Genistein and tyrphostin AG 556 block the action potential shortening in septic shock.

許準榕
Ching CE;Luk HN;Wang TM;Sheu JR;Ding PYA

Abstract

Background. We have previously shown that an increase in NO activity activated ATP-sensitive potassium channel (KATP) and shortened action potential duration (APD) in an endotoxic shock model. Because the increase in NO production and the decrease of APD appear to be downstream late events in endotoxic shock, we hypothesized that a common signaling pathway might mediate these effects. Methods. Using a guinea pig model of endotoxic shock, we investigated the effect of genistein and tyrphostin AG 556 on the cardiac action potential. Adult Hartley guinea pigs (300 to 450 gm) were randomized into 2 treatment parts. In the chronic treatment part, guinea pigs were randomized to receive daily subcutaneous injection of one of the five agents: saline, genistein, tyrphostin AG 556, daidzein, and vehicle for 10 days. In the acute treatment part, these agents were administered by intraperitoneal injection 1 hour before endotoxic shock. The animals were then anesthetized and mechanically ventilated, and underwent 6-hour endotoxic shock or sham experiment. Results. In the chronic treatment part, the plasma nitrate concentration, myocardial guanosine 3',5'-cyclic monophosphate (cGMP) content, and APD at 90% repolarization (APD90) of papillary muscle showed no difference in the five groups before endotoxic shock. After 6-hour endotoxic shock, the elevation of plasma nitrate concentration and myocardial cGMP content was found significant in the control, the daidzein, and the vehicle groups, but was blunted in the genistein and the tyrphostin groups. The shortening of APD90 of papillary muscle was also significant in the control, the daidzein, and the vehicle groups, but blunted in the genistein and tyrphostin groups. There were similar findings in the acute treatment part, except the weaker effect of genistein and tyrphostin. Conclusions. Genistein and tyrphostin AG 556, either administered chronically or acutely, significantly attenuate the cardiac APD shortening in endotoxic shock, presumably through the decrease in the plasma nitrate and the cardiac cGMP production. It is suggested that tyrosine kinase signaling plays an important role in the modulation of APD in endotoxic shock.