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The Effect of Katp

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The Effect of K_{ATP} Channel Mutations on Inhibitor Sensitivity: Implications for Personalized Treatment of Cantu Syndrome

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Cantu Syndrome (CS) is a rare, complex disease characterized by a wide array of cardiovascular features caused by mutations resulting in the overactivity of ATP-sensitive potassium (K_{ATP}) channels. K_{ATP} channels are heteromeric complexes composed of pore-forming Kir6.x and regulatory SURx subunits. Currently, no cure exists for CS, but K_{ATP} inhibitors are promising candidates for the treatment of the disease; however, the effect of CS mutations on drug sensitivity have yet to be established. The goal of this project was to test a range of inhibitors against K_{ATP} channel mutations found in CS patients (Kir 6.1[V65M] and Kir 6.1[C176S]) to investigate their potential clinical benefit. K_{ATP} activity in the presence or absence of inhibitors (glibenclamide, repaglinide [both SURx interacting], and terfenadine [Kir6.x interacting]) was determined by measuring the efflux of radioactive $^{86}Rb^{+}$ from CosM6 cells transfected with wild type or mutated channels. These results show that these mutations resulted in decreased sensitivity to inhibitors of diverse structural classes which bind to different channel subunits. These findings demonstrate the need for comprehensive studies to investigate the effects of CS mutations on inhibitor sensitivity. Furthermore, these results predict poor clinical outcomes of certain K_{ATP} inhibitors for CS patients, which highlights the requirement for the development of novel inhibitors with new mechanisms of action.