EXPERIMENTAL STUDY

Evidence of angiotensin II involvement in prolactin secretion in response to hemorrhage in adrenodemedullated and guanethidine-treated rats

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Abstract

Objective: The present experiments were designed to investigate the influence of the renin–angiotensin system (RAS) on prolactin secretion in response to hemorrhage (1.2 ml/100 g body weight (bw)/2 min).

Methods and Results: Male Wistar rats (250–300 g) were divided into the following experimental groups. (i) Sham-operated animals submitted to intravenous administration of [Sar¹, Thr⁸]-angiotensin II (sarthran), an angiotensin II antagonist (750 ng/100 g bw as a bolus plus an infusion of 25 ng/100 g bw/min over 30 min), which did not alter the prolactin secretion in response to hemorrhage. (ii) Animals submitted to adrenodemedullation which by itself increased the prolactin secretion in response to hemorrhage by 274% ($P < 0.01$). However, sarthran infusion into adrenodemedullated rats completely blocked this increased prolactin secretion in response to hemorrhage ($P < 0.01$). (iii) Intact animals submitted to blockade of sympathetic noradrenergic pathways by pretreatment with guanethidine (10 mg/100 g bw), which also increased the prolactin secretion in response to hemorrhage by 55% ($P < 0.01$). This increased prolactin secretion in response to hemorrhage observed in guanethidine-treated rats was completely blocked by sarthran preinfusion ($P < 0.01$). (iv) Adrenodemedullated animals pretreated with guanethidine, which abolished the prolactin secretion induced by hemorrhage.

Conclusions: Our data suggest a role for circulating catecholamines in the prolactin secretion response to stress. In addition, the experiments reported here demonstrate that RAS has a stimulatory effect on prolactin secretion in circumstances in which sympathetic activity or adrenomedullary secretion is suppressed. These are the first data demonstrating that a physiological prolactin secretion response to stress depends on the RAS.

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Introduction

Several studies suggest that the renin–angiotensin system (RAS) may modulate endocrine functions, including prolactin release, and participate in the regulation of different physiological processes besides those related to blood pressure and volume. Angiotensin II and prolactin are important stress hormones that are significantly increased in both acutely and chronically stressed animals (1–11). Although angiotensin II may activate the sympathoadrenal medulla and hypothalamic–pituitary–adrenal system, its participation in the control of prolactin secretion during stress has been generally neglected. Angiotensin II receptors have been found in adenohypophysis lactotrophs, thyrotrophs, and corticotrophs (12–14).

These receptors are functional because direct application of angiotensin II to pituitary cells *in vitro* results in a stimulation of prolactin (12–15). In addition, it has been shown that angiotensin II participates in the regulation of anterior pituitary hormone secretion by acting either directly on the anterior pituitary or indirectly on the hypothalamus. In the anterior pituitary, angiotensin II directly increases the release of prolactin (12, 15–17). Indirect effects occur through the hypothalamus and medial preoptic area, where angiotensin II increases dopamine release, leading to a decrease in prolactin release (15, 17–21). In addition, a previous study has shown that the angiotensin II receptor AT_{1A} is predominantly expressed in the rat forebrain and that, in contrast, the angiotensin II receptor AT_{1B} subtype predominates in the anterior

pituitary (13). Therefore, neuroendocrine effects of angiotensin II might occur not only at different levels but also through two different receptor subtypes. In adult male rats, about one third of all anterior pituitary cells express AT_{1B} receptor mRNA. A major part (78%) of AT_{1B}-expressing anterior pituitary cells is immunoreactive for prolactin (21). Although the possibility that angiotensin II functions as a hormone influencing prolactin secretion in certain physiological conditions has been proposed (10, 12, 13, 16, 17, 21, 22) experimental data have not been present. Recently, it has been found that *in vivo* stimulation of prolactin release by peripherally injected angiotensin II increases with age, and first responses were observed at 20 days of age in both sexes in rats (12). What makes these observations physiologically meaningful are the data indicating that under certain conditions, notably during hemorrhage, angiotensin in plasma reaches levels that are likely to activate prolactin release (11, 12, 17, 20, 23, 24).

The present experiments were designed to investigate the influence of the renin–angiotensin and sympatho-adrenal system on hemorrhage-induced prolactin secretion. [Sar¹,Thr⁸]-Angiotensin II (sarthran), an angiotensin competitive antagonist (25, 26), was employed to block the effects of angiotensin II. Guanethidine, an adrenergic neuron blocker, and adrenalectomy were employed as tools to delineate the relative roles of sympathetic innervation and circulating catecholamines in prolactin regulation by the RAS. Since guanethidine is thought not to cross the blood–brain barrier and to have no effect on the cholinergic innervation of the adrenals, it was used to block the noradrenergic brain-peripheral links (27–29).

Materials and methods

Animals

Male Wistar rats (250–320 g) had free access to Purina rat chow and tap water and were housed under controlled temperature with 14 h of light (0500–1900 h) per day. At the age of 11 weeks, the rats were placed in individual cages and handled frequently. One week later, they were anesthetized with ether, and a silastic catheter was inserted through the jugular vein into the right atrium for blood sampling by the technique of Harms and Ojeda (30). This catheter was filled with polyvinylpyrrolidone (PVP) solution and rinsed every 2 days with 1 ml saline containing 25 µIU heparin (Liquemine, Roche, Rio de Janeiro, RJ, Brazil). All animals were allowed to recover for one week before being used in an experiment.

Adrenal medullectomy

After insertion of the jugular catheter, the adrenal glands were sequentially exposed via a dorsal approach.

Each gland was gently retracted with a pair of curved, flat forceps. A nick was then made in one of the poles of the gland with iris scissors and the medulla was extruded by gentle compression of the adrenal body with the flat forceps. Next, to ensure a more complete ablation of medullary tissue the tips of very fine forceps were introduced into the nick and slowly rotated several times inside the gland. Upon completion of this procedure the glands were returned to their normal position and the wound was sutured with cotton thread. In sham-operated rats, the adrenals were handled but not incised. All animals were allowed to recover for a week before being used in an experiment. At the end of the experiments the success of the procedure was checked by examination of the glands.

Experimental design

On the day of the experiment the rats (adrenalectomized or sham-operated) had their venous catheter connected to a peristaltic pump one hour prior to hemorrhage. After 30 min, guanethidine (Sigma, St Louis, MO, USA) was given intraperitoneally (i.p.) at a dose of 10 mg/100 g body weight (bw). The same volume of saline solution was administered to the rats not treated with guanethidine. [Sar¹,Thr⁸]-Angiotensin II (Sarthran, Sigma) was then immediately infused over 30 min (750 ng/100 g bw as a bolus plus a continuous infusion of 25 ng/100 g bw/min). Controls were treated with the same volume of saline (0.2 ml as a bolus plus an infusion of 0.007 ml/100 g bw/min). At time zero, sarthran (or saline) infusion was stopped and animals were bled rapidly (1.2 ml/100 g bw/2 min of hemorrhage). Blood samples (0.2 ml) were collected at –30 min (immediately before guanethidine treatment) and at 0, 5, 10, 15 and 30 min after the beginning of bleeding. The volume (0.2 ml) was replaced with saline solution after each sampling.

Four experimental groups were used: (i) sham-operated (controls), (ii) adrenalectomized (ADM), (iii) sham-operated guanethidine-treated (GUA), and (iv) adrenalectomized-guanethidine-treated rats (ADM-GUA). Each group was divided into two subgroups ($n = 7–8$ animals) intravenously infused with sarthran or saline. Two other groups of animals (saline-treated and sarthran-treated) were similarly manipulated in the absence of hemorrhage.

Processing of samples

Plasma prolactin was measured in duplicate by radioimmunoassay using materials supplied by the NIDDK (Bethesda, MD, USA). The samples were run in the same assay with a sensitivity of 2 ng/ml plasma and an intra-assay coefficient of variation of 8%.

Figure 1 Effect of intravenous administration of sarthran (750 ng/100 g bw as a bolus plus an infusion of 25 ng/100 g bw over 30 min) or saline (NaCl 0.15 mol/l) on the hyperprolactinemia induced by hemorrhage (rapid bleeding of 1.2 ml/100 g bw (Hem)) in (A) sham-operated (control), (B) adrenomedullated (ADM), (C) guanethidine-treated (GUA), and (D) adrenomedullated-guanethidine-treated (ADM-GUA) rats. Data are means $\pm$ S.E.M. of 7–8 observations. * $P < 0.01$ vs prehemorrhagic values; + $P < 0.05$ vs prehemorrhagic values; $\phi P < 0.01$ vs saline group; # $P < 0.01$ vs hemorrhage-sarthran group.

Statistical analysis

Differences between groups (area under the curve) were checked by ANOVA followed by the Newman–Keuls test. Values for samples taken before and after the beginning of hemorrhage were compared with basal values by repeated measures ANOVA followed by the Newman–Keuls test.

Results

Effect of sarthran administration on basal and hemorrhage-induced prolactin secretion

As illustrated in Fig. 1A, sarthran administration did not induce any change in basal plasma prolactin levels. However, following bleeding there was an immediate increase in plasma prolactin levels in sham-operated rats. The prolactin release induced by hemorrhage was observed throughout the experimental period when compared with basal values ($P < 0.01$). The increase in plasma prolactin following

hemorrhage was not affected by infusion of the angiotensin II antagonist (sarthran, Fig. 1A). The effect of hemorrhage on prolactin secretion was already evident after 5 min ($P < 0.05$), reaching a peak at 15 min and persisting throughout the experimental period. Figure 2 shows the 30-min integrated area under the incremental prolactin curve. There was no significant difference in the prolactin secretion response to hemorrhage between intact rats treated with sarthran and intact rats treated with saline (Fig. 2).

Prolactin secretion in response to hemorrhage in adrenomedullated rats

In ADM rats, there was a rapid and higher prolactin secretion in response to hemorrhage (Fig. 1B) when compared with intact animals that was observed throughout the experimental period ($P < 0.01$). The area under the prolactin curve showed that adrenomedullation increased the prolactin response to hemorrhage by 247% (Fig. 2, $P < 0.01$). Sarthran infusion into ADM rats completely blocked ($P < 0.01$)

the increased prolactin response induced by hemorrhage to the level observed in intact animals. The inhibitory effect of sarthran on the prolactin secretion in response to hemorrhage in ADM rats was already evident during the first 10 min after bleeding (Fig. 1B).

Prolactin secretion in response to hemorrhage in guanethidine-treated rats

In guanethidine-treated rats, hemorrhage induced a rapid and higher prolactin secretion in response to hemorrhage (Fig. 1C) than in control saline-treated rats (Fig. 1A). Guanethidine treatment increased the prolactin response to hemorrhage by 55% (Fig. 2, $P < 0.01$). This increased plasma prolactin in guanethidine-treated rats in response to hemorrhage was observed throughout the experimental period. However, this increased prolactin secretion in response to hypovolemia was much lower in guanethidine-treated rats than in ADM rats considering the area under the prolactin curve (Fig. 2, $P < 0.01$). The prolactin secretion in response to hemorrhage of guanethidine-treated rats was already seen at 5 min (Fig. 1C, $P < 0.05$). Sarthran infusion into guanethidine-treated rats also completely blocked (Fig. 2, $P < 0.01$) the increased prolactin secretion considering the area under prolactin curve.

Guanethidine pretreatment of ADM rats abolished the prolactin secretion induced by hemorrhage in both saline- and sarthran-infused rats (Fig. 1D, Fig. 2, $P < 0.01$).

Figure 2 Integrated area under the prolactin curve (shown in Fig. 1) in sham-operated (control), adrenalectomized (ADM), guanethidine-treated (GUA) and adrenalectomized-guanethidine-treated (ADM-GUA) rats. Data are means $\pm$ S.E.M. of individual areas calculated by the trapezoidal rule.

* $P < 0.05$ vs saline-treatment; ** $P < 0.01$ vs saline-treatment; + $P < 0.05$ vs control group; ++ $P < 0.01$ vs control group.

Discussion

The experiments reported here show that blockade of the sympathoadrenal system completely eliminates the prolactin secretion in response to hemorrhage. In contrast, the hyperprolactinemic response to hemorrhage was potentiated in rats bearing partial blockade of the sympathoadrenal system, i.e. adrenalectomy produced a 270% increase in prolactin response to hemorrhage compared with control, and guanethidine treatment alone induced a 50% higher hyperprolactinemic response to hemorrhage compared with control. These data suggest a role for circulating catecholamines in the prolactin secretion response to stress. Circulating catecholamines are able to modulate prolactin secretion by both central and peripheral actions – centrally by decreasing the activity of the tuberoinfundibular dopaminergic neurons, and peripherally by increasing renin release which results in an enhanced circulating angiotensin II. Consequently, adrenalectomy followed by inhibition of the presynaptic sympathetic system by guanethidine treatment would decrease prolactin secretion. This proposal is consistent with the observation that the prolactin response to hemorrhage was completely blocked in adrenalectomized-guanethidine-treated rats.

Central adrenoceptors are thought to be involved in stress-induced prolactin release (2) and the participation of central adrenergic mechanisms in prolactin secretion has been demonstrated by systemic (31) and intracerebroventricular administration (31–33) of adrenergic agents. Local intracerebral injection of adrenergic agents suggests that adrenoceptor activation in the preoptic–anterior hypothalamus (PO/AH) and mediobasal hypothalamus stimulate prolactin secretion (33–35). Fuxe and Hökfelt (36) have shown that activation of adrenoceptors by the α_2 -agonist, clonidine, decreases the activity of the tuberoinfundibular dopaminergic neurons, giving support to at least one mechanism by which increased circulating noradrenaline or adrenaline acting on the hypothalamus may contribute to the regulation of prolactin. In addition, the prolactin release induced by circulating catecholamines could also be attributed to an indirect action of angiotensin II on sympathetic nerve activity (37, 38) and/or to a stimulatory effect of this peptide on adrenalectomy secretion (39, 40). Many studies indicate that angiotensin II stimulates both basal and hemorrhage-induced catecholamine secretion. Angiotensin II has a primary role in modulating sympathetic tone and effects through either central or peripheral mechanisms. Centrally, it acts by increasing sympathetic nerve activity (37, 38), and peripherally it facilitates noradrenergic transmission by potentiating neurotransmitter release (37, 41), inhibiting noradrenaline reuptake and stimulating the release of catecholamines from the adrenal medulla (42, 43). The RAS has been implicated in the increased

secretion of adrenal medullary catecholamines which occurs in response to a variety of stimuli, such as in response to hemorrhage, that can be blocked by an angiotensin II antagonist administered into the cerebral ventricles (44, 45) or by nephrectomy (44, 46). Therefore, this interaction between the sympathoadrenal system and RAS that occurs during hemorrhage would potentiate prolactin release.

Our results also indicate that, under circumstances in which adrenal medullary secretion is suppressed or when the peripheral sympathetic noradrenergic pathways are blocked, increased activity of the remaining branch of the sympathoadrenal system may compensate and even potentiate the prolactin secretion in response to stress. The increased adrenal medulla activity may compensate for the absence of the noradrenergic brain–peripheral links blocked by guanethidine treatment. On the other hand, an increased sympathetic noradrenergic drive to periphery may compensate for the absence of adrenal medullary secretion. This proposal is also consistent with the observation that the hyperprolactinemic response to hemorrhage obtained in adrenalectomized animals was completely blocked in adrenalectomized–guanethidine-treated rats.

Our results are also in agreement with experiments describing an increased hormonal response to hemorrhage in adrenalectomized or sympathectomized rats (3, 4). Previous experiments showed potentiated responses to hemorrhage of the vasoactive hormones arginine vasopressin, renin, and noradrenaline in adrenalectomized rats (3, 4). In addition, it has been shown that the renin response to hemorrhage is potentiated by 6-hydroxydopamine-induced lesions in the dorsal noradrenergic bundle (10, 47). It is well known that the sympathetic nerve might stimulate the juxtaglomerular cells in the kidney to release renin which, in turn, elevates the level of angiotensin II in plasma (48, 49). Circulating angiotensin II has been described to stimulate prolactin secretion (12) and its potency in stimulating prolactin release from pituitary cells *in vitro* is one of the highest among potential prolactin-releasing factors (1). Therefore, during hemorrhage the increased circulating angiotensin II acting on pituitary lactotrophs and circulating catecholamines acting on the PO/AH may facilitate prolactin secretion.

The activation of the renin–angiotensin system (RAS) is regulated by the sympathetic nervous system and is mediated by adrenergic receptors (42, 50). During stress, excited sympathetic nerves potentiate the activation of the RAS mediated by β -adrenergic receptors (42, 50). Angiotensin II produced from the RAS subsequently facilitates the additional release of noradrenaline from sympathetic nerve endings (42) and of adrenaline from the adrenal medulla (51–53). This is also a positive feedback leading to a stronger excitation and secretion by the sympathetic–adrenal

medulla system and a greater release of angiotensin II. This interaction between the two systems in initiating prolactin secretion in response to hemorrhagic stress is in agreement with our data showing that the pretreatment of adrenalectomized or sympathectomized rats with sarthran blocked the increased prolactin response to hemorrhage.

Angiotensin II has been shown to possess a differential effect on prolactin, since its central administration inhibits and its peripheral administration stimulates prolactin secretion (12, 17, 19). Whether such opposite central and peripheral effects of angiotensin II on prolactin secretion are physiologically relevant is still unknown. In conclusion, neurochemical studies indicate that central angiotensin II seems to inhibit prolactin secretion by stimulating tuberoinfundibular dopaminergic neurons activity and circulating angiotensin II stimulates prolactin secretion through AT₁ receptors at the pituitary level.

Finally, our data suggest a role for circulating catecholamines in the prolactin secretion response to stress. In addition, the experiments reported here demonstrate that RAS has a stimulatory effect on prolactin secretion under circumstances in which sympathetic activity or adrenalectomy secretion is suppressed. These are the first data demonstrating that a physiological prolactin secretion response to stress depends on the RAS.

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