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# Glibenclamide's action in the hypothalamus alters peripheral glucose homeostasis

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**Abstract**

Bilateral injections of 0.2 nmol of glibenclamide, targeted at the ventromedial hypothalamus of albino rats, significantly impaired recovery of blood glucose levels following insulin-induced hypoglycemia ($P = 0.0026$). Similar injections of 0.2 and 2.0 nmol glibenclamide reduced blood glucose by 23.6 and 40.8 mg%, respectively, in otherwise untreated rats ($P < 0.01$ and $P < 0.001$). Intravenous injection of these doses of the drug did not lower blood glucose. The results support the hypothesis that $K^+_{ATP}$ channels within the hypothalamus serve a counterregulatory function in the maintenance of peripheral glucose levels. 

*Keywords:* Hypothalamus; Glibenclamide; Glucose

The physiologic role of ATP-sensitive potassium ($K^+_{ATP}$) channels is best appreciated in pancreatic β cells where the channels act as metabolic transducers. At this site, $K^+_{ATP}$ channels link the metabolism of energy-yielding substrates to alterations of β cell membrane potential and subsequently, facilitate insulin release under physiologically appropriate conditions. Regulation of the $K^+$ conducting properties of $K^+_{ATP}$ channels is controlled by associated sulfonylurea receptors (SUR), which confer not only ATP sensitivity to the channels, but also act as a primary site of action for the insulin-releasing sulfonylureas employed as hypoglycemic agents in the pharmacotherapy of non-insulin dependent diabetes mellitus (see Seino (1999) for a recent review).

In addition to their localization in pancreas and numerous other peripheral tissues, subtypes of $K^+_{ATP}$ channels (Kir 6.1 or 6.2) and SUR (SUR1 or 2A) are found widely distributed throughout the central nervous system (Treherne and Ashford, 1991) and in a variety of combinations (see Miki et al. (2001)). The physiological relevance of the channels in nonpancreatic tissues has not been well defined. In the brain and in the ventromedial hypothalamus in particular, recent findings indicate that the $K^+_{ATP}$/SUR complexes may complement the pancreas in the control of peripheral glucostasis by serving in a counterregulatory capacity (Miki et al., 2001). Ascribing such a physiological role to the channels in the ventromedial hypothalamus relies on several lines of evidence. For example, 2-deoxy-D-glucose-induced neuroglucopenia, localized to the ventromedial hypothalamus, produces strong peripheral hormonal responses (Borg et al., 1995) and, localized perfusion of glucose into the ventromedial hypothalamus blunts peripheral hormonal counterregulatory responses to systemic hypoglycemia (Borg et al., 1997). Within the hypothalamus, populations of glucose-responsive neurons (those that increase their firing rates when exposed to high levels of glucose availability) express $K^+_{ATP}$/SUR complexes that respond similarly to both glucose and $K^+_{ATP}$ channel antagonists (Lee et al., 1999). Recently, studies on Kir 6.2 knock-out mice, which lack hypothalamic (and other) $K^+_{ATP}$ channels showed a dysfunction of peripheral glucose homeostasis and an inappropriate glucagon response to hypoglycemia, even though the pancreatic α cells of these mice functioned normally in vitro (Miki et al., 2001). Together, these studies suggest that $K^+_{ATP}$ channels have the capacity to act as glucose sensors in the hypothalamus and participate in the mediation of compensatory responses to peripheral hypoglycemia.

In the attempt to provide direct evidence that $K^+_{ATP}$ channels in the hypothalamus are important in the regulation of peripheral glucose homeostasis, we administered

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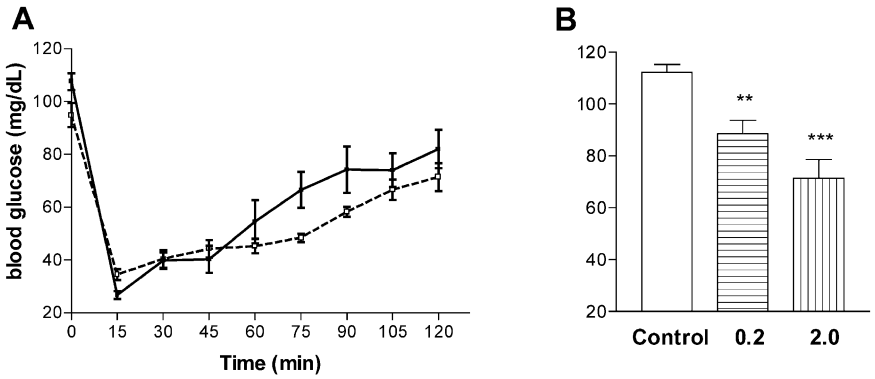


Fig. 1. Panel A shows the effect of hypothalamically administered vehicle (closed symbols) or glibenclamide (0.2 nmol, open symbols), on the recovery of blood glucose following insulin-induced hypoglycemia (0.25 U insulin i.v.). Insulin injections were made at the "0" time point, while glibenclamide was given 20 min prior. Two-way ANOVA (drug vs. time) showed a significant effect due to glibenclamide whether the data analyzed includes the "0" time point ($P = 0.0026$), or begins only at the glucose nadir ($P < 0.01$). Panel B shows the hypoglycemic effect of intrahypothalamic injections of 0.2 and 2.0 nmol glibenclamide on blood glucose 20 min postinjection. The data shown are the means and the S.E.M. Comparisons of both doses are referenced to the vehicle-injected controls (0.2 nmol dose, $P < 0.01$, $n = 9$; 2.0 nmol dose, $P < 0.001$, $n = 5$; vehicle control, $n = 9$). In all instances, hypothalamic injections were made bilaterally and targeted the ventromedial hypothalamic nucleus.

the $K^+_{ATP}$ channel-closing drug, glibenclamide, via microinjection directly into the ventromedial hypothalamus. This study utilized male Sprague–Dawley rats weighing 250–300 g. Under pentobarbital anesthesia, each animal was surgically fitted with catheters in the left jugular vein and carotid artery. The catheters were filled with heparin (50 U/ml) and 55% polyvinylpyrrolidone. Additionally, 22-gauge stainless steel guide cannulae were bilaterally implanted targeting both ventromedial hypothalamic nuclei. Animals were allowed at least 7 days to recover following surgery. On the day of the experiment, animals were intracerebrally injected through both brain cannulae with 0.4 μl of solutions of glibenclamide (0.1 or 1.0 nmol/side) prepared in bicarbonate buffer as previously described (Bounds and Roane, 1999). Twenty minutes later, the rats were injected with 0.25 U/kg of recombinant insulin (Humulin-R) in 0.5 ml/kg through the jugular catheter. Blood samples (0.05 ml) were taken through the carotid catheter and glucose concentrations were measured using a FastTake glucometer. Similar methods were used to test the effects of glibenclamide on normoglycemia. The data were analyzed by one-way and two-way analysis of variance with Dunnett's post hoc test.

The results show that the hypothalamic effects of glibenclamide impair recovery from insulin-induced hypoglycemia ($P = 0.0026$, Fig. 1A) and significantly reduce blood glucose levels ($P < 0.01$) in otherwise untreated rats (Fig. 1B). Identical quantities of glibenclamide administered peripherally did not lower blood glucose (data not shown). The results support the contention that hypothalamic $K^+_{ATP}$ channels play a significant regulatory role in peripheral glucose homeostasis.

It is important to note that the $K^+_{ATP}$ channel antagonist, glibenclamide, is commonly used as a hypoglycemic agent throughout much of the world. Clinically, the drug is associated with causing a severe, life-threatening hypoglycemia in a significant portion of the patient population (Shorr et al., 1997). It will be interesting to discover whether this untoward effect is due, in part, to the drug's action in the hypothalamus.

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