Expression of a constitutively active K^+ channel prevents cell division in the mouse preimplantation embryo

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The activity of a large-conductance, voltage-gated K^+ channel changes during the cell cycle in all stages of mouse preimplantation development. This channel is active during M and G1 phases and inactive during S and G2. In parallel with the oscillations in K^+ channel activity are changes in the cell membrane potential, being hyperpolarized when the channel is active. The channel appears to be regulated by a cytoplasmic cell cycle that can function independent of the activation of the Cdk1/Cyclin B complex, but does also interact with the nuclear cell cycle. The objective of this study was to determine whether the cycling of K^+ channel activity in the mouse early embryo is required for progression of the cell cycle. In these studies we used an adenoviral construct containing a constitutively active mutant of the K^+ channel IRK1 (D172N-IRK1) and GFP under separate promoters. A control adenoviral construct that only contained GFP was used to determine non-specific effects of adenovirus transduction. Quackenbush strain mice were superovulated by intraperitoneal injections of pregnant mares' serum gonadotrophin and human chorionic gonadotrophin (hCG) 48 hours apart. Mice were killed by cervical dislocation approximately 48 hours after hCG injection and 2-cell embryos isolated. Embryos were then transduced with the adenoviruses by incubation in medium M16 containing 1×10^5 pfu/ml adenovirus. Successful transduction of embryos was determined after 16 hours by the expression of GFP. Whole-cell patch-clamping confirmed the expression of an inwardly-rectifying K^+ current in the GFP positive 4-cell embryos. Expression of D172N-IRK1 caused the membrane potential to be hyperpolarized (-59.1 mV) compared with the membrane potential in non-transduced embryos (-34.7 mV). Development of embryos to the 8-cell stage was reduced from 76.9% in non-transduced embryos to 16.3% in embryos expressing D172N-IRK. These results suggest that cyclic changes in K^+ channel activity are important for cell cycle progression in the early embryo. Whether the inhibitory affect is due to hyperpolarization of the membrane potential or loss of cytosolic K^+ requires further study.