used to investigate the role of endogenous somatostatin in lieu of an available selective receptor antagonist. We examined the effects of various doses of subcutaneous cysteamine on baseline and amphetamine-disrupted sensorimotor gating as measured by prepulse inhibition of the acoustic startle reflex. Cysteamine in doses ranging from 50–300 mg/kg reversed decreases in PPI induced by systemic injections of amphetamine (2 mg/kg). Cysteamine had no effect on the amplitude of the acoustic startle reflex itself. The results lend further support to a somatostatin–dopamine interaction within the brain in which endogenous somatostatin facilitates dopaminergic activity. These findings also suggest that endogenous somatostatin might play a significant role in regulation of sensorimotor gating deficits. This has clinical implications as deficient prepulse inhibition is recorded in humans suffering from neuropsychiatric conditions such as schizophrenia. © 1997 Elsevier Science Inc.

Somatostatin Cysteamine Sensorimotor gating Dopamine Prepulse inhibition Schizophrenia

SOMATOSTATIN is a neuropeptide that has been localized in many regions of the brain, with high concentration existing in the caudate-putamen and nucleus accumbens septi (7). Neuroanatomical studies suggest that dopamine afferents in these regions may interact with somatostatin interneurons (43). Somatostatin has been reported to cause an increase in the turnover (2,15) and release (10) of striatal dopamine. Conversely, the dopamine agonist amphetamine has been found to inhibit striatal somatostatin release (36). Chronic administration of dopamine antagonists reduce brain somatostatin immunoreactivity (3,27). Studies suggest that brain somatostatin may play a role in regulation of dopamine-mediated behaviors. Central infusions of low dose somatostatin (0.01–0.1 μg) have been reported to increase spontaneous locomotor activity whereas higher doses decrease it (1–10 μg), possibly due to motor impairment (18,28–30). A similar dose-dependent effect of central somatostatin on self-stimulation behavior has been reported (42). Somatostatin also potentiates the behavioral effects of L-DOPA (30).

Investigation of the role of endogenous brain somatostatin has been limited by the lack of selective receptor antagonists for this peptide. However, cysteamine (2-aminoethanetiol), a sulfhydryl agent that is a normal constituent of mammalian cells, has been found to be a useful pharmacological alternative. Cysteamine administered systemically or centrally has been demonstrated to produce a rapid and prolonged but reversible depletion of somatostatin levels in the brain (31,35). Cysteamine actions on somatostatin appear to be selective because levels of other peptides (25) and monoamines (21,23) are not altered at doses that deplete somatostatin. Cysteamine administered subcutaneously and centrally has physiological and behavioral effects that are opposite those produced by somatostatin (1,6,11,39,40,44). Cysteamine therefore appears to be an effective antagonist of somatostatin activity.

Behavioral studies using cysteamine have supported the notion of functional somatostatin–dopamine interaction within the striatum. Subcutaneous and central pretreatment with cysteamine blocks amphetamine-induced hyperlocomotion and apomorphine-induced stereotypy (21,23). Cysteamine, however, does not alter amphetamine-induced conditioned place preference (23). This effect seems to be mediated by modulation of striatal somatostatin but not dopamine or serotonin, because levels of only the former were found to be altered (21,23). Based upon these findings it has been suggested that endogenous somatostatin may regulate some dopamine mediated behaviors (e.g., motor activity) but not

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others (e.g., reward). The present study sought to evaluate the role of somatostatin–dopamine interactions in sensorimotor gating, a process that is critically regulated by dopamine (33).

Prepulse inhibition (PPI) occurs when the mammalian startle reflex to a sudden intense stimuli (the "pulse") is inhibited by a weaker stimulus presented 50–200 ms earlier (the "prepulse"). PPI is believed to be an operational measure of sensorimotor gating and is regulated by corticostriatal–pallidal–pontine circuitry in which mesolimbic dopamine plays a critical role (33). Dopamine agonists such as amphetamine and apomorphine disrupt PPI (22) and neuroleptic agents reverse this disruption (34).

METHOD

Animals

Male Sprague–Dawley rats ($n = 96$) weighing 225–249 g on arrival were acclimated to the animal facility for 1 week prior to experimentation. Animals were housed in groups of two or three and maintained in a temperature-controlled environment (69 ± 2°), exposed to 12 h of light daily (0600–1800 h), provided food and water ad lib.

Drug Administration

Cysteamine (2-Mercaptoethylamine, Sigma Chemical, St. Louis, MO), was dissolved in 0.9% sodium chloride. Three hours prior to testing, rats were injected subcutaneously with either 0 (saline), 50, 100, 200, or 300 mg/kg cysteamine in a volume of 1 ml/kg body weight. One hundred and fifty minutes later, 30 min prior to behavioral testing, rats were given a subcutaneous (SC) injection of 2 mg/kg amphetamine, a dose reported to significantly reduce PPI in rats (22) or saline. Animals were tested 1 day only.

Behavioral Testing/Startle Response

Three hours after initial the cysteamine injection, animals were placed in separate startle chambers within a sound-attenuated room and exposed to a 65 dB acoustic [A] background white noise. Each chamber is a ventilated enclosure consisting of a Plexiglas cylinder 8.2 cm in diameter resting on a 12.5 × 25.5 Plexiglas frame, under which is located a piezoelectric accelerometer (SR-LAB Startle Systems, San Diego, CA). Following a 5-min acclimation period, acoustic noise bursts were presented from speakers mounted within the chamber 24 cm above each of the animals. The accelerometers detected and transduced the motion within the cylinders, thus, quantifying startle amplitudes.

Rats were exposed to five different acoustic startle conditions: no stimulation, a 40 ms, 120 dB [A] startle pulse alone (P-alone), and P-alone preceded, 100 ms, by prepulses of 20 ms duration that were 3, 5, or 10 dB [A] above background noise. There were a total of 49 stimuli presented, with an average interpulse interval of 15 s (range 9–21 s). Behavioral testing took place between 1100 and 1700 h.

Statistical Analysis

Amplitudes for pulse alone condition were analyzed as a measure of absolute acoustic startle response using a two-way ANOVA with amphetamine condition and cysteamine dose as between factors. Prepulse inhibition was calculated for each of the prepulse conditions as the percentage reduction in average startle amplitude (120 dB pulse alone) produced by prepulse conditions (120 dB pulse + prepulse) and calculated using the formula [100 − (100 × amplitude on prepulse trial/amplitude on P-ALONE trial)]. The resultant percent score indicates the degree of PPI, in which a large value represents strong PPI, and vice versa. The average combined values for the percent PPI obtained for each of the three prepulse intensities tested were was analyzed using a two-way ANOVA with repeated measures, with amphetamine condition and cysteamine dose as between factors. Significant two-way ANOVA results were followed with individual one-way ANOVAs and post hoc individual comparisons of group means using Bonferonni *t*-tests.

RESULTS

Five of 16 animals treated with 300 mg/kg cysteamine developed generalized seizures prior to startle testing and were therefore not tested.

Two-way ANOVA results for the pulse-alone amplitudes revealed no significant effect of amphetamine, $F(1, 86) = 2.16$, NS, or cysteamine, $F(4, 86) = 0.77$, NS, and no significant amphetamine × cysteamine interaction, $F(1, 86) = 1.36$, NS. Although not statistically significant, all doses of cysteamine tended to decrease startle amplitude in amphetamine-treated animals (Fig. 1).

A two-way ANOVA of PPI values revealed a significant amphetamine treatment effect, $F(1, 86) = 26.28$, $p < 0.001$, and a significant cysteamine treatment effect, $F(4, 86) = 2.89$, $p < 0.03$. The cysteamine × amphetamine interaction approached significance, $F(4, 86) = 2.27$, $p = 0.067$. Independent one-way ANOVAs in animals treated with amphetamine revealed a significant cysteamine effect, $F(4, 43) = 9.63$, $p < 0.04$, but not in rats who were not treated with amphetamine, $F(4, 43) = 1.97$, $p = 0.181$. Individual post hoc comparison of group means indicated that amphetamine significantly decreased PPI in animals given the 0 mg/kg dose of cysteamine, $t(21) = -2.48$, $p = 0.02$, but not in animals given any of the active doses of cysteamine tested.

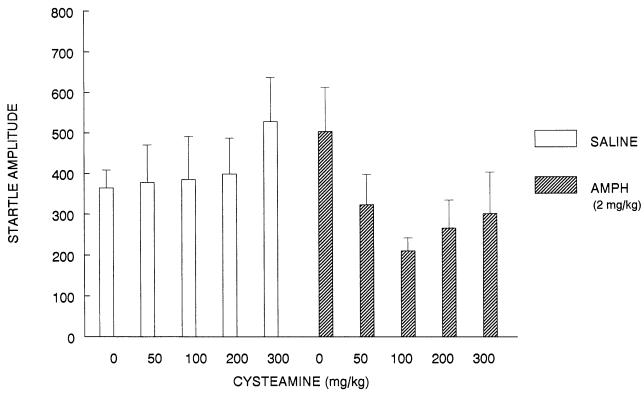

FIG. 1. Mean startle amplitude + SEM following 120 dB acoustic stimuli (without prepulse) in rats treated subcutaneously with saline plus cysteamine ($n = 13, 11, 9, 9$, and 6 for 0, 50, 100, 200, and 300 mg/kg, respectively) or amphetamine (2 mg/kg) plus cysteamine ($n = 13, 10, 10, 10$, and 5 for 0, 50, 100, 200, and 300 mg/kg, respectively).

DISCUSSION

Kungel et al. (20) showed that SC cysteamine blocks the natural increase in acoustic startle reflex that occurs in developing rat pups. They suggested that it does so by depleting somatostatin, which is transiently expressed in the mammalian brainstem during development (19). Fendt et al. (13), on the other hand, found that sandostatin, a somatostatin agonist, infused into the pontine reticular nucleus of adult rats had no effect on baseline acoustic startle amplitude although it blocked fear-potentiated startle. In the present study, cysteamine had no significant effect on amplitude of the acoustic startle reflex, suggesting as did Fendt et al.'s finding that endogenous somatostatin does not play a critical role in regulating the amplitude of the acoustic startle reflex in adult rats.

Cysteamine blocked amphetamine-induced decreases in PPI. This suggests that endogenous somatostatin plays an important regulatory role in the brain mechanisms that modulate the startle reflex via prepulse gating under conditions of excess dopamine (Fig. 2). Cysteamine, across a wide dose range, has been shown to cause a rapid depletion of striatal somatostatin that peaks at approximately 3–4 h and gradually returns to baseline over the course of 2–3 days (17,23). Doses of cysteamine above 100 mg/kg have been shown to also affect brain noradrenaline and dopamine levels (17,41). In contrast, cysteamine doses of 100 mg/kg and lower have been shown to potently decrease brain somatostatin without altering levels of other neurotransmitters (21,23). The ability of all doses of cysteamine tested in this study, including 50 mg/kg, to oppose the PPI-disruptive effects of amphetamine suggests that this cysteamine effect is due to depletion of somatostatin and not other neurotransmitters. Cysteamines' effects on amphetamine-disrupted PPI in this study suggest a dopamine antagonist action similar to that seen with neuroleptics (32,34). This is consistent with previous studies that generally suggest that somatostatin exerts a facilitatory effect on dopaminergic activity (18,26,28–30), and that depletors of somatostatin (cysteamine, panthenine) exert a dopamine inhibitory effect (1,21, 23,38). Dopaminergic afferents to the nucleus accumbens play a critical role in regulating PPI (33). It is thus possible that cysteamine, through depletion of somatostatin in the nucleus accumbens, facilitates PPI. Consistent with such a mechanism, Martin-Iversen et al. (23) and Lee et al. (21) found that infusion of cysteamine into the nucleus accumbens reduced amphetamine-induced hyperlocomotion without having any significant effects on spontaneous locomotion. There is evidence for the presence of somatostatin receptors in the nucleus accumbens (8,12,37). Dournard et al. (12) found evidence of somatostatin receptors on dendrites and perikarya but not axon terminals in the nucleus accumbens and the striatum, suggesting that somatostatin may modulate dopamine activity via a postsynaptic site of action within the nucleus accumbens. Somatostatin receptors were also localized on axon terminals, but not on perikarya or dendrites, in the ventral tegmental area (12). This suggests that somatostatin may modulate mesolimbic dopamine via presynaptic modulation of mesolimbic afferents projecting to dopaminergic cell bodies in the ventral tegmentum.

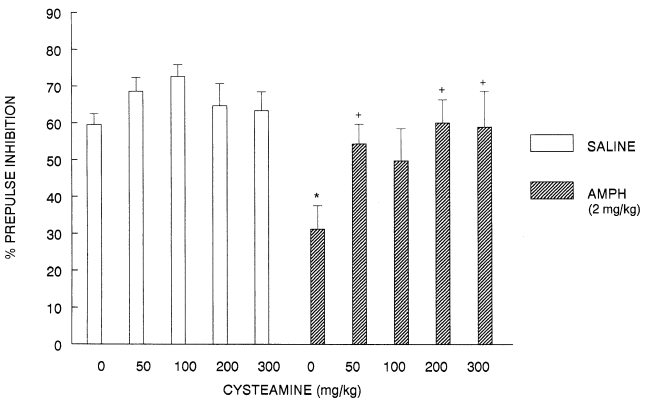

FIG. 2. Mean prepulse inhibition (PPI) + SEM of acoustic startle reflex in rats treated subcutaneously with saline plus cysteamine (n = 13, 11, 9 , 9, and 6 for 0, 50, 100, 200, and 300 mg/kg, respectively) or amphetamine (2 mg/kg) plus cysteamine (n = 13, 10, 10, 10, and 5 for 0, 50, 100, 200, and 300 mg/kg, respectively). Bars represent the %PPI obtained by averaging PPI results using three prepulse intensities (3, 5, and 10 dB) above background noise. *Indicates significantly ($p < 0.05$) lower than animals treated with saline/saline. $^{+}$Indicates significantly ($p < 0.05$) greater than animals treated with amphetamine and 0 mg/kg cysteamine.

PPI can be measured in humans and is considered an operational measure of sensorimotor gating of external stimuli. Deficits in PPI have been reported in humans with schizophrenia (5). Supporting an association between PPI deficits and clinical manifestations of schizophrenia is the finding that schizophrenia patients with maximal PPI deficits show the greatest thought disorder (9). Several studies have explored the possible association between endogenous somatostatin and schizophrenia by examining somatostatin levels in CSF and postmortem brain tissue of schizophrenia patients. The findings, however, are equivocal, with decreased (4,14,24), increased (16) and not significantly different (45) somatostatin levels reported in these patients vs. matched controls. Based upon the results of this study and other preclinical studies it is conceivable that high endogenous somatostatin levels in certain regions of the brain could contribute to the deficits seen in schizophrenia, whereas lowered levels may attenuate those deficits and/or result from a compensatory mechanism in this disorder.

The efficacy of individual antipsychotics, both typical ones such as haloperidol and atypical ones such as clozapine, to normalize PPI in dopamine agonist-treated rats correlates significantly with their clinical efficacy (r = 0.96) (34). These findings in rats parallel the deficits in PPI observed in schizophrenia patients, which also may be corrected by both typical and atypical antipsychotics (34). Therefore, in addition to providing a valuable model for the study of neuroanatomical and neuropharmacological substrates of schizophrenia, dopamine agonist disrupted PPI provides a useful preclinical screen for agents that may possess antipsychotic properties. According to this model of sensorimotor gating deficits, cysteamine may possesses neuroleptic-like properties. Centrally active, selective somatostatin receptor antagonists that can be administered peripherally might have practical therapeutic potential as novel antipsychotic agents.

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