摘出モルモット心房標本におけるセロトニン誘発性、5-HT_3受容体仲介性、ルテニウムレッドおよびカプサイシン感受性の陽性変時作用

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5-HT-Induced, 5-HT_3 Receptor-Mediated, Ruthenium Red- and Capsaicin-Sensitive Positive Chronotropic Effects in the Isolated Guinea-Pig Atrium

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ABSTRACT : We investigated the mechanisms of 5-HT-induced tachycardia, which we reported previously to be triggered by 5-HT_3 receptor stimulation, in the isolated guinea-pig atrium in comparison with that induced by isoproterenol and histamine. We found that 5-HT-induced tachycardia was completely inhibited by ruthenium red. 5-HT-induced tachycardia was reduced in the capsaicin pre-treated atrium as well as in the presence of capsaicin. The effects of isoproterenol and histamine were not affected by ruthenium red or capsaicin treatment. Furthermore, 5-HT-induced tachycardia was found to be potentiated by thiorphan, an inhibitor of peptide degeneration. CGRP (1-37), a full agonist of CGRP1-like receptors, was found to act selectively as a potent stimulator of chronotropic action. CGRP (8-37), an antagonist of CGRP1-type receptors, inhibited 5-HT-induced tachycardia as well as effects induced by CGRP (1-37). The observation that tetrodotoxin failed to affect 5-HT-induced tachycardia excluded the involvement of 5-hydroxytryptaminergic interneurons. Thus, we confirmed that the mechanism of 5-HT-induced tachycardia is distinct from that induced by isoproterenol and histamine. In conclusion, the activation of 5-HT_3 receptors on the sensory nerve terminals brought about ruthenium red-sensitive Ca^{2+} influx and resulted in the release of CGRP from capsaicin-sensitive stores, and then CGRP stimulated $CGRP_1$-like receptors to produce 5-HT-induced tachycardia.

抄録　摘出モルモット心房標本におけるセロトニン誘発性、5-HT_3受容体仲介性の陽性変時作用について薬理学的性質について検討した。このセロトニン誘発性の薬理作用がルテニウムレッドおよびカプサイシン感受性であること、およびペプチダーゼ阻害薬であるチオルファンによって増強されることから何らかの活性ペプチドの遊離を介する作用であることが示唆された。さらに、心房の知覚神経終末に存在する生理活性ペプチドである

CGRPがセロトニンと同様の陽性変時作用を引き起こすこと、CGRPの特異的拮抗薬であるCGRP(8-37)によってセロトニン誘発性陽性変時作用が阻害されることが見出された。以上の結果より、知覚神経終末の5-HT_3受容体の活性化は、ルテニウムレッドおよびカプサイシン感受性のカルシウム流入を介してCGRPの遊離を引き起こし、遊離されたCGRPは$CGRP_1$様受容体を刺激し、その結果セロトニン誘発性陽性変時作用が発現することが示された。

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