Background: In chronic heart failure, the left ventricle becomes sensitive to serotonin (5-HT) through appearance of functional \( G_s \)-coupled \( 5HT_4 \) receptors. Phosphodiesterase (PDE) 3 and 4 account for >90% of the total cardiac cAMP PDE activity with PDE4 as the primary PDE degrading cAMP activated by \( \beta \)-adrenoceptors.

Objective: Explore PDE involvement in the regulation of ventricular \( 5HT_4 \)-mediated positive inotropic effect (PIE) in failing rat and human heart.

Methods: Postinfarction CHF was induced in male Wistar rats by coronary artery ligation. Contractility was measured in left ventricular papillary muscles. Phospholamban phosphorylation was measured by western blot analysis and cAMP by RIA.

Results: In rat papillary muscles \( 5HT_4 \) stimulation exerted a PIE accompanied by increased total cAMP and phospholamban phosphorylation. The PIE was increased by a non-selective PDE inhibitor (IBMX, 10\( \mu \)M) and suppressed by the protein kinase A (PKA) inhibitor H89 (20\( \mu \)M) indicating involvement of the cAMP-PKA pathway. The PDE4 inhibitor rolipram (10\( \mu \)M) did not significantly increase the \( 5HT_4 \) response. The PDE3 inhibitor cilostamide (1\( \mu \)M) increased the PIE of serotonin without changing the potency. Combined PDE3/4 inhibition further enhanced the PIE and increased the sensitivity to serotonin. Stimulation of the \( 5HT_4 \) receptors significantly increased the cAMP levels in the presence of PDE3 and PDE4 inhibitors which correlates accordingly with PIE that was exerted by serotonin in the presence respective PDE inhibitor. In failing human ventricle PDE3 but not PDE4 inhibition significantly increased the PIE.

Conclusions: The inotropic response to \( 5HT_4 \) receptor stimulation is mediated through cAMP and PKA. PDE3 is the main PDE regulating this response and the involvement of PDE4 is demasked by inhibition of PDE3.