

Pressor and Cardioaccelerator Responses to ATP and Lactic Acid in Type 1 Diabetic Rats

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ABSTRACT

Skeletal muscle contraction produces metabolites which stimulate group III and IV muscle afferents and thereby evokes a reflexive increase in sympathetic activity, namely the metaboreflex. ATP and lactic acid are among these metabolites and both play a role in evoking an exaggerated exercise pressor reflex in cardiovascular related diseases. It is not known, however, if ATP and/or lactic acid evoke(s) an exaggerated metaboreflex in type 1 diabetes. **PURPOSE:** To determine the pressor and cardioaccelerator responses to intra-arterial injections of ATP and lactic into the hindlimb vasculature of type 1 diabetic rats. **METHODS:** We injected either Streptozotocin (STZ) or vehicle (CTL) into either sex rats and waited 1 week (STZ: n=11; female STZ: glucose=495±29 mg/dl, HbA1C=6.3±0.2%; male STZ: glucose=408±29 mg/dl, HbA1C=6.5±0.5%; CTL: n=13; female CTL: glucose=195±10 mg/dl, HbA1C=4.5±0.8%; male CTL: glucose=361±12 mg/dl, HbA1C=4.4±0.1%;) or 3 weeks (STZ: n=12; female STZ: glucose=503±37 mg/dl, HbA1C=9.2±0.6%; male STZ: glucose=436±26 mg/dl, HbA1C=10.7±0.2; CTL: n=8; female CTL: glucose=177±28 mg/dl, HbA1C=4.3±0.1%; male CTL: glucose=238±36 mg/dl, HbA1C=5.1±0.7%). On the day of the experiment, we cannulated one jugular vein for fluid delivery and both carotid arteries for blood pressure and heart rate measurement. We also cannulated the superior epigastric artery, which descends into the femoral artery, on the left hindlimb. A snare was placed around the left iliac artery and vein, and when the snare was on, circulation to the hindlimb was greatly reduced. Rats were decerebrated allowing anesthesia to be turned off. ATP (20µg/kg) or lactic acid (24mM) were injected into the arterial supply of the hindlimb with the snare on. Increases in blood pressure and heart rate were recorded. **RESULTS:** We found that 1wk after STZ injection both the cardioaccelerator and pressor responses evoked by lactic acid were significantly greater than those responses in control rats (STZ: Δ MAP= 30±5 mmHg, Δ HR= 11±3 bpm; CTL: Δ MAP= 18±3 mmHg, Δ HR= 3±2 bpm; p<0.05). There were no differences in the pressor or cardioaccelerator responses evoked by ATP in STZ compared to control rats (p>0.05). Conversely, we found that 3wks after STZ injection neither the pressor nor the cardioaccelerator responses evoked by lactic acid were significantly greater than those responses in control rats (p>0.05). Additionally, the pressor but not the cardioaccelerator responses evoked by ATP were significantly greater in STZ rats than control rats (STZ: Δ MAP= 42±6 mmHg; CTL: Δ MAP= 27±5 mmHg, p<0.05). **CONCLUSION:** We conclude that lactic acid plays a role in evoking an exaggerated metaboreflex in the initial phase of type 1 diabetes. As the disease progresses, however, lactic acid no longer contributes to an exaggerated metaboreflex, and ATP begins to play a role in evoking an exaggerated metaboreflex. These findings suggest that different mechanisms involved in evoking the exercise pressor reflex in type 1 diabetic patients may change over the course of the disease.