Octreotide-induced drinking, vasopressin, and pressure responses: role of central angiotensin and ACh

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Octreotide-induced drinking, vasopressin, and pressure responses: role of central angiotensin and ACh. Am J Physiol Regulatory Integrative Comp Physiol 279: R271–R277, 2000.—The involvement of central angiotensinergic and cholinergic mechanisms in the effects of the intracerebroventricularly injected somatostatin analog octreotide (Oct) on drinking, blood pressure, and vasopressin secretion in the rat was investigated. Intracerebroventricular Oct elicited prompt drinking lasting for 10 min. Water consumption depended on the dose of Oct (0.01, 0.1, and 0.4 μg). The drinking response to Oct was inhibited by pretreatments with the intracerebroventricularly injected angiotensin-converting enzyme inhibitor captopril, the AT1/AT2 angiotensin receptor antagonist saralasin, the selective AT1 receptor antagonist losartan, or the muscarinic cholinergic receptor antagonist atropine. The dipsogenic effect of Oct was not altered by prior subcutaneous injection of naloxone. Oct stimulated vasopressin secretion and enhanced blood pressure. These responses were also blocked by pretreatments with captopril or atropine. Previous reports indicate that the central angiotensinergic and cholinergic mechanisms stimulate drinking and vasopressin secretion independently. We suggest that somatostatin acting on sst2 or sst5 receptors modulates central angiotensinergic and cholinergic mechanisms involved in the regulation of fluid balance.

somatostatin; muscarinic; cholinergic; thirst; blood pressure; rat

While studying alterations in rat sleep after subcutaneous administration of the somatostatin analog octreotide (Oct), we noted that the rats often drank water after injections (2). Intracerebroventricular injection of Oct also regularly elicited prompt drinking (1). Previous reports indicate that intracerebroventricularly injected somatostatin induces vasopressin secretion and blood pressure increase in the rat (4, 5, 35). Drinking, vasopressin release, and blood pressure increase are well-documented responses to intracerebroventricularly administered ANG II and cholinergic agonists, e.g., carbachol (6, 11, 14–16, 29, 30). Inhibition of central angiotensinergic mechanisms selectively blocks the hypertensive and dipsogenic activities of ANG II without altering the responses to cholinergic stimulation (7, 15, 20, 25, 30). Similarly, muscarinic cholinergic antagonists do not interfere (11, 15, 25) or only partially reduce (30) the effects of ANG II on blood pressure and drinking, whereas these antagonists eliminate increases in blood pressure and drinking in response to cholinergic stimulation. Hence, the effects of ACh and ANG II on fluid homeostasis and blood pressure are regarded as parallel and fundamentally independent mechanisms (15, 25). Nevertheless, cholinergic and angiotensinergic mechanisms may act in concert, regulating water intake in response to physiological stimuli, e.g., thirst after water deprivation (6, 14).

The aim of our experiments was to characterize the dose-effect relationships in Oct-induced drinking and to determine the involvement of angiotensinergic and cholinergic mechanisms in the drinking, vasopressin, and blood pressure responses to Oct. The rats were pretreated with intracerebroventricular injections of the angiotensin-converting enzyme inhibitor captopril (Cap) and the muscarinic antagonist atropine (Atr) in doses that reportedly inhibit intracerebral formation of ANG II and cholinergic transmission, respectively, and the responses to Oct were studied. Oct-induced drinking was also recorded after intracerebroventricular administration of saralasin (Sar), a peptide antagonist of AT1/AT2 angiotensin receptors, and losartan (Los), a nonpeptide AT1 receptor blocker. Pretreatment with the opioid receptor antagonist naloxone (Nal) was used to determine whether binding of Oct to opioid receptors (34) is involved in the dipsogenic activity. The results suggest a unique role for somatostatin in fluid homeostasis: it may control angiotensinergic and cholinergic mechanisms involved in the regulation of drinking and vasopressin secretion.

METHODS

Animals. Male Sprague-Dawley rats (300–330 g) were used. The surgeries were carried out under ketamine-xylazine (87 and 13 mg/kg, respectively) anesthesia. Stereotaxic equipment (model 900, Kopf) was used to insert a chronic equipment.
intracerebroventricular cannula into the left lateral ventricle (−0.80 mm from bregma, 1.4 mm from midline, and −3.4 mm from the top of the skull according to the atlas by Paxinos and Watson [31]). The location of the cannula was determined by the gravity method (sudden drop in pressure) during implantation. The guide cannula was fixed with dental cement to the skull. Trypan blue (0.25 μg in 5 μl) was injected into the cannula, and the ventricles were examined at the termination of the experiments; only data from those rats in which trypan blue stained the entire ventricular system were used. For blood pressure recording, a silicone rubber catheter was implanted into the descending aorta via the left carotid artery. The rats used for systemic injection of Oct received a chronic silicone rubber heart catheter in the right atrium through the right external jugular vein. The catheters were exteriorized on the back of the neck, and they were flushed daily with heparinized physiological saline (PS, 200–300 IU/day).

The rats were housed in individual Plexiglas cages. The cages were placed in chambers with a 12:12-h light-dark cycle and an ambient temperature regulated at 26°C. Food and water were continuously available. The rats were kept in conditions identical to those in the recording rooms for at least 1 mo before the operation. All tests were performed in the light period. There were no differences in the responses to Oct between tests performed in the morning and those performed in the afternoon, and the data from these sessions were pooled. A 5- to 7-day recovery period was allowed after the surgeries.

**Drinking test.** Water consumption was determined by weighing the water bottles before and 10 min after injection. Previous behavioral experiments in our laboratory indicated that Oct-induced drinking was over in 10 min (1). Oct (0.1 μg/1 μl; Sandostatin, Novartis Pharma, Basel, Switzerland) diluted in PS was injected intracerebroventricularly in doses of 0.01, 0.1, and 0.4 μg in 2 μl. Drinking was tested after intracerebroventricular injection of the vehicle (Veh) of Oct in 10 rats. Veh containing lactate and mannitol was donated by Novartis Pharma, and it was injected in the same dilution as Oct. Veh had no effects, and therefore PS was routinely used for control injections. To determine the mechanisms involved in the mediation of Oct-induced drinking, water consumption was measured after intracerebroventricular injection of 0.1 μg of Oct in rats pretreated as follows: 30 μg of Cap (Sigma-Aldrich, Budapest) in 2 μl or 10 μg of Atr (atropine sulfate, Egis, Budapest) in 10 μl were intracerebroventricularly injected 15 min before Oct, 10 μg of Sar (Peninsula Laboratories, Belmont, CA) in 2 μl were intracerebroventricularly administered 10 min before Oct, 100 μg of Los (Merck Research Laboratories, Rahway, NJ) in 2 μl were intracerebroventricularly injected 5 min before Oct, and 1 mg/kg of Nal (Narcanti, Du Pont Pharma, Bad Homburg, Germany) in a volume of 0.25 ml/100 g was subcutaneously injected 20 min before Oct. The doses of the antagonists corresponded to previously reported doses that were effective in inhibiting carbachol- or ANG II-induced drinking (15, 21, 30). This injection protocol required baseline measurements of water intake after double intracerebroventricular injections of PS/Veh (or subcutaneous + intracerebroventricular PS for the experiments with Nal), after PS/Veh + 0.1 μg Oct, and after pretreatments with each of the compounds above + intracerebroventricular injection of PS/Veh. The rats, however, did not drink after intracerebroventricular PS or Veh, and this was not altered by any of the compounds. Also, prior administration of PS did not modify the drinking response to 0.1 μg of Oct 5–20 min later. Therefore, the data collected after double injections of PS were pooled with the data obtained after single injections of PS or Veh. Also, the water consumption measured after PS + 0.1 μg Oct was pooled with water consumption obtained after a single pretreatment with 0.1 μg of Oct, and water consumption after the compounds above + PS is not reported here. After frequent repeated testing with Oct, the rats developed a tendency to drink an increasing volume of water, even when PS was administered. As a compromise between avoiding false-positive responses and using too many animals, each rat was tested in a maximum of three sessions on different days randomly assigned to the treatments reported above, but the sessions always included at least one dose of Oct without pretreatments with any blocker. The groups of rats used in the various injection protocols were as follows: Veh (n = 10); PS, including PS + PS (n = 29); 0.01 μg of Oct (n = 16); 0.1 μg of Oct, including PS + Oct (n = 63); 0.4 μg of Oct (n = 23); Cap + Oct (n = 22); Sar + Oct (n = 11); Los + Oct (n = 11); Atr + Oct (n = 21); and Nal + Oct (n = 5). The rats (n = 7) in the experiments with systemic injections of Oct received PS, 10 μg/kg Oct, and 100 μg/kg Oct (0.1 ml/100 g volume) via a chronic cardiac catheter on three different days in random order.

**Determination of vasopressin.** Rats with a positive drinking response to Oct were used. Plasma vasopressin concentrations were determined in groups of rats intracerebroventricularly injected with PS + Oct (n = 8), Cap + PS (n = 6), Atr + PS (n = 4), PS + Oct (n = 9), Cap + Oct (n = 9), and Atr + Oct (n = 11). The dose of Oct was invariably 0.1 μg, and the doses of Cap and Atr were the same as those used in the experiments with drinking. The time between injections was 15 min. The rats were killed by means of guillotine 5 min after the second injection, and the trunk blood was collected in chilled polystyrene tubes containing EDTA and then centrifuged. Plasma samples were stored at −20°C until the assay. Vasopressin was extracted from 2-ml plasma samples by using thermally activated Vycor glass powder (Corning Glass Works, Corning, NY). The recovery of the extraction was 77%. The dry residues were redissolved in RIA buffer. Vasopressin concentrations were determined by RIA as described previously (23). The intra- and interassay coefficients were 13.3% and 16.3%, respectively. The detection limit of the assay was 1 pg/tube.

**Measurements of blood pressure.** Rats with positive drinking response to Oct were selected for the implantation of the aortic catheter. A section of silicone rubber tubing filled with PS was connected to the free end of the aortic catheter in the rat and to a pressure transducer (Combitrans, Braun, Melsungen, Germany) outside the cages. The rats were free to move around the cage. The signals from the transducer were amplified and digitized (64-Hz sampling rate) and collected by a computer. Mean blood pressure values were calculated for consecutive 2-min intervals. The intracerebroventricular injection needle was inserted into the guide cannula without touching the rat. Each rat (n = 8) was tested on 4 days in random order with the injections as follows: PS + PS, PS + Oct, Cap + Oct, and Atr + Oct. The dose of Oct was 0.1 μg; Cap and Atr were administered according to the protocol described for the experiments in which water consumption was measured. Blood pressure was recorded for 30 min after the second injection. Previous reports indicated that intracerebroventricular Cap and Atr did not alter baseline blood pressure (30), and, in fact, changes in blood pressure were not observed during the 15 min after the administration of these compounds. Therefore, separate experiments were not performed to record blood pressure after Cap and Atr without subsequent injection of Oct.
RESULTS

Effects of Oct on water intake. Baseline water intake was 0.7 ± 0.33 ml during the first 10 min after systemic administration of PS. In contrast, the rats drank 3.73 ± 0.43 and 4.47 ± 0.38 ml of water in response to 10 and 100 μg/kg systemically administered Oct, respectively. The Oct-induced stimulation of water consumption was significant \([F(2,12) = 34.433, P < 0.05]\), but water intake after the two doses of Oct was not statistically different (Student-Newman-Keuls test).

Intracerebroventricular Oct elicited drinking 1 min. As reported previously (1), drinking activity continued with short interruptions for 4–5 min and then started to decline. Drinking ceased 10 min after the injection, and the rats displayed long periods of grooming, scratching, and eating thereafter. Examination of the staining of the ventricular system at the termination of the experiments showed that the correct placement of the cannula in the lateral ventricle and the communication between the lateral and the third ventricles were mandatory for the drinking response. Oct always elicited drinking when these requirements were met. The quantity of water consumed varied with the dose of Oct (Fig. 1). Comparisons of water intakes after PS (0.27 ± 0.09 ml), Veh (0.29 ± 0.11 ml), and the various doses of Oct (1.73 ± 0.35, 4.41 ± 0.22, and 5.48 ± 0.4 ml after 0.01, 0.1, and 0.4 μg of Oct) indicated significant differences \([F(4,136) = 64.0, P < 0.05]\); the numbers of rats for 0.1 μg of Oct and for PS include those injected with PS + Oct and Oct + PS). Post hoc comparisons showed that Veh was ineffective. Water intake was higher after each dose of Oct than after PS or Veh, and consumption of water differed significantly among the doses of Oct (Student-Newman-Keuls test).

Cap, Atr, Sar, Los, or Nal did not cause measurable alterations in water consumption during the 10-min postinjection period (not shown), but all these pretreatments except Nal altered the dipsogenic action of 0.1 μg of Oct (Fig. 2). Water intake varied significantly among the groups with various pretreatments \([F(6,165) = 50.5, P < 0.05]\); number of rats for PS + Oct includes those injected with only Oct, and number of rats for PS + PS includes those injected with only PS or Veh]. Post hoc analysis indicated that drinking induced by 0.1 μg of Oct (4.41 ± 0.22 ml) was significantly inhibited by prior injections of Cap, Sar, Los, or Atr. Although water consumption tended to be higher when Oct was administered to rats pretreated with Cap (1.07 ± 0.27 ml), Los (0.98 ± 0.40 ml), or Atr (0.65 ± 0.19 ml) than after intracerebroventricular injections of PS/Veh (0.29 ± 0.08 ml), these differences were not significant. The rats injected with Sar + Oct, however, continued to drink more water (1.70 ± 0.50 ml).
Fig. 3. Effects of intracerebroventricular injection of 0.1 µg of Oct on plasma vasopressin concentrations. The rats received double intracerebroventricular injections with 15 min between injections, and vasopressin was determined from blood samples obtained 5 min after the 2nd injection. PS, physiological saline; Cap, 30 µg of captopril; Atr, 10 µg of atropine. Values are means ± SE; n = 8 for PS + PS, n = 6 for Cap + PS, n = 4 for Atr + PS, n = 9 for PS + Oct and Cap + Oct, and n = 11 for Atr + Oct. *Significantly different from PS + PS (ANOVA followed by Student-Newman-Keuls test, P < 0.05).

ml) than the baseline value after PS/Veh (Student-Newman-Keuls test). Nal did not alter water intake elicited by 0.1 µg of Oct. Water consumption was significantly higher after Nal + Oct (4.1 ± 0.8 ml) than after PS/Veh or after any angiotensin blockers or Atr + 0.1 µg of Oct (Student-Newman-Keuls test). Nal altered the behavioral responses to Oct. The rats were excited, and drinking was often interrupted by brief periods of grooming and scratching.

Effects of Oct on vasopressin secretion. ANOVA indicated significant differences in the plasma concentrations of vasopressin among the groups with various combinations of intracerebroventricular injections [F(5,41) = 9.54, P < 0.05]. Oct elicited a 13-fold increase in plasma concentrations of vasopressin (Fig. 3); vasopressin was significantly higher in the rats injected with PS + 0.1 µg of Oct (13.2 ± 3.19 pg/ml) than in any other groups (Student-Newman-Keuls test). Cap (3.6 ± 0.81 pg/ml) and Atr (4.2 ± 1.08 pg/ml) significantly inhibited the Oct-induced vasopressin secretion; in fact, vasopressin concentrations after Cap + Oct and Atr + Oct were not different from the baseline value after PS + PS (2.15 ± 0.31 pg/ml). Cap or Atr itself (Cap + PS, 2.3 ± 0.48 pg/ml; Atr + PS, 1.90 ± 0.61 pg/ml) did not alter baseline vasopressin concentrations.

Effects of Oct on blood pressure. The mean baseline blood pressure in the 2 min before the second intracerebroventricular injection was 105.7 ± 1.95 mmHg. Blood pressure values during 30 min after the second injections (PS or 0.1 µg Oct) varied significantly depending on the pretreatment [PS, Cap, or Atr; F(3,21) = 7.937, P < 0.05]. Increases in blood pressure were observed in response to PS + Oct (Fig. 4); blood pressure was significantly higher after this treatment than after any other treatments (Student-Newman-Keuls test). The mean increase in blood pressure was modest, ~10 mmHg. The variations in blood pressure were a function of time after Oct injection [treatment × time factor: F(42,293) = 1.822, P < 0.05]. Blood pressure rose promptly after Oct in association with drinking. Then the blood pressure tended to decline as the drinking activity subsided. A second rise resulting in a peak in blood pressure occurred at 12–16 min after injection, during a period when the rats had already stopped drinking. This was followed by a gradual decline of blood pressure, although the pressure was still 5 mmHg above baseline at the end of recording. Pre-treatment with Cap or Atr inhibited Oct-induced rises in blood pressure: pressure values after Cap + Oct and Atr + Oct were 1–2-mmHg higher than baseline, but these differences were below the level of statistical significance and the blood pressure after Cap + Oct and Atr + Oct did not differ from blood pressure after PS + PS. Cap or Atr itself did not alter blood pressure.

DISCUSSION

The increased water intake after intracerebroventricular Oct verified our previous observations that subcutaneous or intracerebroventricular administration of Oct was often followed by drinking by the rats (1, 2). In addition, intracerebroventricularly injected

Fig. 4. Effects of 0.1 µg of Oct on blood pressure in rats (n = 8). The rats received double injections of PS + PS, PS + Oct, Cap + Oct, and Atr + Oct with 15 min between injections. Values (means ± SE) depict deviation from the mean blood pressure during 8 min before injection. A: changes in blood pressure after 0.1 µg of Oct (●) and PS (○) when the pretreatment was PS. B: changes in blood pressure in response to Oct after a prior injection of 30 µg of Cap (●) and blood pressure variations after Cap alone (○, Cap was administered as 1st injection). C: changes in blood pressure when Oct was injected after Atr (●) and changes in blood pressure after injection of Atr (○, Atr was administered as 1st injection).
Oct elicited releases of vasopressin and rises in blood pressure. Both of these responses were previously reported after intracerebroventricular injection of somatostatin (4, 5, 35). The present findings extend these observations by implicating cholinergic and angiotensinergic transmissions in the mediation of these somatostatin actions. The results also help identify the subset of somatostatin receptors that modulates water balance and blood volume.

Oct is a potent agonist on sst2 and sst5 receptors, a relatively weak ligand for sst3 receptors, and does not bind to sst1 and sst4 receptors (34, 38). Expression of sst2 receptors is well documented in the hypothalamus and preoptic region (reviewed in Ref. 38), and, recently, prominent expression of sst5 receptors was described in the basal forebrain (41), including the preoptic region. The preoptic area is also implicated in the regulation of drinking (see below). Somatostatin and somatostatin analogs, however, interact with μ-opioid receptors (34). Opioid receptors, particularly μ-receptors, may modulate drinking, although the effects are weak and the reports vary greatly with respect to the nature of this modulation, i.e., stimulation or inhibition (42). Nal, a nonselective opioid receptor antagonist, failed to alter the Oct-induced drinking in our experiments.

Drinking, vasopressin secretion, and increases in blood pressure elicited by Oct mimic the previously reported response triad to intracerebral cholinergic and angiotensinergic stimulation. The pressor response to Oct, however, was smaller than the rises in blood pressure (20–30 mmHg) reported after doses of carbachol or ANG II that elicited drinking responses comparable to those observed in our experiments (15, 30). In the previous studies with intracerebroventricular somatostatin injections, the pressor response was stronger (4) than or similar (35) to our findings after Oct. The stronger pressor response was also associated with larger vasopressin secretion than the vasopressin release elicited by Oct. The rise in blood pressure is attributed exclusively to vasopressin after somatostatinergic stimulation, for vasopressin antagonists block this response (4, 35). In contrast, two mechanisms, vasopressin and sympathetic activation, are implicated in the hypertensive effect of intracerebroventricular angiotensin and cholinomimetics (15, 18). Possible differences in sympathetic activation may explain a less-pronounced pressor response after Oct than after central angiotensinergic or cholinergic stimulation.

Experiments with microinjections, lesions, demonstration of expression of immediate early genes, and recording unit activity identified two circumventricular organs, the subfornical organ (SFO) and the organum vasculosum laminae terminalis, as the major structures mediating the responses to carbachol and angiotensin (reviewed in Refs. 6, 12, 19, and 29). Neurons in the SFO project to the median preoptic nucleus, organum vasculosum laminae terminalis, magnocellular nuclei, and subependymal layer of the walls of the third ventricle (24). Hypothalamic sites involved in the mediation of drinking reside in areas adjacent to the lamina terminalis, such as the medial preoptic nucleus and periventricular preoptic nuclei, whereas stimulation of the magnocellular neurons in the paraventricular nucleus and supraoptic nuclei is the ultimate mechanism of vasopressin release (reviewed in Refs. 19 and 26). The efferent projections from the circumventricular organs are, in part, angiotensinergic, and there are angiotensin receptors throughout the rostral periventricular tissues that are also likely to be involved in the mediation of the responses elicited by intracerebroventricularly injected ANG II (39). Similarly, the SFO is sensitive to cholinergic stimulation (40), but cholinergic receptors in the anterior hypothalamus might also contribute to the effects of centrally injected carbachol (reviewed in Ref. 12). The systemically or intracerebroventricularly administered muscarinic antagonist Atr consistently blocks each component of the response triad to intracerebroventricular carbachol (11, 17, 22, 30). That atropine inhibits each element of the responses to Oct indicates that intact functioning of muscarinic cholinergic transmission is required for drinking, vasopressin release, and increases in blood pressure after intracerebroventricular Oct.

When the precursor ANG I or the enzyme renin is intracerebroventricularly injected, the dipogenic ANG II is produced by the brain, perhaps in the circumventricular organs (33). Inhibition of the intracerebral angiotensin-converting enzyme by means of intracerebroventricular administration of Cap blocks this process and renders the intracerebroventricularly injected ANG I and renin ineffective (7, 10, 48, 49). Hence, our finding that intracerebroventricular Cap suppresses the Oct-induced responses suggests that the intracerebral formation of ANG II is necessary for these effects. Cap is, however, not quite specific for the angiotensin-converting enzyme. For example, Cap may interfere with the metabolism of kinins (9) and substance P (50), and these peptides may also modulate drinking and/or vasopressin secretion and blood pressure (8, 32, 36). Pretreatment with Sar, an antagonist on the AT1 and AT2 angiotensin receptors, provided another piece of evidence for the significance of angiotensinergic mechanisms in the mediation of the Oct-elicited drinking. Predominantly AT1 receptors are found in the rostral periventricular tissue and the SFO (46). The role of AT1 receptors is well documented in the angiotensinergic drinking, vasopressin secretion, and rises in blood pressure (3, 27, 45). The AT1 receptors are also involved in the dipogenic effects of Oct, for the AT1 receptor antagonist Los suppressed this response. Although each angiotensin blocker used in our experiments inhibited Oct-induced drinking, there were some variations in the magnitude of the inhibition: Sar was less effective than Cap or Los. We used doses of these compounds that were previously reported to inhibit angiotensinergic drinking (21, 30), but it could not be excluded that there were some differences in the potency and/or diffusion among the various angiotensin blockers. In addition, unlike Los, Sar also displays...
partial ANG II agonist activity, which makes it a less effective antagonist than Los (reviewed in Ref. 13).

In conclusion, intact cholinergic and angiotensinergic transmission is required for the Oct-induced drinking, vasopressin release, and rises in blood pressure, despite the fact that stimulation of each of these mechanisms in itself can elicit all these responses. Another peculiar feature of the present findings is that it seems unlikely that Oct directly stimulates releases of ACh or ANG II, for somatostatin is an inhibitory neurotransmitter eliciting hyperpolarization via enhanced K+ and decreased Ca2+ conductances in neurons (reviewed in Ref. 38). Our hypothesis is that the baseline activity of cholinergic and angiotensinergic mechanisms or the responsiveness to cholinergic and angiotensinergic stimulation is tonically inhibited under normal conditions (e.g., normal blood volume, osmotic pressure, and blood pressure). Somatostatinergic stimulation may act by suppressing this tonic inhibition. As a result, the baseline cholinergic and the angiotensinergic activities are released from inhibition, or the responsiveness of the receptor structures to these stimuli is enhanced. If either of these pathways is blocked, then the baseline activity of the remaining mechanism is below the threshold of the response, and therefore exogenous Oct is not effective. GABA is a likely candidate to inhibit the angiotensinergic and cholinergic mechanisms, and Oct may act by suppressing the GABAergic inhibition. GABA, in fact, inhibits the dipsogenic activity of intracerebroventricular ANG II and carbachol and also inhibits the pressor and vasopressin responses to ANG II (43). Considering that the drinking response to Oct is very rapid, Oct may act in the circumventricular organs. That somatostatin can inhibit GABAergic transmission has been demonstrated in the striatum (28) and the hippocampus (37). The cells expressing sst5 receptors in the basal forebrain are assumed to correspond to GABAergic neurons (39). In addition to a possible inhibition of GABAergic neurons, somatostatin may also interact with GABA_A receptors and modulate GABAergic transmission postsynaptically (44).

**Perspectives**

Further experiments may determine the validity of the hypothesis proposed above. Regardless of the mechanism, the present results indicate that somatostatinergic transmission is capable of controlling angiotensinergic and cholinergic mechanisms involved in the regulation of blood volume, osmolarity, and water balance. Speculation regarding the physiological significance of this finding might be premature, but it is interesting to note that the vasopressin secretion in hypovolemia is reduced after depletion of hypothalamic somatostatin (5).

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