Hong Z, Cabrera JA, Dutt M, Aloul B, E. Weir E K. Serotonin And Endothelin Increase L-type Calcium Channel Current In Pulmonary Artery Smooth Muscle Cells, Unrelated To Changes In Membrane Potential. Circulation 2008; 118(18) II: S755.

Serotonin (5-HT) and endothelin (ET-1) are both involved in the pathophysiology of idiopathic pulmonary arterial hypertension. In addition to the release of calcium (Ca++) from the internal stores in the smooth muscle cells (SMCs), these agents stimulate entry of Ca++ through the L-type Ca++ channel. In isolated rat pulmonary resistance artery (PA) rings, 5-HT (10 M) caused a contraction of 110 ± 14 % of the contraction elicited by 60 mM KCl. After inhibition of KV and KCa channels by 4-AP and TEA, 5-HT caused a stronger contraction of 176 ± 4% ($p<0.01$). Consequently, we studied the relationship of 5-HT- stimulated contraction to membrane potential (Em) and L-type calcium current in rat resistance PASMCs. Contrary to expectation, 5-HT (1, 10, 100 M) had no effect on IK or Em (n=5 for each). However, 5-HT (10 M) increased L-type calcium current between Em -20 and +30 mV (n=7). This effect was inhibited by a PKC blocker (BIS-1, 3 M), which also caused a marked reduction of 5-HT-stimulated contraction of PA rings (>70% decrease at 10 M 5-HT). In contrast to 5-HT, ET-1 (10 nM) reduced IK and caused membrane depolarization (from -41 ± 5 to -31 ± 3 mV, n=4). In addition to this effect, ET-1, like 5-HT, increased L-type calcium current over the same range of Em (n=7). This increase was inhibited by nifedipine (3 M). These experiments indicate that both 5-HT and ET-1 increase calcium influx through the L-type calcium channel in a manner independent of Em. ET-1 has an additional effect of causing membrane depolarization, which also

increases calcium entry through L-type channels by altering voltage gating of the channel.

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