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Protective Effect of Serotonin (5-HT_2) Receptor Antagonists in Ischemic Rat Hearts

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Summary: Serotonin (5-HT) may play a role in exacerbating thrombosis and coronary spasm during myocardial ischemia, but its role in mediating myocardial damage directly is not clear. We determined the effect of the 5-HT_2 receptor antagonists cinanserin (0.1–10 μM), ketanserin (0.3–10 μM), and LY 53857 (1–10 μM) on time to contracture, recovery of contractile function, and lactate dehydrogenase (LDH) release after 25-min global ischemia and 30-min reperfusion in isolated rat heart. All 5-HT_2 antagonists significantly increased time to contracture in a concentration-dependent manner (EC_{25} = 1.6, 5.5, and 6.1 μM for cinanserin, ketanserin, and LY 53857, respectively). These compounds also significantly reduced LDH release and improved recovery of contractile function during reperfusion. 5-HT $\geq$30 μM significantly reduced time to contracture, indicating a proischemic effect. The proischemic effect of 5-HT was abolished by ketanserin and cinanserin. Inhibition of 5-HT synthesis by parachlorophenylalanine resulted in significant cardioprotection, further indicating the involvement of 5-HT in the pathogenesis of ischemia in this model. Although cinanserin and ketanserin had α_1-adrenoceptor blocking effects, LY 53857 was devoid of this activity at concentrations exhibiting cardioprotection. Therefore, 5-HT may exacerbate ischemic injury in rat heart, and this exacerbation appears to be mediated specifically by 5-HT_2 receptors. **Key Words:** Myocardial ischemia—Serotonin—Cinanserin—Ketanserin—LY 53857—Contractile function—Reperfusion.

Serotonin (5-HT) may play a pathologic role in a number of low blood flow conditions (1). Thrombotic events, precipitating a myocardial ischemic episode, may be aggravated by 5-HT release and the ischemic injury may be further compounded by the coronary constrictor effect of this agent (1,2). 5-HT_2 receptor blockade has been shown to inhibit coronary thrombosis and thrombosis-induced cyclic flow variations in experimental models (2,3). Although the role of 5-HT in aggravating coronary thrombosis seems well established, its direct effect on the ischemic myocardium is still in question, and although 5-HT receptors exist in the myocardium, their role in mediating the direct effects of ischemia on the myocardium itself is still unknown. In a study designed to address this question, Simpson and colleagues (4) showed that the selective 5-HT_2 receptor antagonist LY 53857 had little effect on infarct size in a model of left circumflex coronary artery (LCX) occlusion and reperfusion. The dose of LY 53857 used effectively blocked 5-HT_2 receptors, at least in platelets. Simpson and colleagues concluded that 5-HT did not mediate a direct myocardial ischemic action (at least through 5-HT_2 receptors), because the model used involved a mechanical occlusion of the LCX and significant thrombosis would not be expected (4). Few other studies have been performed to address this question, and we believed that further investigation was warranted. Thus, we determined the effect of several 5-HT_2 receptor antagonists in our model of myocardial ischemia and reperfusion in isolated rat heart. We also determined the effect of parachlorophenylalanine (PCPA; depletes 5-HT) and 5-HT treatment on the severity of myocardial ischemia in this model.

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