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Catecholamine induced endothelial dysfunctions and underlying mechanisms in the setting of Takotsubo syndrome

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Background-Takotsubo syndrome (TTS) is characterized by a transient regional wall motion abnormality with clinical manifestations similar to that of an acute coronary syndrome. Heart failure and life-threatening arrhythmias are common complications of TTS. Catecholamine excess is widely accepted as key player for the pathogenesis of TTS due to the fact that TTS occurs usually after exposure to an extreme stress. Although it is well established that adrenergic stimulation and ß-receptor signaling play important roles for the occurrence of TTS, both clinical and experimental data suggested an involvement of signaling mediated by non-ß-adrenoceptors in the pathogenesis of the disease. The ST-elevation without coronary stenosis in TTS suggests a coronary spasm, which in turn suggests an endothelial dysfunction because endothelium plays important roles for controlling vascular tone. Indeed, endothelial dysfunctions were detected in some TTS-patients. However, studies on endothelial dysfunctions associated with occurrence of TTS remain spars. The mechanisms of endothelial dysfunctions caused by catecholamine excess in the setting of TTS are unknow so far.
Objectives-This study was designed to investigate endothelial dysfunctions in the setting of TTS, focusing on: (1) the alteration of ET-1 and NO production in cells challenged by high concentration of catecholamine, (2) the alteration of ion channel function in cells challenged by high concentration of catecholamine, (3) the relationship between alteration of ion channel currents and ET-1/NO production, (4) the involvement of adrenoceptor signaling, mainly non-ß-adrenoceptor signaling, in catecholamine induced changes of ion channel functions (5) possible mechanisms underlying the alteration of ET-1/NO generation in the setting of TTS.
Methods-Human cardiac microvascular endothelial cells (HCMECs) were treated with toxic concentration of epinephrine (Epi, 0.1 mM for 1h) to mimic the setting of TTS. Different adrenoceptor agonists and antagonists were used to differentiate receptor-specific effects. Patch clamp, PCR, ELISA techniques were employed for the study.
Results-In HCMECs, the small and intermediate conductance Ca^{2+}-activated K^+ channel current (I_{SK1-3} and I_{SK4}), the ATP-sensitive K^+ current (I_{KATP}), and the inward rectifier K^+ current (I_{K1}), but not the big conductance Ca^{2+}-activated K^+ current and T-type Ca^{2+} channel current, were detected. I_{SK1-3}, I_{SK4} and I_{KATP} but not I_{K1} could be activated by high concentration of epinephrine (Epi). Epi suppressed NO production, although it failed influence ET-1 production. Strikingly, the channel blockers apamin (I_{SK1-3} blocker) and TRAM-34 (I_{SK4} blocker) but not glibenclamide (I_{KATP} blocker) attenuated Epi induced reduction of NO production, indicating that I_{SK1-3} and I_{SK4} but I_{KATP} contributed NO-generation. Further studies revealed that both α1- and D1-recepotor signaling mediated the enhancement of I_{SK1-3}, whereas only α1-receptor signaling mediated the increase in I_{SK4}. ROS (reactive oxygen species) signaling participated also in the activation of SK1-3 and SK4 channels because a ROS blocker (NAC) abolished and H_2O_2 mimicked the effect of α1-and D1-agonist on the currents. Application of a blocker and an activator of PKC and PKA demonstrated that PKC is involved in the activation of SK channels by α1-receptor signaling, while PKA is required for the activation of SK1-3 by D1-receptor signaling. In addition, it was figured out that PKC but not PKA is a downstream factor of ROS since a PKC blocker prevented ROS effect on SK currents. Finally, activation of SK channels hyperpolarized membrane potential of HCMECs, but a depolarization induced by KCl failed to enhance, instead reduced NO production, which excluded the possibility that SK channel activation reduced NO production by hyperpolarizing cells.
Conclusion-The study demonstrated that the α1- and D1-receptor signaling plays important roles for endothelial dysfunction by affecting SK channels and NO generation. The ROS-PKC signaling mediated α1-adrenoceptor signaling, whereas ROS and PKA participated in D1-receptor signaling in the modulation SK channels. High concentration of catecholamine can cause endothelial dysfunction via activating α1-and D1-receptor signaling, causing an imbalance of ET-1/NO and coronary spasm in TTS.