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Ouabain treatment changes the role of endothelial factors in rat resistance arteries

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ABSTRACT

This study investigates the participation of the endothelial factors in the α-adrenoceptor contractile responses in mesenteric resistance arteries from 15 days ouabain-treated (25 μg/kg/day) and untreated rats. Ouabain treatment increased blood pressure and heart rate without changing the contractile response to phenylephrine (3 nM–30 μM). Endothelium removal or N^G-nitro-L-arginine methyl ester (L-NAME, 100 μM), increased the responses to phenylephrine. The endothelial modulation was similar in both rat groups, but the L-NAME effects were bigger in arteries from ouabain-treated rats. However, the endothelial NOS expression and the relaxation to acetylcholine (0.1 nM–10 μM) remained unaltered after ouabain treatment. The coincubation with L-NAME and indomethacin (100 μM) leftward shifted the concentration–response curves to phenylephrine in arteries from untreated rats similarly to the displacement after incubation only with L-NAME. However, in mesenteric arteries from treated rats, the co-incubation with indomethacin and L-NAME did not alter the response to phenylephrine. The addition of the inhibitor of calcium activated potassium channels tetraethylammonium (2 mM) further leftward shifted the phenylephrine curves only in arteries from untreated rats. Cyclooxygenase-2 (COX-2) expression was greater in vessels from ouabain-treated rats. In conclusion, the chronic ouabain treatment for 15 days modified the participation of endothelial factors in response to phenylephrine in mesenteric resistance arteries, by increasing the release of NO and prostanoids and impairment the endothelium-derived hyperpolarizing factor (EDHF) release. This was accompanied by an increased COX-2 expression. Although this balance avoids changes in the phenylephrine concentration–response curves, these vascular changes might contribute to maintain the ouabain-induced hypertension.

1. Introduction

Several reports have demonstrated the presence of nanomolar concentrations of a digitalis compound in the plasma of hypertensive humans and rats (Hamlyn et al., 1982; Blaustein, 1993; Hamlyn et al., 1996). This endogenous compound was characterized as ouabain or an isomer of ouabain (Mathews et al., 1991) and its chronic administration to rats increases arterial blood pressure (Yuan et al., 1993; Manunta et al., 1994; Huang et al., 1994; Kimura, et al., 2000; Manunta et al., 2001; Rossoni et al., 2002a,b). Central and peripheral mechanisms seem to be involved in the hypertension induced by chronic ouabain administration. The central mechanism is associated with the increase of sympathetic tone and impairment of the baroreflex (Huang and Leenen, 1999). Among the peripheral mechanisms, the inhibition of the sodium pump is included promoting the increase of intracellular sodium concentration that reduces or reverses the activity of the Na^+/Ca^{2+} exchanger (Marín and Redondo, 1999).

When acutely administered ouabain increases vascular reactivity (Vassallo et al., 1997; Padilha et al., 2004) and increases or reduces the Na^+K^+ATPase activity, depending on its concentration (Rossoni et al., 1999; Padilha et al., 2004). However, after chronic ouabain administration a reduction of vascular reactivity to phenylephrine together with an increased activity and expression of the Na^+K^+ATPase occurs (Rossoni et al., 2002a). In addition, increased endothelial nitric oxide synthase (eNOS) expression and endothelial NO modulation of vasoconstrictor responses was also observed (Rossoni et al., 2002b). However, the vascular effects of the chronic ouabain treatment seem to be dependent on the studied vessel. Thus, in conductance arteries, chronic ouabain treatment increases NO production and impairs prostanoid actions reducing the vasoconstriction produced by α-adrenergic agents (Rossoni et al., 2002b; Xavier et al., 2004b). Meanwhile, in mesenteric

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