THE ROLE OF CALCIUM-PROTEIN KINASE C SYSTEMS IN THE REGULATION OF ACETYLCHOLINE RELEASE IN THE CENTRAL NERVOUS SYSTEM OF SPONTANEOUSLY HYPERTENSIVE RATS

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OBJECTIVE: Previous studies have demonstrated that the central cholinergic system may actively participate in blood pressure control. It was shown that the decrease in the acetylcholine (ACh) content of the hypothalamus, striatum and brain stem caused by hemicholinium-3 (an inhibitor of ACh synthesis) was associated with a reduction in systemic blood pressure in spontaneously hypertensive rats (SHR). The finding also suggests a possible involvement of the central cholinergic system in the pathogenesis of hypertension. However, the precise mechanisms of regulating the cholinergic nerve activity in hypertension are still uncertain. On the other hand, it is well known that an increase in the intracellular Ca²⁺ concentration is the signal which initiates the secretion of neurotransmitter release from nerve endings. In the present study we have examined the effects of the Ca²⁺ channel blocker and the protein kinase C inhibitor on the release of ACh in the central nervous system of SHR, and evaluated the role of Ca²⁺-protein kinase C systems in the regulation of central cholinergic nerve activity in hypertension.

DESIGN AND METHODS: Effects of the Ca²⁺ channel blocker, diltiazem, and the protein kinase C inhibitor, H-7, on the release of [³H]ACh were studied in the striatal slices of normotensive and hypertensive rats in vitro.

RESULTS: (1) Diltiazem inhibited the stimulation-evoked [³H]ACh release from striatal slices of Sprague-Dawley rats in a dose-dependent manner (1 Hz/S2/S1 ratio, control 0.89±0.019, n=6, diltiazem 3.3×10⁻⁶mol/L 0.77±0.005, n=6, P<0.05, diltiazem 1×10⁻⁵mol/L 0.75±0.011, n=6, P<0.05). (2) The protein kinase C inhibitor, H-7, also reduced the stimulation-evoked [³H]ACh release. (3) The stimulation-evoked [³H]ACh release was not different between SHR and age-matched Wistar-Kyoto (WKY) rats. (4) The inhibitory effect of diltiazem on the stimulation-evoked [³H]ACh release was significantly more pronounced in SHR than in WKY rats (S2/S1 ratio in the presence of 1×10⁻⁵mol/L of diltiazem, SHR 0.65±0.008, n=6, WKY 0.79±0.010, n=6, P<0.05). The protein kinase C inhibitor, H-7, reduced the stimulation-evoked [³H]ACh release to a greater extent in SHR than in WKY rats (S2/S1 ratio in the presence of 3.3×10⁻⁵mol/L of H-7, SHR 0.76±0.006, n=6, WKY 0.82±0.013, n=6, P<0.05).

CONCLUSION: These results show that diltiazem and H-7 significantly inhibited the stimulation-evoked ACh release in rat central nervous system, which might indicate that the Ca²⁺—protein kinase C systems could have a crucial role in the control of central ACh release. Furthermore, the pronounced inhibition of ACh release by the inhibitors in SHR suggests a highly Ca²⁺- and protein kinase C-dependent regulation of ACh release in the central nervous system of hypertension.

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