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Dose- and Time-Response Effects of Pantethine on Open-Field Behavior, and on Central Neurotransmission in Rats

LÁSZLÓ VÉCSEI, ERIK WIDERLÖV,[1] ROLF EKMAN AND CHRISTER ALLING

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

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VÉCSEI, L., E. WIDERLÖV, R. EKMAN AND C. ALLING. *Dose- and time-response effects of pantethine on open-field behavior, and on central neurotransmission in rats.* PHARMACOL BIOCHEM BEHAV **35**(1) 165–170, 1990.—In this study the dose- and time-related effects of pantethine on open-field behavior and central neurotransmissions were investigated in rats. Pantethine administered in low doses (0.48–0.96 mM/kg SC) only marginally influenced the activity of the animals, but induced a significant decrease of hypothalamic noradrenaline level without influencing the concentrations of dopamine and DOPAC. Injected in higher doses (1.95–3.90 mM/kg SC), the compound produced a marked depression of both open-field activity and noradrenaline levels, but increased the concentrations of dopamine and DOPAC in the hypothalamus. Twelve hr after the administration of the substance, its effect was attenuated, and 24 hr after the treatment neither the behavioral nor the monoamine parameters differed significantly from the control values. Concerning the somatostatin, pantethine administered in high doses (1.95–3.90 mM/kg SC) decreased the striatal concentration of somatostatin 4 hr after the injection, and this effect was attenuated 24 hr after the treatment. These data suggest that the pantethine-induced behavioral changes are correlated with its effect on central catecholaminergic and somatostatinergic transmission.

Catecholamines Open-field activity Pantethine Rats Somatostatin

PANTETHINE [D-bis(n-pantothenyl-beta-aminoethyl)-disulfide] is the disulfide form of pantetheine, an intermediate of Coenzyme A (CoA) metabolism, which can be phosphorylated by pantothenate kinase and, thus, utilized as a precursor of CoA (11). Orloff and Butler and their colleagues (4,16) reported that after administration of pantethine to leukocytes and fibroblasts, the substance was converted to pantetheine which, in turn, was converted to cysteamine.

Cysteamine is a normal constituent of mammalian cells in which it arises by enzymatic degradation of CoA by the action of the enzyme pantetheinase (4,15). This compound has been shown to deplete somatostatin in nerve cells (17, 20, 23), gut, and pancreas (22,23), and to deplete prolactin in the pituitary (14,21). Furthermore, cysteamine acts as a dopamine beta-hydroxylase inhibitor (6,25) and influences animal behaviors, like active avoidance, open-field activity and T-maze learning (27).

Since there are almost no data concerning the behavioral and neurochemical effects of pantethine, and because the compound seems to be a potentially useful drug in the treatment of several disorders (3, 9, 31), we investigated the dose- and time-response of pantethine on open-field behavior and on hypothalamic catecholamine and striatal somatostatin concentrations in rats. The open-field behavior was studied because several behavioral effects of cysteamine, the pantethine metabolite, are partly mediated by the inhibition of the exploratory activity of the experimental animals (27). The neurochemical effects of cysteamine are most pronounced 4 hr after its application (20), therefore, we have selected this time interval for the present dose-response studies. In the time-response experiments, the disappearance of the effect of pantethine was investigated at 8, 12 and 24 hr respectively, after administration of pantethine.

Contrary to the striatum, the hypothalamus contains high concentrations of both dopamine and noradrenaline. Therefore, this brain region seemed to be a suitable model for the investigation of the alterations in the levels of catecholamines after the inhibition of dopamine beta-hydroxylase activity (25). It is also known that the administration of somatostatin to the striatum influences the motor activity of the rats in a dose-dependent manner (19). Therefore, the correlation between endogenous somatostatin level in the striatum and open-field activity of the animals after pantethine administration was also studied.

METHOD

Drug

Pantethine (Sigma, St. Louis, MO), supplied as a water-

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

soluble oil liquid (originally containing 17% water), was used.

Animals

Male albino rats (Sprague-Dawley, ALAB, Sollentuna, Sweden), weighing 180–200 g, were used in all experiments. They were housed in colony cages, with 6 animals in each cage. All animals were kept on a 12/12-hr light/dark cycle with the light phase from 7 a.m. to 7 p.m. Commercially available laboratory food and tap water were given to the animals ad lib.

Treatments

In the dose-response studies, pantethine was dissolved in saline and administered subcutaneously (SC) in doses of 0.24, 0.48, 0.96, 1.95 or 3.90 mM/kg in a volume of 2 ml/kg, 4 hr before the behavioral session. The control rats received saline alone (2 ml/kg SC). In the time-response experiments pantethine (3.90 mM/kg/2 ml; treated group) or saline (2 ml/kg; control group) were administered 8, 12 or 24 hr before the open-field sessions. All of the three pantethine-treated groups (8 hr, 12 hr, 24 hr) had their own saline-treated control group.

Exploratory Activity

The animals were placed in an open-field box (rectangular 40 cm high wooden box, consisting of 25 equally sized squares; each measuring 20 by 20 cm). Their activity was videorecorded (VHS Movie, NV M5EO, Panasonic, Matsushita Co., Osaka, Japan) during a three-minutes session and scored from a monitor placed in an adjacent room.

During sessions, the testing room was illuminated with dimmed white light. The activity was characterized by the total number of squares explored (horizontal activity), the total number of rearings (vertical activity) and groomings, as well as the number of defecation boluses produced during the three-minutes session (24,28). In cases of uncertainties about the scores, the ratings were later checked from the videotapes.

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

Immediately after the open-field session (4, 8, 12 or 24 hr after the administration of pantethine) the animals were decapitated. The whole brain (without the olfactory bulbs) was quickly removed and placed on a Petri glass over dry ice. The hypothalamus and striatum were dissected, 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 (7, 8, 12, 26). The frozen tissue was homogenized (15 sec, Polytron homogenator) in 1.50 ml perchloric acid (0.4 M) containing $Na_2S_2O_5$ (25 μl 5%), Na_2EDTA (25 μl 10%) and 20 μl alpha-methyldopamine (2.5 mg/ml; Merck Sharpe & Dohme, Rahway, NJ) 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 alpha-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 mobile phase consisted 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).

Determination of Striatal Somatostatin by Radioimmunassay

After weighing, the tissue samples were boiled in 0.9% saline (1 ml/100 mg tissue) for 10 min, followed by homogenization (Polytron, 1–2 min). The homogenates were centrifuged at 4°C, 1000 × g, for 30 min, and the supernatants were collected. The pellets were dissolved in 0.5 M acetic acid and subjected to the same extraction procedure as described above. The supernatants were mixed and lyophilized and stored at −20°C until assayed. The lyophilized samples were dissolved in 0.05 M phosphate buffer (pH 7.4) containing 2.5 g/l of human albumin and centrifuged at 4°C, 2000 × g, for 15 min (2). The supernatants were assayed in serial dilution (duplicate samples) and corrected for unspecific binding.

The somatostatin antiserum (K18 Milab, Malmö, Sweden) was used in a final dilution of "25000." It does not cross-react with any other known neuropeptide besides cyclic somatostatin (100%), linear somatostatin (50%), (Tyr^1)-somatostatin (100%) and (Tyr^{11})-somatostatin (38%). Two hundred μl of antiserum was incubated first with 100 μl of sample extract for 24 hr at +4°C and then with 200 μl (~4000 cpm) of ^{125}I-Tyr^1-somatostatin for another 24 hr at 4°C. Bound and free ^{125}I-Tyr^1-somatostatin were separated using dextran-coated charcoal (0.5% activated charcoal, 0.1% Dextran T-70 in 0.05 M phosphate buffer, pH 7.5, containing 2.5 g/l human serum albumin). The detection limit is 5 pmol/l, and the intraassay and interassay variations are 5% and 9%, respectively (30).

Statistical Analysis

The behavioral and neurochemical data were evaluated by analysis of variance (ANOVA) followed by the Tukey a posteriori test and by the "product-moment" correlational analysis.

RESULTS

The dose-related effects of pantethine on the open-field behavior is presented in Fig. 1.

Compared to saline, pantethine in a dose of 1.95 mM/kg decreased the locomotor activity [$F(5,42) = 15.72$, $p<0.01$ ANOVA; $p<0.05$ Tukey] and defecation [$F(5,42) = 7.59$, $p<0.01$ ANOVA; $p<0.01$ Tukey], while a dose of 3.90 mM/kg suppressed all of the open-field parameters [locomotion: $p<0.01$ Tukey; rearing: $F(5,42) = 7.36$, $p<0.01$ ANOVA; $p<0.01$ Tukey; grooming: $F(5,42) = 2.62$, $p<0.05$ ANOVA; $p<0.05$ Tukey, defecation: $p<0.01$ Tukey]. Lower doses of pantethine (0.24 and 0.48 mM/kg) did not influence the open-field behaviors, while in an intermediate dose (0.96 mM/kg) decreased the number of defecation boluses of the animals ($p<0.01$ Tukey).

The dose-related effects of pantethine on the hypothalamic concentrations of noradrenaline, dopamine and DOPAC are presented in Fig. 2.

Pantethine dose-dependently reduced the concentration of noradrenaline [$F(5,42) = 24.84$, $p<0.01$ ANOVA; 0.48 and 0.96 mM/kg: $p<0.05$; 1.95 and 3.90 mM/kg: $p<0.01$, Tukey], and increased the levels of dopamine [$F(5,42) = 36.28$, $p<0.01$ ANOVA;

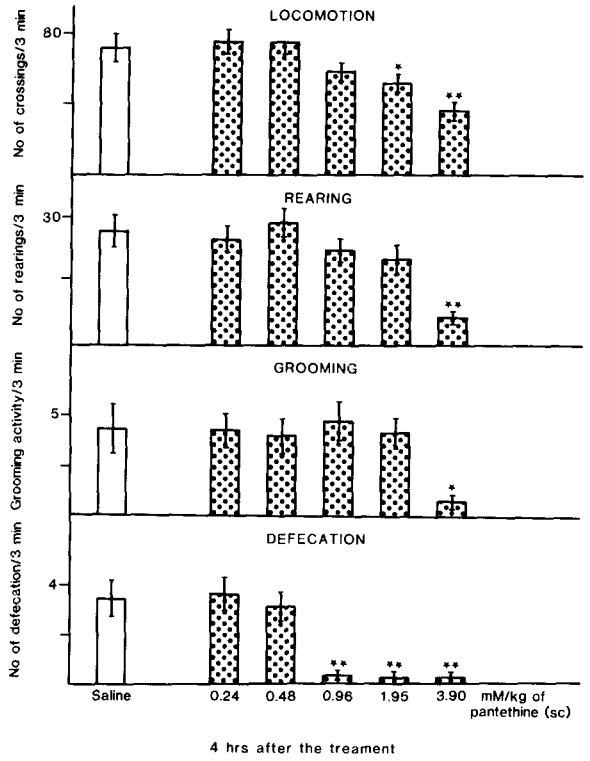

FIG. 1. Effects of different doses of pantethine on open-field behavior in rats. ★ = $p<0.05$, ★★ = $p<0.01$ (vs. control group) (Tukey test). Vertical lines represent the standard error of the mean. (n = 8 animals/group.)

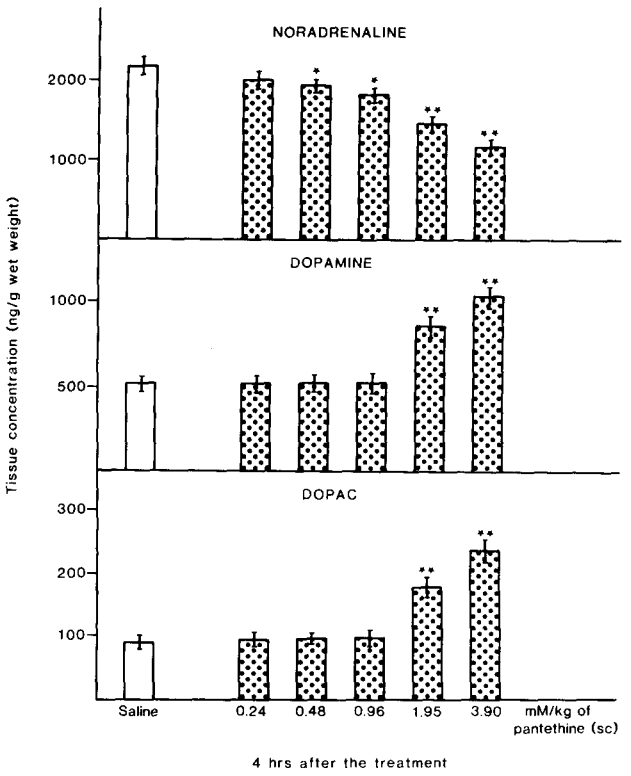

FIG. 2. Effects of different doses of pantethine on hypothalamic noradrenaline, dopamine and DOPAC concentrations in rats. ★ = $p<0.05$, ★★ = $p<0.01$ (vs. control group) (Tukey test). Vertical lines represent the standard error of the mean. (n = 8 animals/group.)

1.95 and 3.90 mM/kg: $p<0.01$, Tukey], and DOPAC [$F(5,42) = 67.72$, $p<0.01$ ANOVA; 1.95 and 3.90 mM/kg: $p<0.01$ Tukey] in the hypothalamus.

The time-related effects of the compound on open-field behavior are presented in Fig. 3.

Pantethine (3.90 mM/kg) decreased the locomotor [8 hr: $F(5,36) = 7.69$, $p<0.01$, ANOVA; $p<0.01$, Tukey; 12 hr: $p<0.05$, Tukey], rearing [8 hr: $F(5,36) = 8.66$, $p<0.01$ ANOVA; $p<0.01$ Tukey] and defecation activities [8 hr: $F(5,36) = 5.71$, $p<0.01$ ANOVA; $p<0.01$ Tukey], but did not influence the grooming activity of the rats at 8, 12 or 24 hr after the drug administration. The open-field parameters did not differ significantly from the control values 24 hr after the administration of the compound.

The time-related effects of pantethine on hypothalamic concentrations of noradrenaline, dopamine and DOPAC are presented in Fig. 4.

Pantethine decreased the concentration of noradrenaline [8 hr: $F(5,36) = 11.93$, $p<0.01$ ANOVA; $p<0.01$ Tukey; 12 hr: $p<0.05$ Tukey], but increased the levels of dopamine [8 hr: $F(5,36) = 9.89$, $p<0.01$ ANOVA; $p<0.01$ Tukey], and DOPAC [8 hr: $F(5,36) = 39.06$, $p<0.01$ ANOVA; $p<0.01$ Tukey; 12 hr: $p<0.05$ Tukey] in the hypothalamus of rats. Twenty-four hr after the administration of the compound, only minor, statistically insignificant neurochemical changes could be observed (decreased noradrenaline, increased dopamine and DOPAC levels).

The dose- and time-related effects of pantethine on striatal concentration of somatostatin are presented in Fig. 5. The higher doses decreased [$F(5,42) = 2.65$, $p<0.05$ ANOVA; 1.95 and 3.90 mM/kg: $p<0.05$ Tukey] the somatostatin concentration 4 hr after the administration. The maximal somatostatin depletion induced by the highest dose of pantethine (3.90 mM/kg) was detected at 12 hr, with a 25% reduction compared to the saline control, $F(5,36) = 4.75$, $p<0.01$, ANOVA; $p<0.01$ Tukey.

The correlational analyses showed the following statistically significant relationships. Dose-related effects: locomotion-noradrenaline content: $r = .73$, $p<0.01$; locomotion-somatostatin content: $r = .29$, $p = 0.06$; rearing-noradrenaline content: $r = .61$, $p<0.01$; rearing-somatostatin content: $r = .34$, $p<0.05$. Time-related effects: locomotion-noradrenaline content: $r = .56$, $p<0.01$; locomotion-somatostatin content: $r = .34$, $p<0.05$; rearing-noradrenaline content: $r = .73$, $p<0.01$, rearing-somatostatin content: $r = .13$, $p =$ NS.

DISCUSSION

Pantethine has been claimed to be a potentially useful drug in the treatment of diseases like cystinosis (3), atherosclerosis (9) and alcohol intoxication (31). A better understanding of its central nervous system effects, behaviorally and biochemically, is, therefore, important also from a clinical point of view.

As mentioned above, cysteamine, which is a metabolic product of pantethine, has dopamine beta-hydroxylase inhibitory action (6). There is a well known correlation between striatal dopaminergic activity and motor performance of the animals (18). However, the striatum contains low level of noradrenaline. Therefore, the hypothalamic region which contains rather high concentrations of both noradrenaline and dopamine was selected for the present experiments.

Recent findings by our group suggest that the lower efficacy of

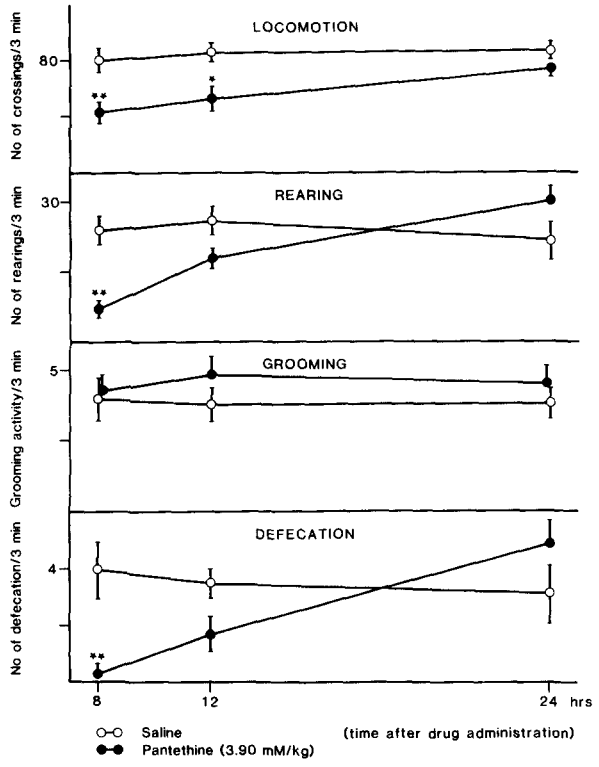

FIG. 3. Time-related effects of pantethine on open-field activity in rats. $\star = p<0.05$, $\star\star = p<0.01$ (Tukey test). Vertical lines represent the standard error of the mean. (n = 7–8 animals/group.)

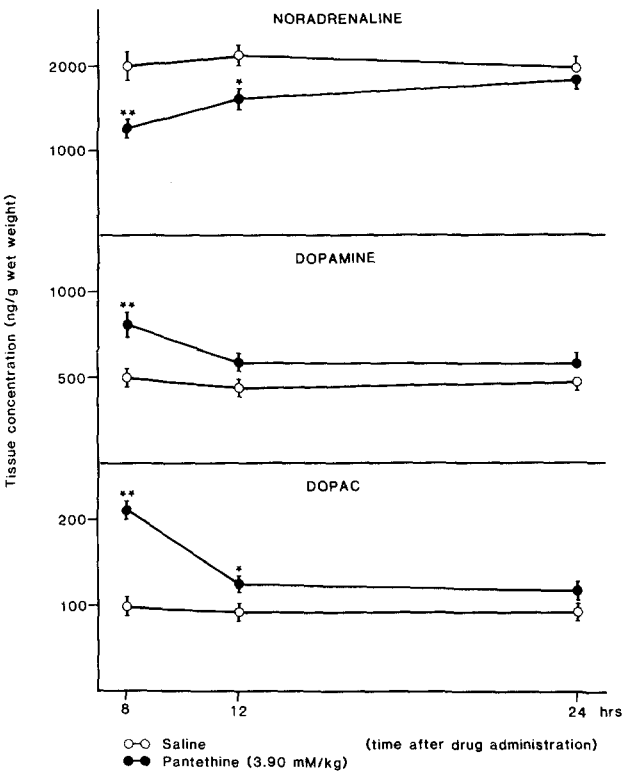

FIG. 4. Time-related effects of pantethine on hypothalamic noradrenaline, dopamine and DOPAC concentrations in rats. $\star = p<0.05$, $\star\star = p<0.01$ (vs. control group) (Tukey test). Vertical lines represent the standard error of the mean. (n = 7–8 animals/group.)

pantethine compared to cysteamine on both behavioral and neurochemical parameters is due to a rate-limiting activity of the enzyme pantetheinase in the conversation of pantetheine to cysteamine (29).

In the dose-response studies the lower doses (0.48–0.96 mM/kg) failed to affect the exploratory behavior, but significantly reduced the hypothalamic noradrenaline content. This suggests that a moderate decrease in hypothalamic noradrenaline level is not enough to induce changes in the exploration. However, administered in higher doses, pantethine produced marked depression both of the open-field activity and noradrenaline levels, possibly because cysteamine, the primary metabolite of pantethine, has dopamine beta-hydroxylase inhibitory activity by chelating the copper in this enzyme (6). The observed change in hypothalamic noradrenaline is a marker for alteration in central nervous system catecholamine metabolism and that some aspect of this is linked to the behavioral effect. The major increase, corresponding to the reduced amount of noradrenaline, is found in dopamine and its principal metabolite, DOPAC. The significant decrease of defecation after the treatment with pantethine might be connected with the suppressive effect on gastrointestinal motility (31,32).

In the time-response studies, the effects of pantethine on the behavioral and catecholamine parameters at 8 hr after the administration were similar to those observed after 4 hr. However, later (12 hr) the effects of the compound became weaker, and at 24 hr after the injection the behavioral and neurochemical parameters of the pantethine-treated group did not differ from the control animals, suggesting that the drug-induced changes are reversible.

Martin-Iverson *et al.* (13) have suggested that the somatostatin-depleting compound cysteamine is an important tool for the study of central actions of endogenous somatostatin. Their results suggest that somatostatin in the nucleus accumbens and caudate-putamen modulates the motor, but not the reinforcing, properties of dopaminergic drugs, possibly via an action postsynaptic to the dopamine-releasing terminals. Concerning our data on the striatal somatostatin we found a similar dose- and time-related alteration as in the case of the behavioral and catecholamine results. However, the effects on somatostatin were less pronounced.

There is evidence supporting the view that the activity of central dopamine neurons is influenced by somatostatin. Somatostatin administered intracerebroventricularly (10), intracisternally (Widerlöv and Breese, unpublished data), or intrastriatally (1) has been shown to increase striatal dopamine turnover. The peptide also appears to increase dopamine release from rat striatal slices and from cat caudate nucleus in vivo (5). Therefore, it is possible that the decrease of endogenous somatostatin concentration in striatum after pantethine treatment has lower modulatory activity on striatal dopaminergic system, and this effect might play a role in the depression of open-field activity of the animals. Indeed, in previous experiments we found that the selective somatostatin-depleting compound cysteamine (23), which is the metabolite of pantethine, decreased the striatal concentrations of dopamine and DOPAC, and also attenuated the exploratory activity of the animals (26). However, the findings in the correlational analyses of the present experiments suggest that the catecholaminergic neurotransmission is more closely linked to the behavioral effects of pantethine than the effect of the compound on the somatostatinergic system. The direct effect of somatostatin on motor activity cannot be excluded.

Whether pantethine (or pantetheine) is active only after conversion to cysteamine, or also has an activity of its own in these

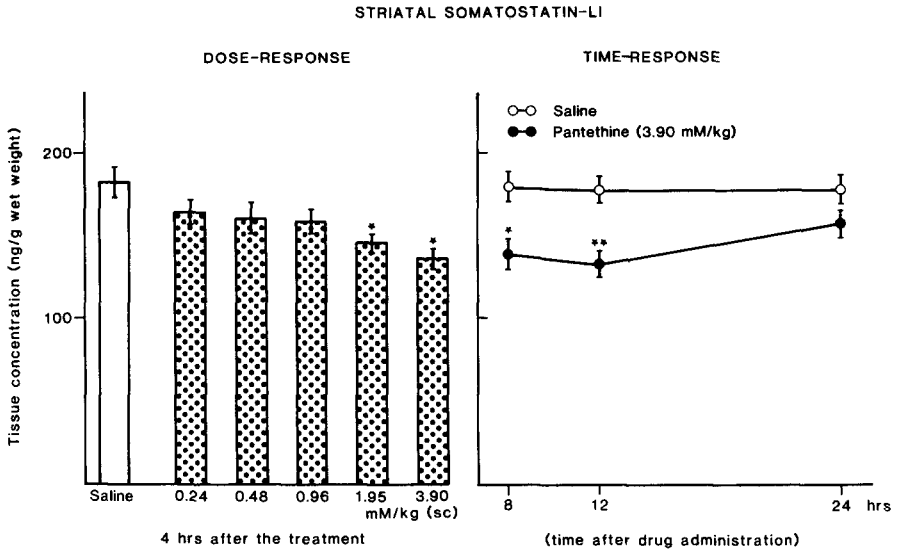

FIG. 5. Dose- and time-related effects of pantethine on striatal somatostatin concentration in rats. $\star = p<0.05$, $\star\star = p<0.01$ (Tukey test). Vertical lines represent the standard error of the mean. (n = 7–8 animals/group.)

tests, still remains to be elucidated. In future studies we plan to investigate the neurochemical and behavioral actions of pantethine following intracerebroventricular administration of the compound.

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REFERENCES

1. Beal, M. F.; Martin, J. B. The effect of somatostatin on striatal catecholamines. Neurosci. Lett. 44:271–276; 1984.
2. Bjartell, A. R.; Ekman, R.; Sundler, F. γ-MSH-like immunoreactivity in porcine pituitary and adrenal medulla. An immunochemical and immunocytochemical study. Regul. Pept. 19:291–306; 1987.
3. Butler, J. DeB.; Zatz, M. Pantethine depletes cystinotic fibroblasts of cysteine. J. Pediatr. 102:796–798; 1983.
4. Butler, J. DeB.; Zatz, M. Pantethine and cysteamine deplete cystine from cystinotic fibroblasts via efflux of cysteamine-cysteine mixed disulfide. J. Clin. Invest. 74:411–416; 1984.
5. Chesselet, M. F.; Reisine, T. D. Somatostatin regulates dopamine release in rat striatal slices and cat caudate nuclei. J. Neurosci. 3:232–236; 1983.
6. DiLiberto, E. J., Jr.; DiStefano, V.; Crispen-Smith, J. Mechanism and kinetics of the inhibition of dopamine-beta-hydroxylase by 2-mercaptoethylguanidine. Biochem. Pharmacol. 22:2961–2972; 1973.
7. Engel, J. A.; Johannessen, K.; Liljequist, S.; Goldstein, M. Activation of alpha$_2$-adrenoreceptors enhances haloperidol-induced suppression of operant behaviour. J. Neural Transm. 66:107–120; 1986.
8. 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.
9. Gaddi, A.; Descovich, G. C.; Noseda, G.; Fragiacomo, C.; Colombo, L.; Craveri, A.; Montanari, G.; Sirtori, C. R. Controlled evaluation of pantethine, a natural hypolipidemic compound, in patients with different forms of hyperlipoproteinemia. Atherosclerosis 50:73–83; 1984.
10. Garcia-Sevilla, J. A.; Magnusson, T.; Carlsson, A. Effect of intracerebroventricularly administered somatostatin on brain monoamine turnover. Brain Res. 155:159–163; 1978.
11. Hoagland, M. B.; Novelli, G. D. Biosynthesis of coenzyme A from phosphopantetheine and of pantetheine from pantothenate. J. Biol. Chem. 207:767–773; 1954.
12. 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.
13. Martin-Iverson, M. T.; Radke, J. M.; Vincent, S. R. The effects of cysteamine on dopamine-mediated behaviors: Evidence for dopamine-somatostatin interactions in the striatum. Pharmacol. Biochem. Behav. 24:1707–1714; 1986.
14. Millard, W. J.; Sagar, S. M.; Landis, D. M. D.; Martin, J. B. Cysteamine: a potent and specific depletor of pituitary prolactin. Science 217:452–454; 1982.
15. Ono, S.; Kameda, K.; Abiko, Y. Metabolism of pantethine in the rat. J. Nutr. Sci. Vitaminol. (Tokyo) 20:203–213; 1974.
16. Orloff, S.; Butler, J. DeB.; 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.
17. Palkovits, M.; Brownstein, M. J.; Eiden, L. E.; Beinfeld, M. C.; Russel, J.; Arimura, A.; Szabo, S. Selective depletion of somatostatin in rat brain by cysteamine. Brain Res. 240:178–180; 1982.
18. Ranje, C.; Ungerstedt, U. High correlations between number of dopamine cells, dopamine levels and motor performance. Brain Res. 134:83–93; 1977.
19. Rezek, M.; Havlicek, V.; Leybin, L.; Pinsky, C.; Kroeger, E. A.; Hughes, K. R.; Friesen, H. Neostriatal administration of somatostastin: differential effect of small and large doses on behavior and motor control. Can. J. Physiol. Pharmacol. 55:234–242; 1977.
20. 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.
21. Scammel, J. G.; Dannies, P. S. Depletion of pituitary prolactin by cysteamine is due to loss of immunological activity. Endocrinology

114:712–716; 1984.
22. Sörensen, R. L.; Grouse, L. H.; Eide, R. P. Cysteamine blocks somatostatin secretion without altering the course of insulin or glucagon release. A new model for the study of islet function. Diabetes 32:377–386; 1983.
23. Szabo, S.; Reichlin, S. Somatostatin in rat tissue is depleted by cysteamine administration. Endocrinology 109:2255–2257; 1981.
24. Vécsei, L.; Alling, C.; Heilig, M.; Widerlöv, E. Effects of cysteamine and pantethine on open-field behavior, hypothalamic catecholamine concentrations, and somatostatin-induced barrel rotation in rats. Pharmacol. Biochem. Behav. 32:629–635; 1989.
25. Vécsei, L.; Balázs, M.; Bollók, I.; Telegdy, G. Selective decrease of hypothalamic noradrenaline by cysteamine. Arch. Int. Pharmacodyn. 274:125–128; 1985.
26. Vécsei, L.; Ekman, R.; Alling, C.; Widerlöv, E. Influence of cysteamine and cysteine on open-field behavior, and on brain levels of catecholamines, somatostatin, neuropeptide Y and corticotropin releasing hormone in the rat. J. Neural. Transm., in press; 1989.
27. Vécsei, L.; Király, Cs.; Bollók, I.; Nagy, A.; Varga, J.; Penke, B.; Telegdy, G. Comparative studies with somatostatin and cysteamine in different behavioral tests on rats. Pharmacol. Biochem. Behav. 21:833–837; 1984.
28. Vécsei, L.; Telegdy, G.; Schally, A. V.; Coy, D. H. Effects of beta-(Tyr^9)melanotropin-(9–18) decapeptide on passive and active avoidance behaviour and open-field activity of rats. Peptides 2: 389–391; 1981.
29. Vécsei, L.; Widerlöv, E.; Alling, C. Effects of pantethine, cysteamine and pantothenic acid on oen-field behavior and brain catecholamines in rats. Arch. Int. Pharmacodyn., in press; 1989.
30. Wallengren, J.; Ekman, R.; Sundler, F. Occurence and distribution of neuropeptides in the human skin. Acta Derm. Venerol. (Stockh.) 67:185–192; 1987.
31. Watanabe, H.; Hobara, N.; Kobayashi, M.; Nakatsukasa, H.; Nagashima, H. Lowering of blood acetaldehyde but not ethanol concentrations by pantethine following alcohol ingestin: different effects in flushing and nonflushing subjects. Alcohol.: Clin. Exp. Res. 9: 272–276; 1985.
32. Wikberg, J. E. S. The pharmacological classification of adrenergic alpha-1 and alpha-2 receptors and their mechanisms of action. Acta Physiol. Scand. [Suppl.] 468; 1979.