The Interaction between vasopressin and modulators of the cardiovascular system

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Summary

Chapter 1

The introduction chapter is dealing with a survey of the cardiovascular functions of vasopressin (AVP). The neurohormone AVP is a nonapeptide released predominantly from the pituitary gland. The important cardiovascular modulating roles of AVP are largely mediated by the V₁-receptor and the V₂-receptor. The most prominent functions of the V₁-receptor are vasoconstriction and possibly also the induction hypertrophy of vascular and cardiac tissues. V₂-receptor activation results in an increased water reabsorption in the kidney. In several vascular beds it causes vasodilation. The V₂-receptor agonist desmopressin has a well-known clinical role of in the treatment of central diabetes insipidus. At present vasopressin itself is under investigation as an alternative for adrenalin as a pressor agent in the treatment of cardiovascular shock. The recent development of non-peptidergic selective AVP-antagonists enables a thorough investigation of the functions of the AVP-system. Furthermore several clinical applications of the AVP-antagonists are currently being evaluated. In the cardiovascular field the treatment of essential hypertension in the negroid and elderly subpopulations seems the most promising option. With respect to the treatment of congestive heart failure the increased aquaresis without disturbances of the electrolyte balance, mediated by V₂-receptor blockade, is the major subject of investigation.

Chapter 2

In the isolated rat mesenteric artery we designed a study to analyse the possible involvement of the V₁- and V₂-receptor in AVP-induced facilitation of the sympathetic nervous system. The direct vasoconstrictor effect of AVP was antagonized by the V₁-antagonist SR-49059 and not by the V₂-antagonist SR-121463. The V₂-agonist desmopressin did not show any direct vasoconstrictor effect; neither did it produce vasodilatation after precontraction induced by Noradrenaline (NA) 10 µM. Electrical field stimulation (EFS) was applied on the artery to mimic the effects of the sympathetic nervous system. The EFS-induced rise in vascular tone could be increased by a sub-pressor concentration of AVP. This facilitation could be antagonized by SR-49059, but
less by SR-121463. Again desmopressin did not influence the increase in vascular tone during EFS. The post-synaptic effect of AVP on the sympathetic nervous system was investigated by exposing the vessels to exogenous NA. Vasoconstriction induced by exogenous NA could be facilitated by a subpressor concentration of AVP and this selective postsynaptic effect could be antagonized by V₁-receptor blockade. These findings suggest a V₁-receptor dependent AVP-induced facilitation of the sympathetic nervous system. This facilitation is and at least partly post-synaptically mediated. Selective evaluation of pre-synaptic effects cannot be evaluated in this model, therefore it cannot be decided to which extent pre-synaptic V₁-receptors may be involved.

Chapter 3

Several studies have shown that AVP potentiates the sympathetic nervous transmission in isolated vessels. The present study investigates such a potentiation in the pithed rat model. Spinal cord stimulation was applied to selectively stimulate the sympathetic activity on the vascular tone. The electrical stimulation was performed in the presence or absence of a subpressor dose of AVP (1 pmol/kg/min). In the pithed rat model endogenously generated angiotensin II facilitates neurally mediated increments in vascular resistance. Without the administration of the AT₁-antagonist irbesartan, the facilitating effect of AVP was not visible. However, after the administration of the AT₁-antagonist irbesartan the facilitating effect of AVP became apparent. The stimulation-induced rise in diastolic blood pressure was enhanced in the presence of the subpressor dose of AVP. The V₁ antagonist SR-49059 completely inhibited this AVP-induced facilitation, whereas both the V₂ antagonist SR-121463 and the V₂-agonist desmopressin did not. In addition, the effect of AVP on post-synaptic α-adrenoceptor mediated responses was studied using exogenously administered NA. The dose response curve of NA was not influenced by AVP. Therefore we concluded that the stimulating effect of AVP on sympathetic neurotransmission is completely dependent on the stimulation of presynaptically located V₁ receptors. The facilitating effect of angiotensin II on the sympathetic nervous system in the pithed rat model masks the facilitating effect of AVP in this preparation.
Chapter 4

Our previous studies have shown that AVP can enhance sympathetic nervous transmission by means of V₁-receptor activation. It was the objective of the third study on this subject to investigate whether in humans a facilitatory role of AVP on sympathetic nerve activity can be demonstrated at the peripheral level. Eight healthy subjects (32 ± 2.3 years) participated in this study. Forearm blood flow (FABF) was measured using the venous occlusion plethysmography model. Each session was performed in the presence of a continuous infusion of AVP in sub-pressor dosage of 0.008 ng/kg/min or NaCl 0.9%. In this study all drugs were infused into the brachial artery. The first protocol consisted of two pressure-response curves produced by progressive lower body negative pressure (LBNP) (-10, -20 and -30 mmHg), to investigate the combined pre- and post-synaptic action of the sympathetic nervous system. After infusion of AVP (0.008 ng/kg/min), the FABF remained unaffected. LBNP caused a pressure dependent decrease in FABF, which AVP significantly enhanced. This procedure was followed by a second protocol in which once more the possible post-synaptic effects of AVP were evaluated by means of intra-arterially infused NA. NA caused a dose-dependent vasoconstriction, unaffected by AVP. Taken together we conclude that in healthy volunteers AVP can facilitate vasoconstriction mediated by the peripheral sympathetic nervous system at the pre-synaptic level.

Chapter 5

In a standard organ bath set-up for isometric recording we tested whether the relaxing properties of vasodilator drugs in vitro may depend on the characteristics of the contractile state of the vessel investigated. The rat isolated thoracic aortae were exposed to different types of pre-contraction. The following vasoconstrictor agents were used: phenylephrine (PhE, a selective α₁-adrenoceptor agonist), St-587 (a partial α₁-adrenoceptor stimulant), U-46619 (U-46 a thromboxane A₂ agonist), and potassium ions (causing receptor independent depolarisation of the membrane), respectively. After pre-contraction various differential vasodilator drugs were investigated: methacholine (MCh, endothelium-dependent), sodium nitroprusside (SNP, NO-
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14 5 5 donor), forskolin (FSK, adenylyl cyclase stimulant) and nifedipine, (a selective L-type calcium-antagonist). The experiments of this study clearly demonstrate that the characteristics of the applied pre-contraction strongly, but differentially influence both the potency and efficacy of various vasodilator drugs in vitro. Accordingly, in vitro characterisation of vasodilator drugs should be performed under a carefully standardized protocol of pre-contraction.

Chapter 6

Concerning the interaction of vasopressin with the endothelium, we identified and quantified the stimulatory and inhibitory activities of endothelial factors on AVP induced contractions. In a standard organ bath set-up for isometric force recording, rabbit isolated renal artery rings were exposed to cumulative concentrations of AVP. Experiments were performed in the presence or absence of functional endothelium, or in the presence of N-Nitro-L-Arginine 10 μM (L-NNA, NO-synthase inhibitor). AVP induced a maximal contractile response comparable in vessels with and without endothelium. The pre-incubation with L-NNA resulted in an enhanced response to AVP. The augmentation of the AVP induced contractile response by NOS inhibition, which was not seen in preparations after the removal of the endothelium, suggests an endothelium dependent factor which is co-released with NO. The unknown nature of this endothelium dependent contractile factor was not influenced by indomethacin 100 μM (cyclooxygenase inhibitor), meclofenamic acid 20 μM (cyclooxygenase and lipoxygenase inhibitor) or bosentan 100 μM (endothelin antagonist). Charybdotoxin 0.1 μM (inhibitor of Ca^{2+} -activated K^{+} channels) specifically increased the contractile force in preparations with and without endothelium, or in the presence of L-NNA. SR-49059 (vasopressin 1 receptor (V_{1}) antagonist) antagonised the effects of AVP, whereas SR-121463 (V_{2} antagonist) was ineffective. In contrast to the results obtained with AVP, desmopressin (V_{2} agonist) showed no effect. In conclusion, the completely V_{1} dependent AVP-induced contraction is partly inhibited by the stimulated release of NO. This was only demonstrable in endothelium intact vessels in the presence of L-NNA and not after removal of the endothelium. This strongly suggests the involvement of an unknown endothelium V_{1} receptor dependent contractile factor that is not influenced by inhibition of the prostaglandin, lipoxygenase or endothelin pathways, or by blockade of the V_{2} receptor.
Chapter 7

In the rat aorta we investigated the possible involvement of the mitogen-activated protein kinase (MAPK) family of extracellular signal-regulated kinase (ERK) 1 and 2 (MAPK\textsuperscript{erk1/2}) in the AVP-mediated vasoconstriction. Rat isolated thoracic aortae were mounted in an organ bath set-up for isometric tension recording, and were exposed to cumulative concentrations of AVP (1 nM-300 nM). Thereafter the MAPK\textsuperscript{erk1/2} phosphorylation in the rat aorta was quantified using Western-blot analysis. AVP (1 nM-300 nM) induced an increase of contractile force. This increase could be inhibited dose-dependently by both the selective MAPK\textsuperscript{erk1/2} kinase (MKK\textsuperscript{mek1/2}) inhibitors under investigation, PD 98059 (10 and 100 µM) and U 0126 (10 and 100 µM). Western blot analysis revealed an increase of the MAPK\textsuperscript{erk1/2} phosphorylation induced by AVP. Again this phosphorylation process could be dose dependently inhibited by both PD 98059 (100 µM) and U 0126 (10 and 100 µM). Therefore we conclude that the contractile force induced by AVP may be partly regulated by the MAPK\textsuperscript{erk1/2} pathway.