Pharmacology Biochemistry & Behavior, Vol. 32, pp. 629–635. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Effects of Cysteamine and Pantethine on Open-Field Behavior, Hypothalamic Catecholamine Concentrations, and Somatostatin-Induced Barrel Rotation in Rats

LÁSZLÓ VÉCSEI, CHRISTER ALLING, MARKUS HEILIG AND ERIK WIDERLÖV[1]

Department of Psychiatry and Neurochemistry, University of Lund
Box 638, S-220 06 Lund, Sweden

Received 2 June 1988

VÉCSEI, L., C. ALLING, M. HEILIG AND E. WIDERLÖV. *Effects of cysteamine and pantethine on open-field behavior, hypothalamic catecholamine concentrations and somatostatin-induced barrel rotation in rats.* PHARMACOL BIOCHEM BEHAV **32**(3) 629–635, 1989.—Cysteamine administered in a dose of 1.95 mM/kg subcutaneously (SC) markedly reduced several open-field behaviors (locomotion, rearing, grooming and defecation), while pantethine, administered in an equimolar dose, reduced the locomotion only. However, administered in a dose of 3.90 mM/kg (SC), pantethine also markedly reduced all open-field parameters. Cysteamine, and to less extent pantethine, reduced noradrenaline, and increased dopamine and DOPAC concentrations in the hypothalamus. It is discussed whether the lower potency of pantethine on open-field behaviors and hypothalamic catecholaminergic neurotransmission is connected with the limited activity of pantetheinase, the cysteamine-generating enzyme. Intracerebroventricularly (ICV) administered somatostatin did not influence the pantethine-induced (1.95 mM/kg SC) behavioral changes in the open-field test. It is possible that the peptide did not reach at the receptor sites in a sufficient concentration because of the reduced endogenous somatostatin content, or that the pantethine-induced noradranline depletion is connected with the ineffectiveness of somatostatin. Furthermore, pretreatment with cysteamine (1.95 mM/kg SC) or pantethine (1.95 mM/kg or 3.90 mM/kg SC) attenuated the somatostatin-induced (10 μg ICV) barrel rotation, suggesting that the level of endogenous somatostatin may play a role in the pathogenesis of this motor disturbance.

Barrel rotation Catecholamines Cysteamine Hypothalamus Open-field Pantethine

CYSTEAMINE (2-aminoethanethiol) is a cysteine derivative that in pharmacological doses produces duodenal ulcer, adrenal hemorrhagic necrosis, and dissecting aortic aneurysm in rats (16, 19, 28–32). It was reported by Szabo and Reichlin (31) that the drug rapidly depletes somatostatin-like immunoreactivity (SLI) in the gut and hypothalamus of rats. Later, Sagar *et al.* (27) found that cysteamine given systemically caused generalized depletion of SLI in the rat central nervous system. This reduction was rapid and reversible with nearly complete recuperation within 72 hr. Somatostatin and prolactin are thus far the only neuropeptides studied that are significantly affected by the drug, whereas luteinizing hormone-releasing hormone, vasoactive intestinal polypeptide, cholecystokinin octapeptide, arginine vasopressin, substance P, thyrotropin releasing hormone, beta-endorphin and neuropeptide Y remain unaltered (7, 22, 24, 27).

Cysteamine forms the terminal region of the coenzyme A molecule where it is linked to the pantethenic acid moiety by a peptide bond. Reichlin and Bollinger-Gruber (25) found that pantethine (a stable disulfide precursor of pantetheine, Fig. 1) in a dose of 2.64 mM/kg markedly reduced the tissue concentrations of SLI (approx. 40%) and prolactin (approx. 75%), as has previously been demonstrated for equimolar amounts of cysteamine.

Somatostatin has been suggested to be involved in the regulation of motor function. Following intracerebroventricular (ICV) or intracerebral injection of the peptide increased locomotor activity has been demonstrated following lower doses (26, 35, 36), whereas higher doses caused disturbed motor performance (26,36). Cohn and Cohn (8) first reported that following ICV injection of

[1]Requests for reprints should be addressed to Erik Widerlöv, M.D.

somatostatin to nonlesioned rats, they developed a twist around the long axis of the body and repeatedly rolled laterally, a phenomenon named "barrel rotation." This behavior has later been described also by other investigators (14, 17, 21, 37). Burke and Fahn (4) concluded that barrel rotation was due to a pharmacological action of somatostatin on the vestibular nuclear complex (VNC). The involvement of endogenous somatostatin in the vestibular function is further supported by the observation that somatostatin immunoreactive fibers exist in VNC (12,13), and on the ability of iontophoretically applied somatostatin to inhibit lateral vestibular neurons (6).

Previous studies suggest that central catecholaminergic transmission plays an important role in the organization of open-field behavior (35,38). Cysteamine, administered in high doses, inhibits the dopamine-β-hydroxylase activity (9) and thus interferes with the noradrenaline biosynthesis (33). Furthermore, the hypothalamus contains high concentrations of somatostatin (3) and catecholamines (33) and the peptide influences both noradrenergic and dopaminergic transmission (14) in this brain region.

On the basis of these findings, in the first part of the present study, the effects of cysteamine and pantethine were investigated on open-field behavior and on the hypothalamic concentrations of noradrenaline, dopamine and dihydroxyphenylacetic acid (DOPAC).

Earlier data suggested that somatostatin did not significantly influence the cysteamine-induced behavioral changes (36). Therefore, in the second part, the effects of ICV administered somatostatin on pantethine-induced open-field activity were investigated in rats.

In the third part the effects of pretreatment with cysteamine and pantethine on the somatostatin-induced barrel rotation in rats were investigated.

METHOD

Drugs

Pantethine, supplied as a water-soluble oil liquid (originally containing 17% water), and cysteamine (both drugs from Sigma, St. Louis, MO) were used. Somatostatin was generously supplied from Ferring AB (Malmö, Sweden).

Animals

Adult male Sprague-Dawley albino rats (ALAB, Sollentuna, Sweden), weighing 200–220 g at the time of the first open-field test, or operation, were used for the experiments. The rats were housed in large plastic cages with 6 animals in each cage. They were kept on a 12/12 hr light/dark cycle with the light phase from 07.00–19.00 hr. Laboratory chow and tap water were available to the animals ad lib. All experiments were performed between 9 a.m. and 3 p.m.

Exploratory Activity

The animals were placed in an open-field box (100 by 100 cm; 40 cm high, black-painted wooden box, the floor consisting of 25 equally sized squares measuring 20 × 20 cm each). Their activity during the three min sessions were video recorded (VHS Movie, NV-M5EO, Panasonic, Matsushita Co., Osaka, Japan). During experimental sessions, the testing room was illuminated with dimmed white light. Their behavior was characterized by the total number of squares explored (horizontal activity), the total number of rearings (vertical activity), the number of groomings and the number of defecation boluses produced during the 3-min session.

All scorings were made directly from the TV monitor placed in an adjacent room. In cases of uncertainties about the scores, the ratings were later checked from the videotapes.

In the first experiment the open-field test was performed 4 hr after a subcutaneous (SC) administration of cysteamine (1.95 mM/kg) or pantethine (1.95 mM/kg, or 3.90 mM/kg SC). In the second experiment rats were tested 30 min and 24 hr after an ICV administration of somatostatin (1 μg or 3 μg) or saline. In this experiment the animals were pretreated with SC injection of pantethine (1.95 mM/kg) or saline 4 hr prior to the ICV injection.

Barrel Rotation Activity

After ICV injection of somatostatin (10 μg) each rat was immediately placed in an observation plastic cage (20 × 14 × 36 cm). Four hr before the ICV injection the animals were pretreated with SC injections of saline, cysteamine (1.95 mM/kg) or pantethine (1.95 mM/kg or 3.90 mM/kg). The number of turnings, lying-turnings or barrel rotations were observed during the 15 min observation. During the "lying-turning" the animal turned around his vertical axis, but since it was not able to stand on its feet, it turned in a lying position. The barrel rotation response was defined as the following sequence of behavioral events: the rat first developed fore- and hindpaw extension on one side, then it developed a twist around the long axis of the body so that the rostrodorsal aspect rotated away from the side of limb extension; the twist then culminated in repeated rolling (4).

Surgery and ICV Injection

Rats were anesthetised with 0.5 ml ketamine, 50 mg/ml (Ketalar Parke-Davis, Barcelona, Spain) and 0.2 ml xylazine, 30 mg/ml (Rompun Vet., Bayer AB, Sweden), intraperitoneally (IP). They were placed in a Kopf (David Kopf Instruments, Tujunga, CA) stereotactic apparatus, and in the flat skull position three stainless-steel anchor screws were secured in the skull. A stainless-steel 23-gauge guide cannula (Plastic Products Company, Roanoke, VA) was placed into the right lateral cerebroventricle and fixed to the skull with dental cement. Coordinates were 0.5 mm caudal and 1.5 mm lateral to the bregma, with the cannula extending 3.5 mm ventral to skull surface. After the surgical procedure 0.25 ml Intencillin (LEO, Helsingborg, Sweden, containing 1,650,000 IE benzylpenicillin + 600,000 IE benzylpenicillinprocaine in a volume of 5 ml/ampoule) were given SC. The rats were used after a recovery period of 9 days, and during this period they were handled every second day and sham-injected (15). The correct positioning of the cannula was checked by dissection of the brain at the end of the experiment.

Somatostatin (1 μg or 3 μg in the open-field test, and 10 μg in the barrel rotation test) dissolved in 5 μl sterile 0.9% saline, or saline alone, was injected ICV over a period of 60 sec. The injection was performed through a 29-gauge internal cannula which extended 1.0 mm beyond the guide cannula tip. The internal cannula was inserted and fixed in place with a plastic screw collar, so that there was no reflux of the injection solution between the internal and external cannulae. The internal cannula was attached to a Hamilton microliter syringe with approximately 30 cm of polyethylene tubing, allowing the animals to move freely during the injection period. Between injections, guide cannulae were closed with a plastic plug to prevent contamination.

Determination of Hypothalamic Noradrenaline, Dopamine and Dihydroxyphenyl Acetic Acid (DOPAC)

Four hr after the administration of cysteamine (1.95 mM/kg, SC) or pantethine (1.95 or 3.90 mM/kg, SC), immediately after the open-field session, the animals were decapitated. The whole

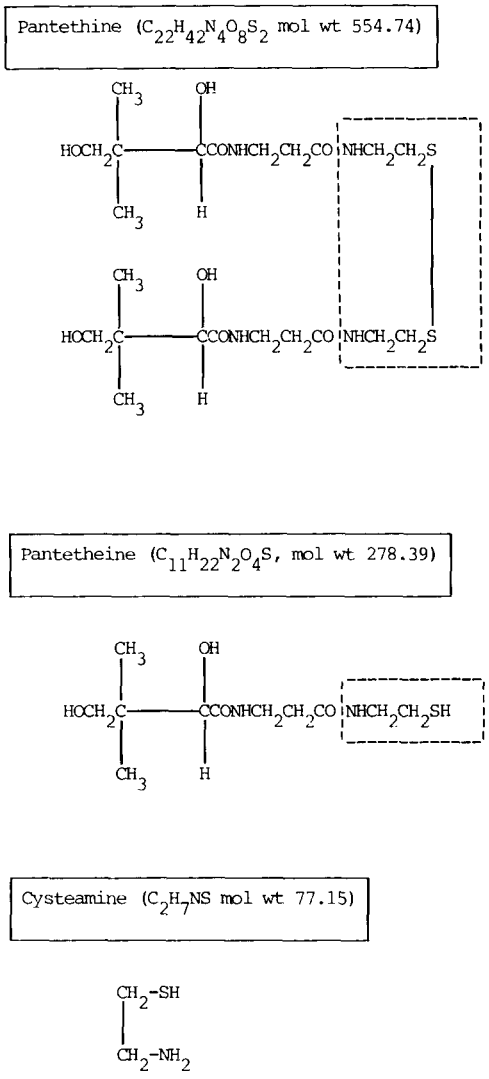

FIG. 1. The chemical structure of pantethine, pantetheine and cysteamine.

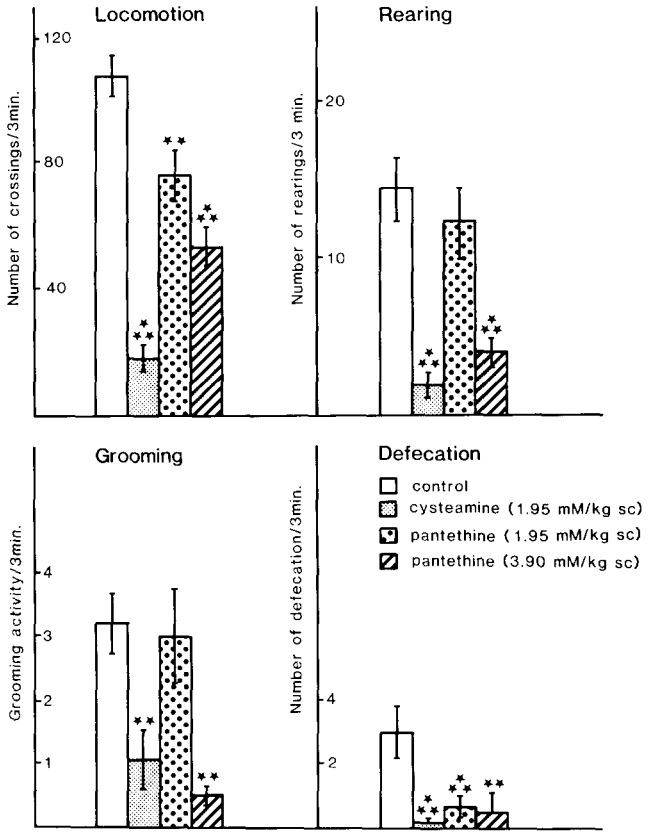

FIG. 2. Effects of cysteamine and pantethine on open-field behavior in rats. ★★ = $p<0.01$, ★★★ = $p<0.001$ (Mann-Whitney U-test). Vertical lines represent the standard errors of the mean (n = 10 animals/group.)

brain (without the olfactory bulbs) was quickly removed and placed on a Petri glass over dry ice. The hypothalamus was dissected (33), immediately frozen on dry ice and stored at −80°C until assay.

For the estimation of the hypothalamic noradrenaline, dopamine and DOPAC levels high-performance liquid chromatography with electrochemical detection (HPLC EC) was used (10, 11, 20). The frozen tissue was homogenized (15 sec, Polytron homogenator) in 1.45 ml perchloric acid (0.4 M) containing $Na_2S_2O_5$ (25 μl 5%), Na_2EDTA (25 μl, 10%) and 20 μl α-methyldopamine (2.5 mg/ml) (Sigma, St. Louis, MO) as internal standard. After centrifugation (4°C, ≅15000 × g, 13000 rpm, 20 min) in a Beckman centrifuge (J21 with JA 20 rotor), 1 ml of the supernatant was taken for the analysis of the catecholamines. Twenty mg preactivated acidic Al_2O_3 was added to the supernatant. Under vigorous mixing 1.5 ml 3 M Tris-buffer (pH 8.6) was added. After rotating for 10 min, samples were washed twice with 1 ml distilled water and finally eluted from the alumina by vortexing with 200 μl of water solution containing boric acid (0.25 M) and citric acid (0.125 M). After 1 min of mixing, centrifugation was performed (5 min, 2000 × g). The supernatant containing noradrenaline, dopamine, DOPAC and α-methyldopamine was analysed by HPLC, using a Waters 6000 pump and a Resolve Spherical C-18 5 μm, 15 cm by 3.9 mm column (Waters Associates, Milford, MA). The electrochemical detection was performed using the LC-4 B Bioanalytical Systems (Glassy carbon electrode TL-5, electrode potential: 750 mV). The catechols were chromatographed using a mobile phase of formic acid (0.1 M), Na-octanesulfonate (0.36 mM), citric acid (1.0 mM), Na_2EDTA (0.1 mM), diethylamine (0.2% v/v) and acetonitrile (LiChrosolv, 5.0% v/v; Merck, Darmstadt, FRG).

Statistical Analysis

For the behavioral data, a Kruskal-Wallis analysis of variance by ranks was performed with respect to the treatment effect. When significant, this was followed by the Mann-Whitney U-test for group comparisons. The neurochemical data were evaluated by analysis of variance (ANOVA) followed by the Tukey test.

RESULTS

The results from the open-field experiment are presented in Fig. 2. Both cysteamine and pantethine decreased the locomotion of the animals (cysteamine: 1.95 mM/kg SC, U = O, $p<0.001$; pantethine; 1.95 mM/kg SC, U = 15.5, $p<0.01$, 3.90 mM/kg SC, U = 5, $p<0.001$, M.W. test; H = 28.45, $p<0.001$ K.W. test).

The rearing activity of the rats was also reduced by cysteamine

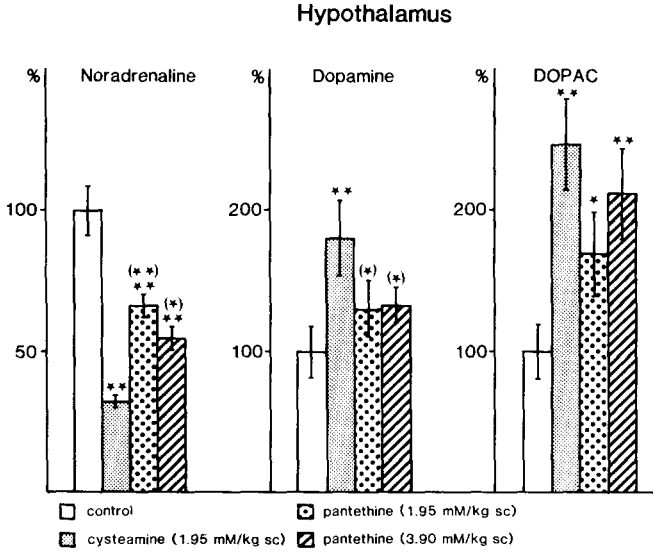

FIG. 3. Effects of cysteamine and pantethine on levels of noradrenaline, dopamine and DOPAC in the rat hypothalamus. ★ = $p<0.05$, ★★ = $p<0.01$ (vs. the saline control group), (★) = $p<0.05$, (★★) = $p<0.01$ (vs. the cysteamine-treated group). ANOVA followed by Tukey test. Vertical lines represent the standard errors of the mean (n = 10 samples/group.)

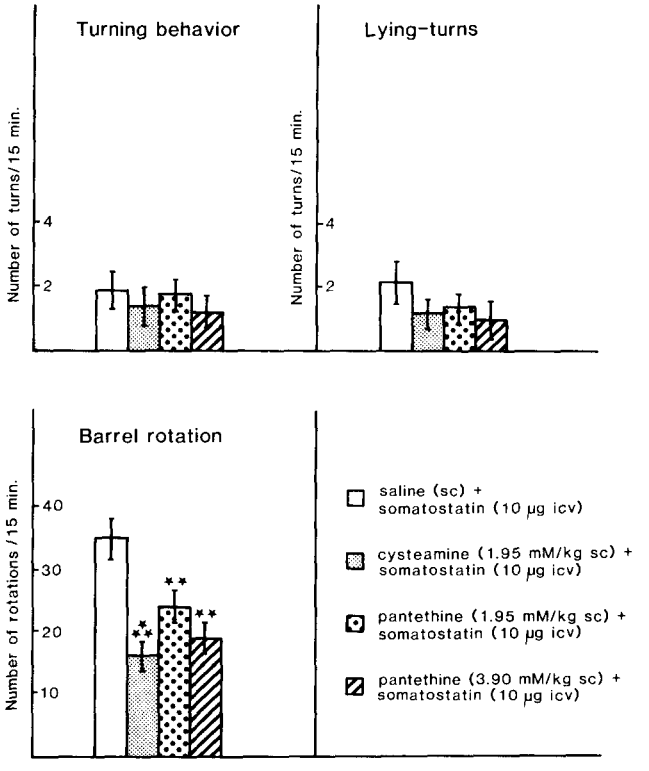

FIG. 4. Effects of pretreatment with cysteamine and pantethine on the somatostatin-induced barrel rotation in rats ★★ = $p<0.01$, ★★★ = $p<0.001$ (Mann-Whitney U-test). Vertical lines represent the standard errors of the mean. (n = 8 animals/group.)

(1.95 mM/kg SC, U = O, $p<0.001$, M.W. test), while pantethine administered in the lower dose (1.95 mM/kg SC) had no influence. However, the higher dose (3.90 mM/kg SC) markedly reduced rearing (U = 4, $p<0.001$, M.W. test; H = 26.85, $p<0.001$, K.W. test).

Cysteamine and pantethine reduced the grooming activity (cysteamine: 1.95 mM/kg SC, U = 17, $p<0.01$; pantethine: 3.90 mM/kg SC, U = 11.5, $p<0.01$, M.W. test; H = 7.84, $p<0.05$, K.W. test), and also the number of defecation boluses (cysteamine: 1.95 mM/kg SC, U = 0, $p<0.001$; pantethine; 1.95 mM/kg SC, U = 8, $p<0.001$; 3.90 mM/kg SC, U = 10, $p<0.01$, M.W. test; H = 17.6, $p<0.01$, K.W. test).

The effects of cysteamine and pantethine on the hypothalamic concentrations of noradrenaline, dopamine and DOPAC are presented in Fig. 3. Cysteamine and pantethine markedly reduced the hypothalamic noradrenaline concentration [cysteamine: 1.95 mM/kg SC, $p<0.01$; pantethine: 1.95 mM/kg SC, $p<0.01$; 3.90 mM/kg SC, $p<0.01$, Tukey test; $F(3,36) = 22.61$, $p<0.001$, ANOVA]. The cysteamine- (1.95 mM/kg SC) induced noradrenaline depletion is significantly higher than in the pantethine-treated groups (pantethine: 1.95 mM/kg SC, $p<0.01$; 3.90 mM/kg SC, $p<0.05$ Tukey test). Furthermore, cysteamine (1.95 mM/kg SC) markedly elevated the dopamine content of the hypothalamus [compared with the control group: $p<0.01$; compared with the pantethine-treated groups: $p<0.05$, Tukey test; $F(3,36) = 8.83$, $p<0.001$, ANOVA]. Both cysteamine and pantethine markedly increased also the DOPAC concentration in the hypothalamus [cysteamine: 1.95 mM/kg SC, $p<0.01$; pantethine: 1.95 mM/kg SC, $p<0.05$; 3.90 mM/kg SC, $p<0.01$, Tukey test, $F(3,36) = 15.43$, $p<0.001$, ANOVA].

In Fig. 4 the interactions of cysteamine and pantethine on the somatostatin-induced motor impairment and barrel rotation are presented. After the ICV injection of a high dose of somatostatin (10 μg) the animals became calm, later catalepsy appeared, sometimes some turning and lying-turning appeared with combination of uncoordinated movements. Approximately 40–60 sec after the administration of the peptide barrel rotations were observed. If the animal began to move in his plastic cage this behavior was observed again.

Both cysteamine and pantethine attenuated the somatostatin-induced barrel rotation (cysteamine: 1.95 mM/kg SC, U = 4, $p<0.001$; pantethine: 1.95 mM/kg SC U = 9, $p<0.01$; 3.90 mM/kg SC, U = 5.5, $p<0.01$, M.W. test; H = 14.46, $p<0.01$, K.W. test).

The ICV administered somatostatin in a dose of 1 μg increased, while a dose of 3 μg decreased the locomotor activity of the animals, however, without differing significantly from the performance of the control animals. The locomotor activity of the two somatostatin-treated groups differed, however, significantly from each other (U = 22, $p<0.05$, M.W. test, H = 17.52, $p<0.01$, K.W. test). Pantethine alone (1.95 mM/kg SC) decreased the locomotion of the animals (U = 19.5, $p<0.05$), and the ICV administered somatostatin did not significantly influence this reduction. All the pantethine-treated animals had a lower defecation activity both at 30 min and at 24 hr after the drug administration (saline vs. pantethine treatment, 30 min: U = 6.5, $p<0.001$, M.W. test, H = 41.84, $p<0.001$, K.W. test; 24 hr: U = 18.5, $p<0.02$, M.W. test, H = 13.1, $p<0.05$, K.W. test), see further, Table 1.

DISCUSSION

In the first experiment of the present study we found that cysteamine markedly decreased all of the open-field parameters studied, while pantethine administered in an equimolar dose

TABLE 1

INTERACTIONS BETWEEN PANTETHINE AND SOMATOSTATIN ON OPEN-FIELD BEHAVIORS IN RATS

Treatment	Total Number of Squares/3 min	Total Number of Rearings/3 min	Total Number of Groomings/3 min	Defecation Boluses/3 min
	Open-Field Behavior 30 min After the ICV Injections			
Sal + sal	93.2 ± 8.6	17.0 ± 2.4	3.6 ± 1.1	3.9 ± 0.6
sal + som (1 μg)	110.3 ± 9.9	20.3 ± 2.7	3.0 ± 0.9	4.8 ± 0.4
sal + som (3 μg)	66.7 ± 7.6*	14.8 ± 2.1	3.2 ± 0.7	3.1 ± 0.4
pant + sal	58.1 ± 6.6†	14.2 ± 2.1	2.9 ± 0.8	0.3 ± 0.2§
pant + som (1 μg)	62.2 ± 7.4	16.2 ± 2.0	2.7 ± 0.9	0.4 ± 0.2
pant + som (3 μg)	69.3 ± 8.2	14.9 ± 2.7	2.5 ± 0.6	0.4 ± 0.2
	Open-Field Behavior 24 hr After the ICV Injections			
Sal + sal	65.4 ± 5.8	7.1 ± 0.9	7.7 ± 0.9	1.0 ± 0.3
sal + som (1 μg)	58.8 ± 7.6	7.7 ± 1.1	6.9 ± 0.7	0.7 ± 0.3
sal + som (3 μg)	60.4 ± 5.4	8.0 ± 0.6	6.3 ± 0.9	1.2 ± 0.4
pant + sal	62.8 ± 7.4	6.7 ± 0.8	7.3 ± 0.9	0.1 ± 0.1‡
pant + som (1 μg)	58.3 ± 6.5	5.6 ± 0.9	6.2 ± 0.7	0.3 ± 0.2
pant + som (3 μg)	67.0 ± 7.7	6.1 ± 0.7	7.8 ± 0.8	0.4 ± 0.2

Rats were tested 30 min and 24 hr, respectively, after the administration of somatostatin (som; 1 μg/5 μl or 3 μg/5 μl ICV) or saline (sal; 5 μl ICV). Animals were pretreated with pantethine (pant; 1.95 mM/kg SC) or saline (SC) 4 hr to the ICV injection. (n = 10 animals/group.)

Values are given as means ± SEM. *$p<0.05$, vs. somatostatin- (1 μg) treated group, M.W. test; †$p<0.05$, vs. control group, M.W. test; ‡$p<0.02$ vs. control group M.W. test; §$p<0.001$ vs. control group, M.W. test.

decreased the locomotion only, without influencing (1.95 mM/kg) the rearing and grooming activity. However, when pantethine was administered at a higher dose (3.90 mM/kg), the effects of this compound approached those of cysteamine, indicating that cysteamine is approximately twice as potent as pantethine on these behaviors.

Cysteamine is synthesized in animals by only one known mechanism: the irreversible cleavage of pantetheine (23). Pantetheinase activity has been demonstrated by several authors (1,5) on a limited number of mammals, and by Orloff *et al.* (23) in human fibroblasts and leukocytes. Each mole of pantethine contains 2 moles of cysteamine (Fig. 1). Thus, if these drugs are administered in an equimolar dose, the pantethine dose will contain twice as much cysteamine as the administration of cysteamine itself. After the exogenous administration of pantethine the activity of pantetheinase will determine the concentration of cysteamine in the body. However, the rate of this conversion is presently not known. Therefore, the actual amount of cysteamine after the pantethine administration may in fact be lower than that after the administration of cysteamine in spite of the same molar dose. This might be the reason for the lower effect of pantethine on open-field behaviors. In the present experiment cysteamine was not administered in a dose of 3.90 mM/kg (SC) because in a preliminary investigation this dose was found to have a very marked depression on the activity of the animals.

Whether pantethine is active only after conversion to cysteamine or also has an activity of its own still remains to be further elucidated. However, today no data are available that indicate any activity of pantethine itself.

Cysteamine is a compound which chelates copper, and therefore, in high doses the compound inhibits the copper-sensitive enzyme dopamine-β-hydroxylase activity (9). This action probably explains the markedly reduced noradrenaline and increased dopamine and DOPAC levels in the hypothalamus. Our data indicate that a significant amount of dopamine, which is not β-hydroxylated to noradrenaline, is rapidly deaminated by monoamine oxidase and thus causing a dramatic increase of DOPAC, the principal metabolite of dopamine. The effects of the pantethine on hypothalamic monoamine concentrations were similar to that of cysteamine, although with a lower potency.

In the second behavioral experiment we found that the ICV administered somatostatin did not influence the pantethine-induced behavioral changes in the open-field test. Brown *et al.* (2) have found that ICV administration of a potent somatostatin analog (ODT8-SS) to cysteamine-pretreated animals inhibited the elevation of plasma concentrations of adrenaline and glucose, with no effect on the elevated plasma noradrenaline level. This means that the analog only partially antagonized the action of cysteamine on the metabolism. Furthermore, in a previous study, it was found that somatostatin administered ICV did not influence significantly the cysteamine-induced behavioral changes (36). Concerning the present study, it is thus possible that the ICV administered somatostatin did not cause a sufficient peptide concentration at the receptor sites to restore the normal behavior. However, the possibility that peripheral effects of cysteamine or pantethine can affect the behavior of the animals cannot be excluded (29). Furthermore, pantethine also decreased the brain noradrenaline concentration and thus influencing the behavioral responses, including open-field activity, where noradrenergic transmission also plays an important role (38). Indeed, phenoxybenzamine, an α-adrenergic receptor blocker administered in higher doses to rats can significantly decrease the behavioral activity of the animals (18,34).

The inverted U-shaped dose response curve found in the open-field experiment has previously also been found by others (26,36), indicating different behavioral actions of low and high doses of centrally administered somatostatin.

Cohn and Cohn (8) in their pioneer work found that pretreat-

ment of the rats with haloperidol, apomorphine or reserpine did not alter the number of barrel rotations induced by somatostatin. In contrast, atropine completely inhibited the somatostatin-induced barrel rotation, suggesting that somatostatin may be acting, at least partly, through cholinergic mechanisms (8).

The fact that the somatostatin-depleting agents decreased the peptide-induced barrel rotation suggested that the endogenous somatostatin level might play some role in the development of this behavior. However, both cysteamine and pantethine reduced also the locomotor activity and this change may also contribute to suppression of the barrel rotation.

In future studies we plan to further investigate the dose- and time-related effects of cysteamine and pantethine on central catecholaminergic and somatostatinergic neurotransmission in order to elucidate the relative importance of these systems in the behavioral effects of the two compounds.

ACKNOWLEDGEMENTS

This study was supported by grants from H. Lundbeck A/S, Copenhagen, Denmark, the Bank of Sweden Tercentenary Foundation (85/77) and the Faculty of Medicine, University of Lund. The statistical advice from Zvonimir Cesarec, Ph.D., the skillful technical assistance by Mrs. Greta Thalén, and the kind gift of somatostatin from Ferring AB (Malmö, Sweden) is greatfully acknowledged. L.V. holds a visiting scientist fellowship at the Department of Psychiatry and Neurochemistry at Lund University.

REFERENCES

1. Abiko, Y. Investigations on pantothenic acid and its related compounds. II. Biochemical studies. (4) Separation and substrate specificity of pantothenate kinase and phosphopantothenoyl-cysteine synthetase. J. Biochem. 61:290–296; 1967.
2. Brown, M. R.; Fisher, L. A.; Sawchenko, P. E.; Swanson, L. W.; Vale, W. W. Biological effects of cysteamine: Relationship to somatostatin depletion. Regul. Pept. 5:163–179; 1983.
3. Brownstein, M.; Arimura, A.; Sato, H.; Schally, A. V.; Kizer, J. S. The regional distribution of somatostatin in the rat brain. Endocrinology 96:1456–1461; 1975.
4. Burke, R. E.; Fahn, S. Studies of somatostatin-induced barrel rotation in rats. Regul. Pept. 7:207–220; 1983.
5. Cavallini, D.; Dupre, S.; Gruziani, M. T.; Tinx, M. G. Identification of pantetheinase in horse kidney extract. FEBS Lett. 1:119–123; 1968.
6. Chan-Palay, V.; Ito, M.; Tongroach, P.; Sakurai, M.; Palay, S. Inhibitory effects of motilin, somatostatin, (Leu)enkephalin, (Met) enkephalin, and taurine on neurons of the lateral vestibular nucleus: Interactions with γ-aminobutyric acid. Proc. Natl. Acad. Sci. USA 79:3355–3359; 1982.
7. Chattha, G. K.; Beal, M. F. Effect of cysteamine on somatostatin and neuropeptide Y in rat striatum and cortical synaptosomes. Brain Res. 40:359–364; 1987.
8. Cohn, M. L.; Cohn, M. Barrel rotation induced by somatostatin in the non-lesioned rat. Brain Res. 96:138–141; 1975.
9. DiLiberto, E. J., Jr.; DiStefano, V.; Crispin-Smith, J. Mechanism and kinetics of the inhibition of dopamine-β-hydroxylase by 2-mercaptoethylguanidine. Biochem. Pharmacol. 22:2961–2972; 1973.
10. Engel, J. A.; Johannessen, K.; Liljequist, S.; Goldstein, M. Activation of α_2-adrenoreceptors enhances haloperidol-induced suppression of operant behaviour. J. Neural Transm. 66:107–120; 1986.
11. Eriksson, B-M.; Persson, B-A. Determination of catecholamines in rat heart tissue and plasma samples by liquid chromatography with electrochemical detection. J. Chromatogr. 228:143–154; 1982.
12. Finley, J. W. C.; Maderdrut, J. L.; Roger, L. J.; Petrusz, P. The immunochemical localization of somatostatin-containing neurons in the rat central nervous system. Neuroscience 6:2173–2192; 1981.
13. Forssmann, W. C.; Burnweit, C.; Shehab, T.; Triepel, J. Somatostatin-immunoreactive nerve cell bodies and fibers in the medulla oblongata et spinalis. J. Histol. Cytochem. 27:1391–1393; 1979.
14. Garcia-Sevilla, J. A.; Magnusson, T.; Carlsson, A. Effect of intracerebroventricularly administered somatostatin on brain monoamine turnover. Brain Res. 155:159–164; 1978.
15. Heilig, M.; Murison, R. Intracerebroventricular neuropeptide Y suppresses open field and home cage activity in the rat. Regul. Pept. 19:221–231; 1987.
16. Jayaraj, A. P. Dissecting aneurysm of aorta in rats fed with cysteamine. Br. J. Exp. Pathol. 64:548–552; 1983.
17. Kastin, A. J.; Coy, D. H.; Jacquet, Y.; Schally, A. V.; Plotnikoff, N. P. CNS effects of somatostatin. Metabolism 27:1247–1252; 1976.
18. Liljequist, S.; Berggren, U.; Engel, J. The effect of catecholamine receptor antagonists on ethanol-induced locomotor stimulation. J. Neural Transm. 50:57–67; 1981.
19. McComb, D. J.; Kovacs, K.; Horner, H. C.; Gallagher, G. T.; Schwedes, U.; Usadel, K. H.; Szabo, S. Cysteamine-induced adrenocortical necrosis in rats. Exp. Mol. Pathol. 35:422–434; 1981.
20. Magnusson, O.; Nilsson, L. B.; Westerlund, D. Simultaneous determination of dopamine, DOPAC and homovanillic acid. Direct injection of supernatants from brain tissue homogenates in a liquid chromatography-electrochemical detection system. J. Chromatogr. 221:237–247; 1980.
21. Malthe-Sørenssen, D.; Wood, P. L.; Cheney, D. L.; Costa, E. Modulation of the turnover rate of acetylcholine in rat brain by intraventricular injections of thyrotropin-releasing hormone, somatostatin and angiotensin II. J. Neurochem. 31:685–691; 1978.
22. Millard, W. J.; Sagar, S. M.; Badger, T. M.; Carr, D. B.; Arnold, M. A.; Spindel, E.; Kasting, N. W.; Martin, J. B. The effects of cysteamine on thyrotropin and immunoreactive β-endorphin secretion in the rat. Endocrinology 112:518–525; 1983.
23. Orloff, S.; Butler, J. D.; Towne, D.; Mukherjee, A. B.; Schulman, J. D. Pantetheinase activity and cysteamine content in cystinotic and normal fibroblasts and leukocytes. Pediatr. Res. 15:1063–1067; 1981.
24. Palkovits, M.; Brownstein, M. J.; Eiden, L. E.; Beinfeld, M. C.; Russel, J.; Arimura, A.; Szabo, S. Selective depletion of somatostatin in the rat brain by cysteamine. Brain Res. 240:178–180; 1982.
25. Reichlin, S.; Bollinger-Gruber, J. A. Pantethine, a cysteamine precursor, depletes immunoreactive somatostatin and prolactin in the rat. Endocrinology 117:492–495; 1985.
26. Rezek, M.; Havlicek, V.; Leybin, L.; Pinsky, C.; Kroeger, E. A.; Hughes, K. R.; Friesen, H. Neostriatal administration of somatostatin: differential effect of small and large doses on behavior and motor control. Can. J. Physiol. Pharmacol. 55:234–242; 1977.
27. Sagar, S. M.; Landry, D.; Millard, W. J.; Badger, T. M.; Arnold, M. A.; Martin, J. B. Depletion of somatostatin-like immunoreactivity in the rat central nervous system by cysteamine. J. Neurosci. 2:225–231; 1982.
28. Seiler, M.; Szabo, S.; Ourieff, S.; McComb, D. J.; Kovacs, K.; Reichlin, S. The effects of the duodenal ulcerogen cysteamine on somatostatin and gastrin cells in the rat. Exp. Mol. Pathol. 39: 207–218; 1983.
29. Szabo, S. Duodenal ulcer disease. Animal model: cysteamine-induced acute and chronic duodenal ulcer in the rat. Am. J. Pathol. 93: 273–276; 1978.
30. Szabo, S.; McComb, D. J.; Kovacs, K.; Huttner, I. Adrenocortical hemorrhagic necrosis. The role of catecholamines and retrograde medullary-cell embolism. Arch. Pathol. Lab. Med. 105:536–539; 1981.
31. Szabo, S.; Reichlin, S. Somatostatin in rat tissues is depleted by cysteamine administration. Endocrinology 109:2255–2257; 1981.
32. Szabo, S.; Reynolds, E. S. Structure-activity relationships for ulcerogenic and adrenocorticolytic effects of alkyl nitriles, amines, and thiols. Environ. Health Perspect. 11:135–140; 1975.
33. Vécsei, L.; Balázs, M.; Bollók, I.; Telegdy, G. Selective decrease of hypothalamic noradrenaline by cysteamine. Arch. Int. Pharmacodyn. 274:125–128; 1985.
34. Vécsei, L.; Balázs, M.; Telegdy, G. Action of somatostatin on the central nervous system. In: Telegdy, G., eds. Neuropeptides and brain function (Frontiers of Hormone Research, vol. 15). Basel: Karger; 1987:36–58.
35. Vécsei, L.; Bollók, I.; Telegdy, G. Comparative studies with cyclic

and linear somatostatin on active avoidance behaviour and open-field activity in rats. Acta Physiol. Hung. 61:43–49; 1983.
36. Vécsei, L.; Király, C.; Bollók, I.; Nagy, A.; Varga, J.; Penke, B.; Telegdy, G. Comparative studies with somatostatin and cysteamine in different behavioural tests on rats. Pharmacol. Biochem. Behav. 21:833–837; 1984.
37. Vijayan, E.; McCann, S. Suppression of feeding and drinking activity in rats following intraventricular injection of thyrotropin releasing hormone. Endocrinology 100:1727–1730; 1977.
38. Widerlöv, E.; Lewander, T. The relationship between amphetamine antagonism and depletion of brain catecholamines by alpha-methyl-p-tyrosine in rats. Naunyn Schmiedebergs Arch. Pharmacol. 304: 125–134; 1978.