Pressor Mechanisms of Vasopressin in DOC-salt Hypertensive Rats
—Interaction with Autonomic Nervous System—

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Recent studies suggest that vasopressin may contribute importantly to deoxycorticosterone (DOC) and salt-induced hypertension in rats. However, there are unanswered questions regarding to the mechanisms of augmented vascular responses to vasopressin. In normal animals vasopressin regulates vascular resistance by directly acting on the blood vessels as well as by modulating the effects of the autonomic nervous system. There is ample evidence that DOC-salt treatment is associated with augmented vascular reactivity to any constrictor stimulus. However, there is virtually no study which examined the possibility that augmented vascular responses to vasopressin in DOC-salt hypertension is resulted from the interaction between vasopressin and the autonomic nervous system. This possibility was investigated in the present study through two different experiments.

Male Sprague-Dawley rats were uninephrectomised. Subsequently, subcutaneous injection of DOC-pivalate (weekly dose 50 mg/kg) and 1% saline as drinking water were given in a test group, and sham treatments were given in a control group. Paired feeding was performed to minimized the difference of body weight between the groups.

After 3 weeks of the DOC-salt or sham treatment, the first experiment was performed to investigate the relative role of vasopressin and neurogenic factors in control of vascular resistance of the autoperfused hindquarters in DOC-salt and control rats. DOC-salt rats had elevated hindquarters vascular resistance (p < 0.05). Vasopressin and neurogenic tone contributed significantly (p < 0.05) to increased resistance. Vaso-

dilator responses to a specific vasopressin antagonist, 1-deaminopenicillamine-4-valine-8-D-arginine vasopressin (dPVDAVP), and lumbotomy in separate DOC-salt groups accounted for 40 ± 5% (x ± SE) and 43 ± 6%, respectively, of the total vasodilator capacity. In contrast, corresponding responses to dPVDAVP and lumbotomy in control rats were smaller (p < 0.01), different (p < 0.05), and accounted for 8 ± 3% and 20 ± 3%, respectively, of the total vasodilator capacity. Effects of dPVDAVP compared in innervated hindquarters of DOC-salt and control rats were greater in DOC-salt rats (p < 0.001); in the denervated hindquarters, effects of dPVDAVP were similar in DOC-salt and control rats (39 ± 4% and 31 ± 5%, respectively, of residual vasodilator capacity). Therefore, effects of vasopressin on vascular resistance were augmented in DOC-salt hypertensive rats; furthermore, this augmented effect was dependent on an intact innervation.

Vasopressin could have influenced neurogenic vascular tone in DOC-salt rats by acting on peripheral or central mechanisms. For example, a facilitatory action of vasopressin at sympathetic neuroeffector terminals could explain an exaggerated vasodilator response to antagonist, dPVDAVP, in DOC-salt-treated rats. This has been considered by other investigators but our own work has failed to detect an effect of low or high plasma vasopressin levels on vascular responses to adrenergic stimuli in rat hindquarters. Furthermore, a local interaction of vasopressin and sympathetic neuroeffector mechanisms might be expected to yield a selective facilitation of the vasoconstrictor effects of vasopressin.

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in innervated hindquarters. This was not detected in the present study. Therefore, an interaction of vasopressin and peripheral neurogenic mechanisms in DOC-salt rats seems unlikely. The possibility that vasopressin affected central neurogenic mechanisms also must be considered. However, previous work demonstrated that neurogenic mechanisms activated by vasopressin counteracted pressor responses to the peptide. Therefore, antagonism of a neurogenically mediated vasodilator influence of vasopressin could have offset antagonism of the direct constrictor influence of vasopressin. In support of this interpretation, subsequent α-adrenergic blockade with phentolamine produced additional marked hindquarters' vasodilatation. Implicit in the interpretation that vasopressin suppressed a neurogenic constrictor influence in control rats is the speculation that this action may have been impaired in DOC-salt treated rats. Thus, DOC-salt treated rats may have been unable to respond to central inhibitory effects of vasopressin, which in control rats mediated reflex suppression of peripheral sympathetic activity.

A possible explanation for this difference could be DOC-salt induced baroreflex dysfunction. In the second experiment, to elucidate this possibility, baroreflexes and pressor responses to intravenous infusion of vasopressin and phenylephrine were evaluated in conscious, less severely hypertensive DOC-salt rats (5 days of treatment), hypertensive DOC-salt rats (15 days of treatment) and corresponding control rats. Pressor responses were reexamined after ganglion blockade. Phenylephrine has been used as a pressor intervention to test baroreflex function in previous studies of conscious animals and humans. In the present study, increased pressor responses to phenylephrine after ganglion blockade provided an indication of baroreflex restraint on responses. By comparing effects of ganglion blockade on vasopressin responses with effects on phenylephrine responses, it was possible to evaluate whether baroreflexes contributed importantly to the pressor effects of vasopressin. In control rats, pressor responses to vasopressin were augmented more than to phenylephrine after ganglion blockade; thus vasopressin uniquely appeared to augment baroreflex buffering. In hypertensive DOC-salt rats, baroreflexes were impaired (p < 0.05); pressor responsiveness to vasopressin was augmented compared to control rats (p < 0.05). After ganglion blockage, augmentation of pressor responses was similar for vasopressin and phenylephrine. In less severely hypertensive rats, baroreflexes were normal; pressor responses to vasopressin and phenylephrine were like those in control rats before and after ganglion blockade. These results suggest that vasopressin augments baroreflex buffering which imposes a restraint on pressor effects of vasopressin that is not evident with phenylephrine. In hypertensive DOC-salt rats, a defect in baroreflex buffering during infusion of vasopressin may contribute to augmented pressor effects of vasopressin. In accord with their observation, Cowley et al. reported that pressor action of vasopressin augmented by 60–100 times after baroreceptor denervation in conscious dogs.

The results of our two studies are consistent with the view that pressor action of vasopressin in DOC-salt hypertensive rats are augmented because of the defect of autonomic function, especially baroreceptor dysfunction. Based on these studies the pathogenesis of hypertension in DOC-salt treated rats could be explained as follows. Increases in vascular reactivity as a results of DOC-salt treatment may occur early. Bereczek and co-workers reported increases in vascular reactivity to vasopressin and adrenergic stimuli 4 days after the treatment was started. The preservation of baroreflex function at this stage as suggested by the present study may effectively buffer the tendency of arterial pressure to increase as a result of increased vascular reactivity. However, impaired baroreflex function after 15 to 17 days of treatment may facilitate full expression of increased vascular reactivity. Furthermore, significant elevations in plasma vasopressin could add pressor influence because a normal baroreflex component of its action could be absent.

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