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Changes in the Vascular Expression of Na^+, K^+ ATPase and Contractions Generated by Phenylephrine in Ouabain Induced Hypertension

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ABSTRACT

In rats treated with ouabain (25 mg day 71, s.c., 5 weeks) or vehicle, the development of hypertension, contraction produced by phenylephrine and Na^+, K^+-ATPase functional activity and protein expression were assessed in the Aorta (AO), Tail (TA) and Superior Mesenteric (SMA) arteries. Ouabain therapy raised systolic blood pressure (127+1 vs. 160+2 mmHg, n=24, 35; P50.001), although in AO (102.8+3.9 vs. 67.1+10.1% of KCl response, n=12, 9) and SMA (82.5+7.5 vs. 52.2+5.8%, n=12, 9), the maximal response to phenylephrine was decreased (P50.01). In segments from rats treated with ouabain, the phenylephrine response was more strongly enhanced by endothelium ablation. Consequently, for control and ouabain treated rats, the Differences in the Area Under the concentration-response Curves (dAUC) in endothelium-denuded and intact segments were, respectively: AO, 56.6+9.6 vs. 198.3+18.3 (n=9, 7); SMA, 85.5+15.4 vs. 165.4+24.8 (n=6, 6); TA, 13.0+6.1 as opposed to 39.5+10.4% of the reference AUC (n=6, 6); P50.05. Segments from both groups showed similar relaxation to KCl (1 ± 10 mM). The effects of 0.1 mM ouabain on KCl relaxation were observed in rats administered with ouabain in the following ways: AO (dAUC: 64.8+4.6 vs. 84.0+5.1%, n=11, 14; P50.05), SMA (dAUC: 39.1+3.9 vs. 43.3+7.8%, n=6, 7; P40.05) and TA (dAUC: 62.1+5.5 vs. 41.4+8.2%, n=12, 13; P50.05). Rats treated with ouabain had increased protein expression of both the a1 and a2 isoforms of Na^+, K^+-ATPase in AO, unchanged in SMA and decreased in TA. Six these findings imply that long term ouabain administration causes both hypertension and possible changes in the vascular system in the affected area.

Keywords: Ouabain; Hypertension; Na^+, K^+-ATPase; A-isoforms; Phenylephrine

INTRODUCTION

The biochemical manifestation of the electrogenic Na^+ pump, Na^+, K^+-ATPase, is accountable for preserving the potential of the cell membrane and has the ability to control the tone and contractility of the vasculature. It has been demonstrated that humans and other mammals have an endogenous circulating Na^+, K^+-ATPase inhibitor. According to Mathews et al., this inhibitor was identified as ouabain or an isomer of ouabain. It has been reported to be present in the adrenal cortex, brain and plasma. Higher levels of endogenous ouabain in the blood have been shown in many animal models of hypertension, humans with essential hypertension and congestive heart failure [1-5].

According to Blutein, Huang and Leenen, ouabain is linked to the onset and maintenance of hypertension through both central and peripheral pathways and it appears to have a role in blood pressure regulation. Peripheral mechanisms: In isolated vascular preparations, ouabain at nanomolar concentrations increases agonist induced contractions. Ouabain causes contraction at micromolar concentrations. This contraction can be caused by the myogenic component of ouabain, which acts directly on the vascular smooth muscle or by the neurogenic component, which releases norepinephrine from the perivascular adrenergic nerve endings. Furthermore, this glycoside might cause the production of relaxing factors that are dependent on the endothelium, such as Nitric Oxide (NO) or Endothelium Derived Hyperpolarizing Factor (EDHF), which counteracts the vasoconstriction and the ouabain induced sensitization of vascular smooth muscle. Furthermore, it has been proposed that unidentified endothelial factors may activate the sodium pump and offer some protection against ouabain's suppression of Na^+, K^+-ATPase. Several reports have shown that the chronic administration According to a number of studies, chronic ouabain administration to Wistar rats causes hypertension. However, other studies have not reported a hypertensive effect following ouabain treatment. Increased sympathetic activity and a decrease in arterial baroreceptor reactivity have also been linked to ouabain induced hypertension. It is currently unknown; nevertheless, if this changed vascular reactivity contributes to ouabain induced hypertension [6-10].

Therefore, the current study's objective was to ascertain whether long term ouabain therapy caused hypertension in Wistar rats and whether this hypertension was linked to modifications in vascular reactivity and in the Na^+, K^+-ATPase's functional activity and protein expression. We assessed the effects of long term ouabain treatment on the following:

- Vascular responses to phenylephrine and acetylcholine.

- Endothelial modulation of vascular reactivity.
- Relaxation to K^+ in the presence and absence of ouabain, as a measure of the Na^+, K^+-ATPase's functional activity.
- Protein expression of the subunit's isoforms.

Because regional divergences in vascular reactivity and endothelial modulation of a-adreno-ceptor agonists as well as in the Na^+, K^+-ATPase activity have been reported, this study was performed in three deferent vessel preparations: Thoracic aorta, superior mesenteric and tail artery. This method was used to prevent bias that could arise from modeling a single vascular bed as the basis for characterization.

LITERATURE REVIEW

The current study's findings demonstrate that time dependent hypertension develops as a result of long term ouabain administration. The phenylephrine induced contractions are related with a decrease in hypertension, most likely as a result of an increase in the endothelium regulation of this contraction. Additionally, changes in the ouabain sensitive Na^+, K^+-ATPase activity and a-isoform protein production are linked to this hypertension. There are regional variations in the vasopressor responses to phenylephrine as well as in the protein expression and ouabain sensitive Na^+, K^+-ATPase activity following ouabain administration. Several mammals' plasma contains the endogenous digitalis component ouabain; endogenous levels have been shown to be elevated in some pathological circumstances, such as hypertension. The induction of hypertension by ouabain has been attributed to various mechanisms, including central mechanisms and peripheral mechanisms, increased vascular reactivity to pressor agents and increased myocardial contraction and vascular smooth muscle tone. Our findings support the theory that ouabain may play a role in the development of hypertension by demonstrating that peripheral administration of ouabain for five weeks resulted in hypertension in Wistar rats, which was noticeable as early as the first week of treatment [11].

Numerous investigations demonstrate that long term ouabain therapy causes hypertensive effect following ouabain administration in rats and sheep, but other studies found no hypertensive effect in rats. These conflicting findings may be the consequence of variations in the rat strains, age at treatment initiation, dosage, duration or mode of ouabain administration. We investigated the contraction brought on by phenylephrine in rings from the thoracic aorta, superior mesenteric and tail arteries in order to ascertain the potential involvement of the vascular component in the ouabain induced hypertension. The effect of ouabain on the phenylephrine reaction in the three vessels under investigation's rings. Thus, there were reductions in both E_{max} and sensitivity in the aorta, just E_{max} in the mesenteric artery and neither parameter was different in the tail artery. However, in the three vessels under investigation, the contractile response to elevated potassium did not change following ouabain administration; this shows that the medication does not affect the smooth muscle cells' capacity to contract. The aortic ring results are consistent with the findings of Cargnelli et al., even in the absence of a systolic blood pressure rise. But according to a different recent study, long term therapy with Although a decrease in negative endothelial modulation has also been shown in Spontaneously Hypertensive Rats (SHR), a-adrenergic responses are increased in SHR. However, recent research by Rossoni et al., indicates that nanomolar quantities of ouabain may cause the release of a relaxing substance produced from endothelium that appears to open potassium channels. According to other research, ouabain either promotes the production of inducible NO synthase in vascular smooth muscle cells or induces the release of nitric oxide in cultured endothelial cells. The vasoconstrictor response to phenylephrine was enhanced in endothelium denuded segments from the aorta and superior mesenteric artery and this increase was more pronounced in segments from rats treated with ouabain. These findings are in opposition to those of Cargnelli et al., who discovered that in the aorta of rats treated with ouabain, the ablation of the endothelium decreased the contractile response to phenylephrine [12].

DISCUSSION

According to our findings, there appears to be a rise in the negative endothelial modulation of phenylephrine induced reactions following ouabain therapy. This mechanism may account for our observations of hyporesponsiveness to phenylephrine induced contraction. However, more research is required to determine which endothelial factor(s) may be elevated following ouabain administration. When endothelium was denuded, the phenylephrine response increased more in the tail artery segments of rats treated with ouabain, but it was still much less than in the aorta and mesenteric artery. It is possible that the response to a-adrenergic stimulation is less affected by ouabain if it causes the release of an endothelial vasodilator factor and the endothelium controls vasoconstrictor responses less in the tail artery than in other vascular beds Ouabain therapy. It is noteworthy that the extent to which acetylcholine may induce relaxation appears to be correlated with the size of the rise in phenylephrine-induced contraction following endothelium ablation [13-15]. This could potentially impact the endothelium's capacity to release vasoactive substances. But as was already mentioned, ouabain therapy had no effect on the endothelium dependent relaxation to acetylcholine. Therefore, it appears that there are differences in the mechanisms underlying the release of endothelial factors, even while ouabain stimulates the release of endothelial vasodilator factors in response to phenylephrine but not in response to acetylcholine. Since ouabain's effects are typically explained by its capacity to inhibit Na^+, K^+-ATPase, Webb and Bohr's standard technique was used to measure this pump's activity. K^+ was added, causing concentration dependent relaxations that nearly completely restored the phenylephrine-induced tone in the three arteries under study in a K^+ free solution. Endothelial factors have been suggested to be able to boost the Na pump and shield it from ouabain induced inhibition to some extent [16-20]. Our findings confirm that the Na pump in the three arteries under investigation is positively endothelially modulated. Segments from rats treated with ouabain showed a somewhat stronger endothelial modulation, which is consistent with the higher endothelial modulation observed in these arteries. In intact segments from ouabain treated and control rats, the inhibitory effect of a high concentration of ouabain on the relaxation caused by K^+ was different. Animals treated with ouabain showed a greater reduction in the K^+ induced relaxation in their thoracic aorta compared to animals in the control group. Within The effect of ouabain was similar in the superior mesenteric arteries but smaller in the tail artery in rats treated with ouabain compared to controls. These findings imply that in the rats with ouabain induced hypertension, there was an increase in ouabain sensitive Na^+, K^+-ATPase activity in the aorta, a decrease in tail artery and no change in mesenteric rings. Although enhanced activity has also been reported in SHR, arteries from SHR and renal hypertensive dogs have been shown to have decreased Na^+ pump activity. Redondo et al., discovered that there were no differences in the quantity or activity of Na^+ pump sites in the aorta cultures of smooth muscle from SHR and Wistar Kyoto mice, despite the regulation of its behavior appears to be noticeably different. The catalytic component is represented by the subunit of the Na^+ pump, which is made up of two main subunits, a and b [21-24].

There have also been reports of a third subunit called g, however it is unclear what function it may have. There are four distinct isoforms of Na^+, K^+-ATPase, a1, a2, a3 and a4. They have varying capacities for digitalics and are expressed differently depending on the species and tissue. It has been shown that only the a1, a2 and a3 isoforms are expressed in rat vascular tissues. According to our findings, only the a1 expression was present in the rat aorta, superior mesenteric and tail arteries and it was possible to find a2 isoforms. Cross reaction with the a2 isoform could be caused by minute quantities of the a3 isoform in vascular smooth muscle and a very poor sensitivity of the employed antibody, which would account for the absence of a3 expression detection. Similar to the alterations seen in ouabain sensitive Na^+, K^+-ATPase activity, chronic ouabain treatment altered the protein expression of the a-subunit isoforms of Na^+,K^+-ATPase, depending on the vessel investigated. As a result, both a1 and a2 expressions were elevated in the thoracic aorta of rats treated with ouabain; no change in either isoform was observed in the superior mesenteric arteries; however, the expression of a1 and a2 proteins was decreased in the tail artery of the same rats treated with ouabain. In agreement, a recent study indicates that

long term care with Tissue-specific differential regulation of the Na^+ pump a subunit mRNA is induced by either ouabain or digoxin. Furthermore, previous studies had already revealed changes in the expression of an isoform in a number of diseases, including hypertension. In a culture of aortic smooth muscle cells, ouabain administration for one to four days has been shown to upregulate the a1 and a2-subunit isoforms of Na^+, K^+-ATPase. Mechanical strain, another technique that raises intracellular Na^+, was also found to upregulate the a1 and a2 subunits of the sodium pump in cultured aortic smooth muscle cells. These increases stimulate the transcription of these subunits in smooth muscle cell cultures. The precise location of the vascular wall's Na^+ pump alterations is unknown. But since smooth muscle cells are more numerous than endothelium, it appears more likely that the muscular layer is where the changed protein expression could occur. However, it is challenging to explain the disparate outcomes of ouabain treatment in the three veins under investigation. According to several researchers, there is an inverse relationship between the catecholamine content and the activity of the Na^+ pump in the thoracic aorta, mesenteric and tail arteries [25-27]. Differences in adrenergic innervation and anatomical variations across blood arteries may be connected to the various alterations in Na pump activity and model of hypertension. Differences in the contraction generated by phenylephrine in the arteries of rats with ouabain induced hypertension may be explained by the localized changes in the ouabain-sensitive Na^+, K^+-ATPase activity and protein expression. Along with the rise in endothelial modulation, the increase in ouabain sensitive Na^+, K^+-ATPase activity that would promote hyperpolarization would also cause a decrease in maximal responsiveness and sensitivity to phenylephrine found in rats' aortas after receiving ouabain treatment. Reduced activity of ouabain sensitive Na^+, K^+-ATPase in the tail artery raised intracellular concentrations of Na^+ and Ca^{2+}, which in turn increased contractile activity. Nevertheless, the increased endothelial function seen in this vessel offset the contractile activity, causing the rats treated with ouabain and control to contract similarly to phenylephrine. Only the maximal response was decreased by ouabain therapy in mesenteric arteries, where endothelial modulation is increased but alterations in Na^+ pump function are not seen. To sum up, the findings presented here suggest that long term use of ouabain causes hypertension.

CONCLUSION

This result lends credence to the theory that the endogenous Na^+ pump inhibitor, known as ouabain or an isomer, may have anything to do with the origin and/or or the preservation of hypertension. While some studies have proposed the involvement of central mechanisms in this hypertension model, there are also vascular mechanisms that exhibit regional changes in the vasopressor responses to phenylephrine, the ouabain sensitive Na^+ pump activity and protein expression.

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