PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **188**, 485–488 (1988)

Effects of Cysteamine on Blood Pressure: Possible Mediation through Vasopressin Release (42765)

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Abstract. Cysteamine (β-mercaptoethylamine, CSH) has been reported to have various effects on the neuroendocrine system. Reports indicate CSH decreases pituitary oxytocin (OT) without affecting pituitary vasopressin (VP). However, preliminary studies from our laboratory strongly indicate that CSH has an effect on VP release. Experiments were conducted with dibenzyline-treated, urethane-anesthetized, male Sprague–Dawley (SD) rats. Rats were injected with 4 mU of standard VP and 4 mg/100 g of CSH. Administration of VP resulted in an increase in mean arterial pressure (MAP) of 23.5 ± 3.2 mm Hg. Administration of CSH resulted in a consistent. immediate decrease in MAP of 13.0 ± 2.0 mm Hg prior to an increase of 21.0 ± 2.6 mm Hg. The effects due to VP and CSH were strikingly different; the CSH-induced MAP rise took longer to peak and to return to baseline. Both the VP- and CSH-induced MAP rise were markedly inhibited by a prior administration of a specific VP antagonist $d(CH_2)_5$[Tyr(Me)]AVP. In addition, the typical increase in MAP observed in SD rats following CSH administration was substantially reduced when the same dose was administered in homozygous diabetes insipidus (HODI) rats. The data presented here strongly suggest that CSH-induced MAP elevation is due to the release of VP from the pituitary gland.

Cysteamine, β-mercaptoethylamine (CSH), forms a functional group at the terminal end of acetyl coenzyme A (1). CSH is a small compound, with a mol wt of 113, and can be found in the mammalian cell when acetyl coenzyme A is hydrolyzed by the enzyme pantethinase (2).

Cysteamine is a drug which has recently received a great deal of attention due to its profound effects on the neuroendocrine system. Temporary depletion of somatostatin in the stomach, duodenum, pancreas, and hypothalamus has been reported after treatment with cysteamine (3). Millard *et al.* (4) demonstrated that CSH could disrupt normal episodic secretion of growth hormone 4 hr after treatment and hypothesized that this phenomenon may be due to the drug's ability to deplete somatostatin.

The mechanism by which CSH acts to decrease somatostatin is not understood. Lorenson and Jacobs (5) proposed that cysteamine acts through a thiol:disulfide interaction, altering the ability to assay the hormone. To better understand the activity of cysteamine, one should examine other disulfide-containing peptides in greater detail. One such compound is antidiuretic hormone, also called vasopressin (VP), which consists of nine amino acids and one disulfide bond. It is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the neurohypophysis. Receptors for VP are present on the smooth muscle cells of blood vessel walls. When stimulated, these cells cause an increase in blood pressure. The present study was designed to investigate the effect of peripheral CSH administration on VP release.

Materials and Methods. Ten male Sprague–Dawley (SD) rats weighing between 300 and 350 g obtained from Taconic Farms (Germantown, NY) were used in these experiments. Animals were anesthetized with urethane (175 mg/100 g ip) and prepared for the blood pressure assay, according to the method of Dekanski (6). The jugular vein and carotid artery were cannulated with polyethylene (PE) 10 and PE 50 tubing, respectively. The arterial cannula was connected to a pressure transducer and the pulsatile blood pressure was recorded on a polygraph (Grass Instruments, Quincy, MA). All rats received a subcutaneous injection of dibenzyline (1 mg).

Vasopressin, its antagonist, and CSH were injected through the intravenous (iv) cannula. The injection protocol had two stages.

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First, a graded dose of VP or CSH was injected to establish the sensitivity of the preparation. Next, a specific VP antagonist ($d(CH_2)_5$[Tyr(Me)]AVP) was administered (2 μg/100 g) 5 min prior to the 4-mU injection of VP. Ten to fifteen minutes later, the rat was injected with 4 mg/100 g CSH.

The effect of CSH was also tested on six male homozygous diabetes insipidus (HODI) rats (345 ± 10 g) obtained from Blue Spruce Farms (Altmont, NY). The urine output of these rats was measured (36 ± 6 ml/24 hr/100 g) prior to the beginning of the experiments. The rats were given 4 mU VP, followed by 4 mg/100 g CSH.

Sufficient time was allowed for blood pressure to return to baseline position prior to the next injection.

Results. Figures 1a and 1b represent typical experiments demonstrating the MAP responses to VP and CSH, respectively. Administration of either VP or CSH caused a definite rise in blood pressure; however, a distinct difference in the patterns of response were seen. With the injection of 4 mU VP, a rise of 23.5 ± 3.2 mm Hg was obtained which was followed by a gradual fall of pressure to the baseline level (Fig. 1a). With 4 mg

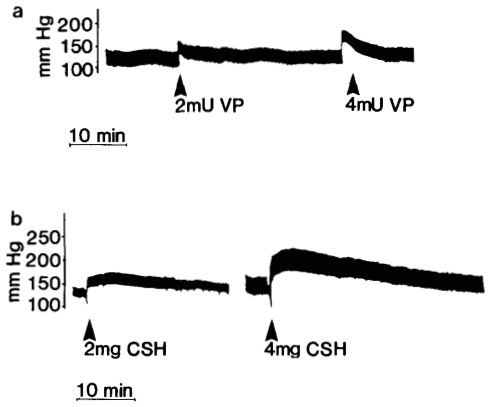

FIG. 1 (a) Arterial pressure response to vasopressin. The rise in blood pressure is directly proportional to the dose of vasopressin administered. Each increase in pressure is followed by a gradual fall in pressure until baseline is obtained. (b) Arterial pressure response to cysteamine. The time interval between the two doses of cysteamine was 104 min. Cysteamine's effect on blood pressure differs from that of vasopressin in that the increase in pressure is sustained over a longer period of time before reaching baseline. Furthermore, prior to each increase in pressure, a marked decrease occurs.

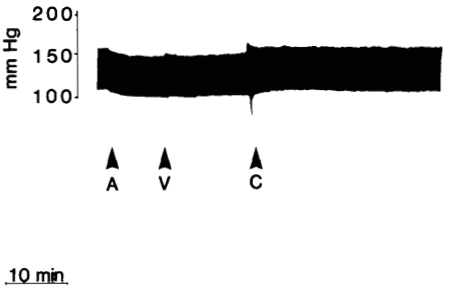

FIG. 2. Inhibition of response to both vasopressin and cysteamine by a vasopressin antagonist (A). The rise in blood pressure due to a 4-mU injection of vasopressin (V), followed by a 4 mg/100 g injection of cysteamine (C), is inhibited by administration of $d(CH_2)_5$[Tyr(Me)]-AVP. Cysteamine's pressor effect is almost completely blocked by the vasopressin antagonist; however, the depressor effect remains.

CSH, a similar rise in pressure, i.e., 21 ± 2.6 mm Hg, was observed, but response was maintained over a longer period. Furthermore, prior to each CSH-induced pressure response, a depressor response of 13 ± 2 mm Hg was observed (Fig. 1b).

It was hypothesized that the CSH-induced increase in mean arterial pressure (MAP) was due to VP release. Therefore, in the next series of experiments, a specific VP antagonist ($d(CH_2)_5$[Tyr(Me)]AVP) was administered prior to the injection of CSH. As can be seen in Fig. 2, iv administration of the VP antagonist at a dose of 2 μg/100 g prior to the injection of VP and CSH almost completely blocked the pressor effect of both VP and CSH.

These data strongly indicate that the CSH-induced pressor response is due to VP release. To further strengthen this hypothesis, experiments were conducted with six HODI rats. As can be seen in Fig. 3, 4 mU of VP produced a rise in MAP similar to that obtained with SD rats while 4 mg/100 g of CSH did not. In HODI rats, 4 mg/100 g CSH elevated MAP by 2.3 ± 0.3 mm Hg, while in SD rats the same dose of CSH produced a MAP increase of 21 ± 1.2 mm Hg. These additional data further support the hypothesis that the CSH-induced rise in MAP in normal rats is most likely due to the release of VP from the pituitary.

Discussion. The results of this study clearly demonstrate that iv administration of

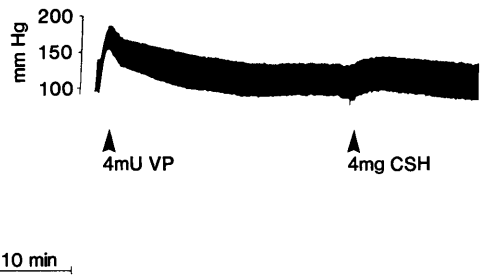

FIG. 3. Arterial responses of diabetes insipidus rats to both vasopressin and cysteamine. Diabetes insipidus rats show the expected increase in blood pressure due to vasopressin treatment. However, a dose of 4 mg/100 g of cysteamine has a considerably reduced pressor effect, indicating that the rats are unable to respond due to their lack of pituitary vasopressin. Depressor effects of cysteamine are also attenuated.

CSH caused an initial decrease followed by an increase of MAP. Presently, the mechanism of the CSH-induced depressor response is not known.

The pressure effect of CSH could result from direct vasoconstriction of blood vessels or through stimulation of the posterior pituitary, with subsequent release of VP. Bioassay results showing a blood pressure elevation maintained over a long period of time would suggest that CSH stimulates the posterior pituitary to release VP (Fig. 1b). With an injection of 4 mg/100 g of CSH MAP returned to baseline 31 min after the drug was administered, whereas the MAP rise caused by 4 mU VP injection returned to baseline within 14 min. These results indicate that CSH is acting centrally to release VP from the posterior pituitary.

To test this hypothesis, a VP antagonist was given prior to CSH administration. The antagonist almost completely blocked the rise in MAP caused by both VP and CSH. These results indicate that CSH causes the release of VP.

Results obtained with HODI rats following injections of VP and CSH further support our hypothesis. These rats responded to VP injections with an increase in MAP; however, CSH administration had considerably less of an effect on the MAP of HODI. It is logical to assume that the inability of HODI rats to respond to CSH was perhaps due to the lack of pituitary VP. If the site of action of CSH was on the blood vessel walls one would expect a pressor response in the HODI rats; however, no pressor effect was observed. Therefore, the site of action of CSH must be central rather than peripheral. CSH's depressor effect was not blocked by the VP antagonist.

Palkovitz observed no change in VP content of median eminence, anterior hypothalamus, or posterior pituitary following CSH administration (7). Also, the results of the experiments by Franco-Bourland suggest that CSH does not affect biosynthesis or degradation of VP in the hypothalamus or pituitary (8, 9). It is possible that our results differ from those of Palkovitz and Franco-Bourland due to the fact that our experimental design allowed us to measure the immediate effect of drug administration whereas in the experiments of Palkovitz and Franco-Bourland the effect of CSH was determined 4 and 2 hr after CSH treatment, respectively. Our results showed CSH administration caused an immediate rise of MAP which returned to baseline within 31 min.

VP is released in response to certain stressors such as fluid restriction (10). The pressor response we report here is both immediate and VP dependent, as indicated by the VP antagonist results as well as the results of the HODI rat experiments. CSH might be acting as a stressor, releasing VP and causing the immediate rise in blood pressure. However, it is not yet known how CSH acts to release VP.

In conclusion, the results presented here strongly indicate CSH causes a rise in MAP by effecting VP release from the neurohypophysis.

This research was supported by Grant NSF PCM 8312200. Our sincere thanks to Dr. W. H. Sawyer for his gift of the vasopressin antagonist.

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Received July 6, 1987. P.S.E.B.M. 1988, Vol. 188.
Accepted April 26, 1988.