44524 - RESERPINE PREVENTS CVS DYSFUNCTION AFTER RAISED ICP IN RATS

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INTRODUCTION: Central sympathetic nervous system hyperactivity has been shown to play an important role in the development of cardiac complications associated with intracranial hypertension (1,2). However, norepinephrine (NE) release in the myocardium may play a greater role than catecholamines within the systemic circulation. This study examined the impact of depleting myocardial NE stores with reserpine on the cardiac consequences of acute intracranial hypertension and assessed the functional integrity of the cardiac sympathetic nerve terminals following the autonomic surge.

METHODS: All procedures and experiments were conducted in accordance with the guidelines of the Canadian Council of Animal Care and the Queen's University Animal Care Committee. Following pretreatment with reserpine (1.0 mg/kg/day x 3 days) or vehicle, halothane anesthetized rats underwent inflation of a subdural balloon catheter over the left frontoparietal cortex to induce acute intracranial hypertension. Hemodynamics, LV pressures and ECG changes were recorded. Plasma and myocardial catecholamines were determined. After 60 minutes, rats were given pargyline (10 mg/kg, i.v.) followed by tyramine (16 µg, i.v.) to determine the functional status of the cardiac sympathetic nerve endings.

RESULTS: In vehicle-pretreated rats (n=5), raised intracranial pressure (ICP) resulted in an increase in MAP ($146 \pm 24\%$ of baseline, $P < 0.01$), HR ($144 \pm 19\%$ of baseline, $P < 0.001$), LVP ($129 \pm 9\%$ of baseline, $P < 0.05$), LVEDP ($383 \pm 137\%$ of baseline, $P < 0.001$) and cardiac dysrhythmias. These changes occurred with an increase in circulating catecholamines (peak NE 356 ± 176 , $P < 0.05$ and epinephrine $1042 \pm 15\%$ of baseline, $P < 0.001$). The transient hyperdynamic phase was followed by a progressive deterioration in cardiac function. 60 minutes following raised ICP, tyramine infusion resulted in an elevation in MAP, HR, and LV pressure and its first derivative ($\pm dP/dt$). Cardiac dysrhythmias were displayed in all rats. These changes were found to occur with a substantial increase in plasma NE ($447 \pm 98\%$ of 60 minute level, $P < 0.01$). In reserpine-treated rats (n=5) (> 99% decrease in myocardial NE content), the increase in circulating catecholamines was attenuated, cardiac dysrhythmias following raised ICP were blocked, and cardiac function was maintained. In addition, the tyramine-induced hemodynamic and electrocardiographic changes were abolished.

DISCUSSION: The results of this study provide evidence for a key pathogenic role of excessive endogenous NE in the deterioration of cardiac function following acute intracranial hypertension.

Secondly, the cardiovascular response to tyramine suggests that the efferent nerve terminals remain functional following the raised ICP hemodynamic response. The precise myocardial changes underlying the deterioration in cardiac function require further study.

REFERENCES: 1. Circ 1992 85: 790-804. 2. J Mol Cell Cardiol 1985 17: 291-306.