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Vasopressor mechanisms in acute aortic coarctation hypertension

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Abstract

Angiotensin II (ANG II) and vasopressin (AVP) act together with the mechanical effect of aortic constriction in the onset of acute aortic coarctation hypertension. Blockade of ANG II and AVP V_1 receptors demonstrated that ANG II acts on the prompt (5 min) rise in pressure whereas AVP is responsible for the maintenance (30-45 min) of the arterial pressure elevation during aortic coarctation. Hormone assays carried out on blood collected from conscious rats submitted to aortic constriction supported a role for ANG II in the early stage and a combined role for both ANG II and AVP in the maintenance of proximal hypertension. As expected, a role for catecholamines was ruled out in this model of hypertension, presumably due to the inhibitory effect of the sinoaortic baroreceptors. The lack of afferent feedback from the kidneys for AVP release from the central nervous system in rats with previous renal denervation allowed ANG II to play the major role in the onset of the hypertensive response. Median eminence-lesioned rats exhibited a prompt increase in proximal pressure followed by a progressive decline to lower hypertensive levels, revealing a significant role for the integrity of the neuroaxis in the maintenance of the aortic coarctation hypertension through the release of AVP. In conclusion, the important issue raised by this model of hypertension is the likelihood of a link between some vascular territory - probably renal - below the coarctation triggering the release of AVP, with this vasoconstrictor hormone participating with Ang II and the mechanical effect of aortic constriction in the acute aortic coarctation hypertension.

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Mechanical *vs* renal factor

For a long time two schools of thought have attributed different mechanisms to chronic aortic coarctation hypertension. Whereas one school suggested that the mechanical effect of aortic constriction was the main factor promoting high blood pressure (1-3), others (4-6) argued that a renal factor was involved in the arterial pressure elevation. However, it was only in 1968 (7) that studies on young dogs with hypertension induced by chronic aortic coarctation hypertension provided a clear-cut demonstration that both factors, i.e., mechanical and renal factors, were operative in this model for hypertension. Later, these observations were confirmed in adult dogs submitted to aortic constriction, indicating a major role for the renal mechanisms in the development of hypertension, associated with a role played by aortic constriction (8).

The experimental model of aortic coarctation hypertension has been extensively studied under both acute and chronic conditions. Since the sixties the rat has become one of the most important species employed for studies of several hypertensive models including coarctation of the aorta (9). Chronic experiments have been carried out on rats (10,11) and especially on dogs (12,13). Acute experiments lasting minutes or a few hours have been performed mainly on anesthetized dogs (14).

We developed in our laboratory a technique for long-term implantation of a pneumatic cuff around large arterial vessels (aorta and carotid artery) of rats which permits the study of cardiovascular responses to procedures such as aortic constriction (15). Using this technique in conscious intact and bilaterally nephrectomized rats submitted to acute (45 min) partial aortic constriction above the renal arteries, we demonstrated that nephrectomized rats exhibited a blunted hypertensive response compared to intact rats, which was mainly due to the mechanical effect of aortic constriction imposed by the pneumatic cuff (16). Because in that study the aortic resistance was not measured and the degree of constriction of the aorta was monitored by keeping the distal pressure to the occlusion at a fixed level (50 mmHg), this observation was confirmed more recently (17) in conscious intact or bilaterally nephrectomized rats by measuring the change in aortic flow with a pulsed Doppler flowmeter, a technique that provides a reliable measurement of the change in aortic resistance. Nevertheless, removal of the kidneys eliminates hypertensive mechanisms other than the renin-angiotensin system (RAS), such as R_2 renal chemoreceptors which are activated by reduction of renal blood flow and by changes in the interstitial ionic environment (18-20). In addition, it has been reported that in anesthetized rats afferent information from the kidneys selectively alters the activity of vasopressin (AVP) neurosecretory cells of the hypothalamus (supraoptic cells) and may contribute to a reflex pathway through which the kidneys may alter the release of AVP (21,22).

The renin-angiotensin system and vasopressin

Based on previous studies from our laboratory (16) and others (23,24) showing that the RAS plays a pivotal role in the onset of the hypertensive response to aortic constriction and that activation of renal afferences might trigger the release of AVP (21,22), we designed a protocol in which angiotensin II (ANG II) receptors were blocked with saralasin and AVP V_1 vascular receptors were blocked with $d(CH_2)_5$Tyr(Me) AVP (Manning's compound) during aortic constriction (25). In that study, experiments carried out using this pharmacological approach demonstrated that conscious unrestrained rats treated with Manning's compound presented a prompt rise in carotid pressure similar to that of untreated (control) rats but, in contrast to this group, the pressure started to decline. Rats treated with saralasin presented a delay in the onset of hypertension right after coarctation, but attained values similar to those for control rats. It is noteworthy that rats treated with both antagonists showed a blunted carotid pressure elevation throughout the period of coarctation, resembling the change in pressure observed in nephrectomized rats, which was attributed almost exclusively to the mechanical factor of the constriction (16). For a more direct evaluation of the contributions of these humoral mechanisms we determined the changes of plasma renin activity (PRA), plasma AVP and plasma catecholamines (epinephrine and norepinephrine) after 15 and 45 min of aortic constriction (26). Plasma AVP concentration did not differ from that observed in control rats after 15 min of coarctation, but showed a five-fold increase after 45 min. On the other hand, PRA was already significant-

ly increased after 15 min of coarctation and remained elevated at 45 min when compared with control rats. Overall, the results indicated that, in addition to the mechanical effect of aortic constriction, ANG II acts during the prompt (5-15 min) rise in pressure, whereas AVP is responsible for the maintenance (30-45 min) of the arterial pressure elevation. Recently (27) it has been reported that elevated AVP may contribute to preoperative and postoperative hypertension in patients with chronic aortic coarctation.

Low renal perfusion pressure can trigger a sympathoexcitatory vasoconstrictor reflex (28-30). In our laboratory (31,32) we studied the role of the sympathetic drive during aortic constriction by measuring the hypertensive response in conscious animals chronically (5 weeks) sympathectomized with guanethidine or acutely (10 min) treated with prazosin. Chronically sympathectomized rats exhibited a similar hypertensive response to aortic constriction as the control (intact sympathetic nervous system). On the other hand, prazosin did not affect the hypertensive response of intact animals. Taken together, these findings indicate that sympathetic activity does not play a role during aortic constriction, presumably due to the countereffect of the arterial (sinoaortic) baroreceptors mentioned above. It should be pointed out that baroreceptor activation reduces the sympathetic nerve activity on the vessels and the heart and increases vagal activity, producing a remarkable reflex bradycardia (33-35). The literature has reported more direct evidence of sympathetic inhibition during constriction of the aorta in anesthetized cats (36). These authors demonstrated that occlusion of the descending aorta inhibits renal sympathetic activity almost completely (98%). Plasma norepinephrine concentration was consistently reduced, probably due to the countereffect of the sinoaortic baroreceptors. Nevertheless, in contrast to anesthetized dogs submitted to cross-clamping of the aorta (24,37), plasma epinephrine concentration of conscious rats submitted to partial aortic constriction did not differ from that observed in their control counterparts. Similar findings were obtained in conscious dogs submitted to 24 to 48 h of aortic constriction (12). These data provided further evidence for an effective vasopressor role for AVP in the maintenance of acute (45 min) aortic coarctation hypertension in conscious rats. In addition, the results confirmed that the RAS participates earlier (15 min) in the onset of coarctation hypertension, but ruled out a significant vasopressor role for catecholamines.

Electrolytic lesion of the median eminence of the hypothalamus is a well-known experimental model of chronic as well as acute lack of vasopressin (38). In conscious rats submitted to previous (48 h) median eminence lesion of the hypothalamus, we investigated (39) the time course of action and the relative roles played by AVP and ANG II in the onset of the hypertensive response by means of pharmacological blockade of the pressor effect of these peptides with Manning's compound and saralasin, respectively. Lesioned rats exhibited a prompt rise in pressure in response to acute aortic constriction followed by a progressive decline, in contrast to sham-lesioned rats which exhibited a prompt hypertensive response which leveled off during the experiment (45 min). Lesioned rats treated with saralasin presented a blunted hypertensive response throughout the period of coarctation, whereas the sham-lesioned rats submitted to the same treatment presented only a delay in the onset of hypertension. Moreover, blockade of the AVP V_1 vascular receptors did not affect the hypertensive response of the lesioned rats, but elicited a progressive decline of the arterial pressure response of sham-lesioned rats. Collectively, these data demonstrated that the integrity of the median eminence of the hypothalamus plays a pivotal role in the maintenance (30-45 min) of acute aortic co-

arctation hypertension, presumably involving the release of AVP from the neurohypophysis, whereas ANG II mainly accounts for the prompt (5-15 min) rise in pressure.

It has become increasingly evident that the renal nerves contribute to the control of renal function and to homeostasis under normal conditions and are important in the pathogenesis of experimental hypertension (40,41). It seems that the renal nerves are involved in the early stages of hypertension in the spontaneously hypertensive rat, whereas their importance in other forms of hypertension is controversial (42). There is evidence that afferent renal fibers carry mechanical and chemical information from the kidneys to specific brain nuclei which may influence the neurohumoral control of the kidney itself, or the circulation in general (43-45). It has been demonstrated that sensory information from the kidneys alters the release of AVP from the neurohypophysis, suggesting that afferent renal nerves are an important component of the neural circuitry controlling arterial pressure (46). Studies from our laboratory performed on conscious renal-denervated rats allowed us to investigate the contribution of sensory information originating in the kidneys to the release of AVP during an acute hypertensive response to partial aortic constriction (47). The hypertensive response observed in renal-denervated rats did not differ significantly from that observed in intact animals. Nevertheless, the previous intravenous administration of Manning's compound to renal-denervated rats did not affect the hypertensive response of these animals when compared to that of untreated renal-denervated subjects. Therefore, the lack of an effect of the V_1 vascular receptor antagonist on the renal-denervated rats precludes a role for AVP in this response, presumably due to the absence of sensory information from the kidneys to the central nervous system (CNS) to trigger the release of AVP. In contrast, when renal-denervated rats were treated with saralasin, the hypertensive response following aortic constriction was significantly blunted throughout (45 min) the experiment. This finding was consistent with the hypothesis that only the RAS was playing a role in the hypertensive response of renal-denervated rats to aortic constriction. In addition, this finding indicates that blockade of the RAS in renal-denervated rats causes the mechanical component of the constriction to be the principal factor in the rise of the arterial pressure, as observed in anephric (16) and intact animals treated with Manning's compound plus saralasin (25). Moreover, the data obtained with renal-denervated rats treated with saralasin suggest that when one vasopressor system is hampered, as is the case for AVP due to the lack of signaling from the kidneys to the CNS, other mechanisms, e.g., the RAS, take over the major role in increasing the arterial pressure associated with the mechanical component of coarctation (47,48). Although total renal denervation is not selective in eliminating renal sensory input to the CNS, affecting also efferent axons to the kidneys, data from our laboratory (47) have suggested that renal afferent feedback plays a role in the pathogenesis of aortic coarctation hypertension involving the release of AVP into the circulation.

It is well known that AVP release is controlled by osmotic and non-osmotic mechanisms. The stimuli for vasopressin release include an increase in plasma osmotic pressure, reduction in blood pressure and blood volume, nausea and pain (49). However, alternate pathways such as circulating ANG II (50-52) and renal afferences (25,46,47,53) have been suggested to stimulate AVP release besides the well-known osmotic and non-osmotic mechanisms. More recently, experiments performed on chronic sinoaortic-denervated (SAD) rats and chronic nucleus tractus solitarius (NTS)-lesioned rats (54) have supported the hypothesis that when afferent stimuli from cardiovascular (arterial and cardiac) receptors are hampered, other

mechanisms may take over the control of AVP release (39,48,55).

In conclusion, the different approaches used in our laboratory to investigate the physiopathogenesis of acute (45 min) aortic coarctation hypertension, i.e., pharmacological blockade of AVP and ANG II (25), renal denervation (47), electrolytic lesions of the median eminence of the hypothalamus (39), and plasma hormone (AVP, PRA and catecholamines) assays (26), support the hypothesis that some territory below the coarctation is able to trigger the release of AVP into the circulation under special conditions such as low renal perfusion pressure, leading AVP to play a role in the hypertensive response during aortic constriction.

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