ATP-sensitive potassium channel blockade: Mechanisms for decreased exercise tolerance

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Glibenclamide (GLI), a sulfonylurea drug prescribed for Type II diabetes increases insulin release by inhibiting ATP-sensitive potassium (K_{ATP}) channels and depolarizing pancreatic beta cells. These channels are also found in vascular smooth muscle cells, whose depolarization causes vasoconstriction and reduced muscular blood flow. It was hypothesized that K_{ATP} channels support exercise tolerance by increasing and sustaining muscular blood flow and oxygen delivery. Therefore, K_{ATP} channel inhibition would reduce muscle blood flow and interstitial oxygen availability. Male Sprague-Dawley rats (~4 months old) were evaluated for submaximal exercise tolerance (critical speed; n=10), interstitial oxygen pressure ($PO_2$is; n=9), and muscle blood flow at the site of $PO_2$is measurement site. Critical speed was determined via 4-5 runs to exhaustion at constant speed. Under anesthesia, $PO_2$is was measured via phosphorescence quenching during 180s electrically-induced contractions of the mixed gastrocnemius muscle during control and following muscle GLI superfusion (GLI: 5 mg/kg BW). Blood flow was determined via fluorescent microsphere technique. GLI reduced critical speed (32.27 ± 0.90 vs 29.73 ± 1.09 m/min), blood flow (50 ± 5 vs. 35 ± 4 mL/min/100g) and $PO_2$is (Nadir: 6.60 ± 0.63 vs. 5.36 ± 0.35 mmHg; Endpoint: 8.69 ± 0.95 vs. 6.85 ± 0.58 mmHg O_2; $p \leq 0.05$ for all) compared to control. These data support the hypothesis that K_{ATP} is crucial for exercise tolerance through adequate muscle blood flow and oxygen delivery. Improper use of sulfonylurea drugs when blood flow is already impaired, e.g. in heart failure, can lead to an exacerbation of exercise intolerance and further impairment of prognostic outcomes.

Research Support: National Institutes of Health Heart, Lung and Blood Institute, HL-2-108328 and HL137156-01A1

Scholar Support: KSU CVM Office of Research