INFLUENCE OF SKF 91488, HISTAMINE N-METHYLTRANSFERASE INHIBITOR, ON THE CENTRAL CARDIOVASCULAR REGULATION DURING CONTROLLED, STEPWISE HEMORRHAGIC HYPOTENSION IN RATS

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The histaminergic system influences various activities of the central nervous system, including cardiovascular regulation. Histamine administered intracerebroventricularly (icv) in anesthetized rats produces the increase in mean arterial pressure (MAP) and heart rate (HR), however, in contrast to normotensive animals, histamine-induced rises in MAP and HR in critically hypotensive animals are significantly higher. Similarly to exogenous histamine, inhibition of the central histamine N-methyltransferase (HNMT) activity (the enzyme catabolizing histamine in the central nervous system) resulting in the increase in endogenous histamine concentration, also leads to the pressor effect in normotensive rats. The present study was designed to determine the role of endogenous central histamine in cardiovascular regulation in a rat model of blood volume-blood pressure controlled hemorrhagic hypotension. In normotensive animals, HNMT inhibitor SKF 91488 produced dose-dependent (20–100 µg icv) pressor effect accompanied by tachycardia, similarly as exogenous histamine (0.5–5 µg icv) did. The subpressor dose of SKF 91488 (10 µg) evoked the increase in blood volumes necessary to induce hypotension of 40 and 20 mmHg and the action was accompanied by the rise in histamine concentrations in the hypothalamus (5.18 ± 0.45 vs 4.23 ± 0.41 nmol/g; p < 0.05) and medulla oblongata (0.41 ± 0.05 vs 0.30 ± 0.06 nmol/g; p < 0.05), with no changes in the cortical histamine concentrations (0.84 ± 0.18 vs 0.75 ± 0.17 nmol/g), compared to the control icv saline-treated group. The effect of SKF 91488 was inhibited by H1 histamine receptor antagonist chlorpheniramine, whereas neither H2 receptor blocker ranitidine, nor H3 receptor antagonist thioperamide affected the action.

In conclusion, the study demonstrates that the histaminergic system influences the central cardiovascular regulation during pronounced hemorrhagic hypotension, probably as a result of the activation of compensatory mechanisms.

Key words: SKF 91488, histamine, cardiovascular regulation, hypotension, rat

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