Inhibition of ATP-sensitive potassium channels by haloperidol

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1 Chronic haloperidol treatment has been associated with an increased incidence of glucose intolerance and type-II diabetes mellitus. We studied the effects of haloperidol on native ATP-sensitive potassium (K\textsubscript{ATP}) channels in mouse pancreatic β cells and on cloned Kir6.2/SUR1 channels expressed in HEK293 cells.

2 The inhibitory effect of haloperidol on the K\textsubscript{ATP} channel was not mediated via the D2 receptor signaling pathway, as both D2 agonists and antagonists blocked the channel.

3 K\textsubscript{ATP} currents were studied using the patch-clamp technique in whole-cell and outside-out patch configurations. Addition of haloperidol to the extracellular solution inhibited the K\textsubscript{ATP} conductance immediately, in a reversible and voltage-independent manner. Haloperidol did not block the channel when applied intracellularly in whole-cell recordings.

4 Haloperidol blocked cloned Kir6.2/SUR1 and Kir6.2ΔC36 K\textsubscript{ATP} channels expressed in HEK cells. This suggests that the drug interacts with the Kir6.2 subunit of the channel.

5 The IC\textsubscript{50} for inhibition of the K\textsubscript{ATP} current by haloperidol was 1.6 μM in 2 mM extracellular K\textsuperscript{+} concentration ([K\textsuperscript{+}])o and increased to 23.9 μM in 150 mM [K\textsuperscript{+}])o. The Hill coefficient was close to unity, suggesting that the binding of a single molecule of haloperidol is sufficient to close the channel.

6 Haloperidol block of K\textsubscript{ATP} channels may contribute to the side effects of this drug when used therapeutically.

Keywords: Haloperidol; ATP-sensitive potassium channel; K\textsubscript{ATP} channel; pancreatic β cell; diabetes mellitus; D2 receptor

Abbreviations: K\textsubscript{ATP}, ATP-sensitive potassium channel; Kir, inwardly rectifying potassium channel; [K\textsuperscript{+}])o, extracellular K\textsuperscript{+} concentration; SUR, sulfonylurea receptor

Introduction

Haloperidol is frequently used in clinical practice to treat psychotic disorders and neurological diseases, and to control the symptoms of Tourette's syndrome (Kapur & Remington, 2001). Its pharmacological effect is believed to be due to the ability of the drug to block the dopamine signaling pathway in the central nervous system (for a review, see Seeman & Van Tol, 1994). It is well established that treatment with antipsychotic agents is often associated with excess body weight gain, abnormal glucose metabolism, and, in some cases, even diabetes mellitus (DM) (Baptista et al., 2002). A large-scale cohort study showed the relative risk of DM in haloperidol-treated patients to be three-fold greater than in an untreated control population (Buse et al., 2003). The exact mechanisms underlying the development of DM in haloperidol-treated patients are still unknown, but it has been proposed that the dopamine signaling pathway might be involved (Hågg et al., 1998). Haloperidol has been shown to directly inhibit various types of ion channels, including the G-protein-activated inwardly rectifying potassium channel (Kobayashi et al., 2000), the calcium-activated potassium channel (Akamine et al., 2002), HERG and HEAG potassium channels (Shuba et al., 2001; Gessner & Heinemann, 2003), and L-, N-, and P-type calcium channels (Galizia et al., 1986; Sah & Bean, 1994).

The ATP-sensitive potassium (K\textsubscript{ATP}) channel links the metabolic state to membrane electrical excitability in many cell types, including pancreatic β cells, heart, and neurons (Ashcroft & Rorsman, 1989; Carmeliet 1999; Chiou & How, 2001). In pancreatic β cells, the K\textsubscript{ATP} channel couples elevation in the blood glucose level to insulin secretion (Ashcroft & Rorsman, 1990; Miki et al., 1998). Closure of this channel at elevated glucose leads to membrane depolarization, opening of voltage-gated calcium channels, and a rise in intracellular calcium that triggers insulin secretion (for a review, see Kanno et al., 2002).

The K\textsubscript{ATP} channel is a heterotetrameric complex, composed of four Kir6.2 and two sulfonylurea receptor (SUR) subunits. Kir6.2 is an inwardly rectifying K\textsuperscript{+} channel that serves as a common pore-forming subunit of the K\textsubscript{ATP} channel in most tissues except vascular smooth muscle (Inagaki et al., 1995). It possesses inhibitory binding sites for ATP and drugs such as phentolamine (Proks & Ashcroft, 1997; Tucker et al., 1997). SUR is a regulatory protein that confers sensitivity to MgADP and drugs such as K-channel openers and sulfonylureas (which block the channel) (for a review, see Aguilar-Bryan et al., 1998). There are two SUR genes, which exhibit different tissue distributions: SUR1 is found in β cells, gut L cells, and some neurons, SUR2A in cardiac and skeletal muscle and SUR2B in smooth muscle and neurons. Different SURs confer different sensitivities to drugs and nucleotides (Reimann et al., 2000). Both Kir6.2 and SUR1 are required for correct trafficking of...
the $K_{\text{ATP}}$ channel to the plasma membrane; however, deletion of the last 26 residues of Kir6.2 (Kir6.2AC26) removes an endoplasmic reticulum retention signal and enables Kir6.2AC26 to reach the surface membrane in the absence of SUR (Tucker et al., 1997; Zerangue et al., 1999). This construct therefore provides a useful tool for examining the subunit of the $K_{\text{ATP}}$ channel that is targeted by a drug.

In this study, we investigated the effects of haloperidol on native $K_{\text{ATP}}$ channels in mouse pancreatic $\beta$ cells and cloned $\beta$ cell (Kir6.2/SUR1) $K_{\text{ATP}}$ channels expressed in HEK293 cells. We found that haloperidol blocks $K_{\text{ATP}}$ channels by binding to an external site on Kir6.2, and that this effect is modulated by extracellular $K^+$ concentration ($[K^+]_o$).

**Methods**

**Isolation of islet cells**

All animal studies were conducted according to the National Institutes of Health’s Guidelines for Care and Use of Experimental Animals and were approved by the Committee on Animal Care and Use of the local institution and state. Adult male NMRI mice were killed by cervical dislocation. Liberase (0.3 mg mL$^{-1}$) (Roche, U.S.A.) was dissolved in Hank’s buffer salt solution (Invitrogen, U.S.A.) and injected into pancreas via the bile duct. The pancreas was then removed and digested for 20-30 min at 37°C. Islets were first enriched by Ficoll gradient centrifugation (Amersham, Sweden) and then hand picked. Isolated islets were shaken in CMRL-1066 medium (Invitrogen, U.S.A.) plus 2 mM EGTA, then triturated into single cells. Cells were plated onto poly-L-ornithine-coated coverslips and cultured in CMRL-1066 medium supplemented with 10% fetal bovine serum (Invitrogen, U.S.A.), 100 U mL$^{-1}$ penicillin G, and 0.1 mg mL$^{-1}$ streptomycin in a humidified atmosphere of 5% CO$_2$/95% O$_2$ at 37°C. Cultured cells were used within 4 days.

**Cloned channel expression**

Mouse Kir6.2 (Genbank D50581; Bond et al., 1995; Inagaki et al., 1995) and rat SUR1 (Genbank L40624; Aguilar-Bryan et al., 1995) cDNAs were cloned into the pcDNA3 plasmid. A truncated form of Kir6.2 (Kir6.2C36), which lacks the C-terminal 36 amino acids and forms functional channels in the absence of SUR, was prepared as described previously (Tucker et al., 1997).

HEK293 cells were cultured in DMEM (Sigma) containing 10% FBS (Life Technologies, Paisley, Scotland), 3 mM glucose, and 2 mM glutamine at 37°C in a humidified atmosphere of 5% CO$_2$/95% O$_2$ at 37°C. Cells were plated on poly-L-ornithine-coated glass coverslips and cultured in CMRL-1066 medium supplemented with 10% fetal bovine serum (Invitrogen, U.S.A.), 100 U mL$^{-1}$ penicillin G, and 0.1 mg mL$^{-1}$ streptomycin in a humidified atmosphere of 5% CO$_2$/95% O$_2$ at 37°C. Cultured cells were used within 4 days.

**Electrophysiology**

$K_{\text{ATP}}$ currents were recorded using the whole-cell patch-clamp configuration by an EPC9 and EPC10 amplifier (HEKA Electronik, Germany). Data were acquired at 20 kHz with PULSE8.6 software (HEKA Electronik). Pipettes were pulled from 1.5 mm borosilicate glass capillaries (Harvard Apparatus Ltd, U.K.) and their tips were heat polished using a microforge (MF830, Narishige, Japan). Pipette resistances were 2-4 MΩ in the standard intracellular solution. The series resistances of whole-cell configuration ranged between 5 and 20 MΩ. β Cells were identified by their larger size (>5 μF; Göpel et al., 2000) and their electrophysiological properties. In particular, they did not exhibit voltage-gated Na$^+$ currents at a holding potential of ~70 mV, but this could be activated in most cells by a conditioning pulse to ~ −150 mV, as previously described (Göpel et al., 1999). Single-channel currents were recorded from outside-out patches at ~−70 mV and digitized at 10 kHz. The pipette resistances were 5-10 MΩ. All experiments were carried out at room temperature.

**Solutions and chemicals**

The extracellular solution contained (in mM): 150 NaCl, 10 HEPES, 2 KCl, 2 CaCl$_2$, 1 MgCl$_2$, pH 7.2. (adjusted with NaOH). The potassium concentration was varied by equimolecular replacement of NaCl with KCl, and 150 mM [K$^+$], solution was used in single-channel recordings. The intracellular solution contained (in mM): 150 KCl, 10 HEPES, 1 MgCl$_2$, 5 EGTA, pH 7.2 (adjusted with KOH). For whole-cell recordings in native β cells, Na$ATP$ (0.5 mM) was added to the intracellular solution to prevent rundown of $K_{\text{ATP}}$ currents. The osmolarity of all solutions was 300±10 mOsm. The recording chamber had a volume of 2 ml and solutions containing chemicals were perfused focally by gravity.

L-741,626 and sulpiride were purchased from Tocris (Biotrend, Germany) and all other chemicals from Sigma (Sigma-Aldrich, Germany). However, different batches of haloperidol were purchased from both companies. Haloperidol, sulpiride, and L-741,626 were dissolved in DMSO, tolbutamide was dissolved in ethanol. The final concentrations of DMSO were less than 0.1%, which did not affect the $K_{\text{ATP}}$ currents.

**Data analysis**

Concentration-dependent curves were fitted by the Hill equation:

\[
\frac{G}{G_0} = \frac{1}{1 + \left(\frac{\text{haloperidol}}{IC_{50}}\right)^n}
\]

where $G$ and $G_0$ are the $K_{\text{ATP}}$ conductance in the presence and absence of haloperidol, respectively, [haloperidol] is the concentration of haloperidol, $IC_{50}$ is the half-maximal inhibitory concentration of haloperidol and $n$ is the slope parameter (Hill coefficient). The conductance was measured as a slope conductance between ~100 and ~50 mV of a 100 ms voltage ramp, independently of whether the current flow was inward (as at high $[K^+]_o$) or outward (as at low $[K^+]_o$). This is justifiable as experiments at a given $[K^+]_o$ showed that neither the extent nor rate of block varied with membrane potential or the direction of current flow. The control conductance was taken as the mean of that recorded in control solution before and after drug addition.
Curve fitting was carried out using PulseFit v8.65 (HEKA Electronik, Germany), Matview (Matlab extension, Wise Technologies, Slovenia), and SigmaPlot v8.0 (Jandel Scientific, U.S.A.). Single-channel data were analyzed using TAC v4.1.5 (Bruxton, Seattle, WA, U.S.A.). Recordings were analyzed before and after haloperidol treatment and the average data were taken as the control. For measurements of open and closed times, events were detected using 50% threshold level method. The open time distribution was fitted by a Gaussian distribution, and the closed time distribution was best fitted by the sum of two Gaussian distributions. The burst duration was defined by two openings separated by an interval of <1 ms (approximately twice the mean short closed time).

Data are given as mean ± s.e.m., and n indicates the number of cells analyzed. Statistical significance (P < 0.05) was determined using Student’s t-test or one-way ANOVA test.

Results

Haloperidol inhibition of K$_{ATP}$ channels does not involve the D2 receptor

In whole-cell recordings on β cells, the K$_{ATP}$ conductance was induced by dialysis with low [ATP]$_i$ (<0.5 mM) and quantified by measuring the slope conductance between −100 and −50 mV of a 100 ms voltage ramp. Addition of the D2 receptor antagonist haloperidol to the extracellular solution (2 mM [K$^+$]) significantly reduced the whole-cell K$_{ATP}$ conductance, an effect which was reversible upon wash out of haloperidol (Figure 1a and b). The simplest explanation of this observation is that haloperidol acts as a direct channel blocker. However, it is also possible that the drug blocks a tonic activation of D2 receptors, caused by low levels of dopamine in the extracellular solution. To exclude this possibility, we tested the effect of other D2 receptor

![Figure 1](https://example.com/figure1.png)

**Figure 1** Inhibition of K$_{ATP}$ conductance by tolbutamide, D2 receptor agonist, and antagonists in pancreatic β cells (2 mM [K$^+$]). (a) Haloperidol block in a concentration-dependent manner, which can be reversed upon washout, is shown. The K$_{ATP}$ currents were elicited by 100 ms voltage-ramp stimulation (−100 to −50 mV, 1 Hz) from holding potential −110 mV. (b-f) K$_{ATP}$ current–voltage relation before (control) and after application of: (b) 100 μM haloperidol (HAL), (c) 10 μM L741-626 (L), (d) 100 μM sulpiride (SUL), (e) 20 μM quinpirole (QUIN), 20 μM quinpirole plus 100 μM haloperidol, and (f) 100 μM tolbutamide (TOL). (g) Comparison of mean K$_{ATP}$ conductances in the presence of the drugs indicated normalized to control solution. Numbers of cells tested are indicated in parentheses. One-way ANOVA indicated a significant difference between 100 μM sulpiride and the other D2 antagonists (P < 0.001). Haloperidol and quinpirole plus haloperidol were not significantly different (t-test, P = 0.86).
antagonists and agonists. The specific D2 antagonist L-741,626 also partially blocked the K\textsubscript{ATP} current (Figure 1c); however, the antagonist sulpiride had no effect (Figure 1d). We next tested if the D2 receptor agonist quinpirole (20 \textmu M) could increase the K\textsubscript{ATP} conductance and reverse the effect of haloperidol. In contrast to our expectations, quinpirole partially inhibited the K\textsubscript{ATP} conductance when applied alone, and it did not prevent the inhibitory effect of haloperidol (Figure 1e). All the drugs we tested have comparable affinities for the D2 receptor (IC\textsubscript{50}, 1–10 nM), but the extent of K\textsubscript{ATP} channel block they caused was significantly different (Figure 1g). These results suggest that haloperidol inhibition is unlikely to involve the D2 receptor signaling pathway.

**Haloperidol binding site is on Kir6.2. subunit**

To determine whether haloperidol binds to the Kir6.2 or SUR1 subunit of the K\textsubscript{ATP} channel, we compared its effect on the cloned K\textsubscript{ATP} channels Kir6.2/SUR1 and a C-terminal-deleted Kir6.2 construct, Kir6.2AC36, expressed in HEK293 cells. Figure 2 shows that the extent of haloperidol block was independent of whether Kir6.2 was expressed alone or in combination with SUR1. This result demonstrates that haloperidol block only requires Kir6.2. In addition, this experiment provides further support for the idea that the D2 signaling pathway is not involved, because HEK293 cells do not express endogenous D2 receptors (Senogles et al., 2004).

**Haloperidol-binding site is extracellular**

To determine the location of the haloperidol-binding site, we used native \( \beta \) cells and diazoyed them intracellularly with 100 \textmu M haloperidol, a concentration that blocked more than 90\% of K\textsubscript{ATP} current when applied extracellularly in 2 mM [K\textsuperscript{+}]. (Figure 1). To prevent extracellular accumulation of haloperidol following diffusion across the plasma membrane, cells were constantly perfused with standard extracellular solution. However, the K\textsubscript{ATP} current still developed following washout of ATP, and could only be blocked when haloperidol was applied extracellularly (Figure 3a and d). This suggests that haloperidol can only access its binding site from the extracellular side of the membrane. In contrast, when \( \beta \) cells were diazoyed with 10 \textmu M glibenclamide, which is thought to act at an intracellular site (Ashcroft & Gribble, 1999), no discernible K\textsubscript{ATP} current developed during 10 min of dialysis (Figure 3b and c).

**Voltage dependency of haloperidol blockage**

It has been reported that haloperidol blocks other potassium channels, such as HERG, in a strongly voltage-dependent manner (Suessbrich et al., 1997). We examined this effect using cloned K\textsubscript{ATP} channels expressed in HEK293 cells (which do not possess significant endogenous voltage-dependent currents), to avoid interference from voltage-gated channels in \( \beta \) cells. [K\textsuperscript{+}], was raised to 10 mM to increase the inward current and the cells were held at \( E_{K} \), the potassium equilibrium potential (−68 mV). As shown in Figure 4, currents elicited by either +50 mV (outward current) or −50 mV (inward current) pulses were blocked equally by 10 \textmu M haloperidol, indicating that the block is not voltage dependent.

**Haloperidol block is reduced by increasing [K\textsuperscript{+}]\textsubscript{o}**

In the previous section, we found that in 10 mM [K\textsuperscript{+}], haloperidol only blocked the K\textsubscript{ATP} current by 67% (Figure 4c), whereas approximately 80\% of the current is blocked in standard extracellular solution which contains 2 mM [K\textsuperscript{+}].
(Figure 1a). This implies that $[K^+]_o$ might affect haloperidol binding. To explore this possibility, we constructed concentration-inhibition curves for haloperidol block of mouse $\beta$-cell K$_{ATP}$ currents at different $[K^+]_o$. As Figure 4b shows, haloperidol block was not voltage dependent, did not depend on the direction of current flow, and exhibited comparable block kinetics at all potentials. The K$_{ATP}$ conductance at different haloperidol concentrations was normalized to that in the absence of the drug, and is plotted against the haloperidol concentration in Figure 5a. The results clearly show that haloperidol block is reduced at higher $[K^+]_o$, the IC$_{50}$ increasing from 1.67 to 23.88 $\mu$M when $[K^+]_o$ was raised from 2 to 150 $\mu$M (Figure 5b). The Hill coefficient was close to unity (Figure 5c), suggesting that binding of a single molecule of drug was sufficient to block the K$_{ATP}$ channel.

Single-channel analysis

We also examined the effect of haloperidol on native $\beta$ cell K$_{ATP}$ currents at the single-channel level (Figure 6). Since haloperidol can only access to its binding site from the extracellular side (Figure 3), we used outside-out patch recordings. In ATP-free solution, K$_{ATP}$ channel currents rundown exponentially with a time constant of 1–2 min, followed by a sustained phase of activity (Nichols et al., 1991). We measured the effect of haloperidol on the single-channel kinetics during this sustained phase. The results are summarized in Table 1. As seen in Figure 6, K$_{ATP}$ channel openings occurred in bursts, which were separated by longer closed intervals. The short closed time is primarily determined by openings within a burst and the long closed time reflects the interburst intervals. Our long closed time is longer than previously published data (Proks & Ashcroft, 1997), which we attribute to K$_{ATP}$ channel rundown. Neither the open time nor the short closed time was altered by haloperidol and the unitary current size was not affected. These data indicate that
haloperidol does not act as an open channel blocker. However, the drug markedly decreased the channel open probability by prolonging the long closed time, which accounts for the reduced macroscopic whole-cell conductance.

Discussion

In this study, we found that haloperidol blocks both native K\textsubscript{ATP} channels in mouse pancreatic β cells and the cloned β-cell type of K\textsubscript{ATP} channel (Kir6.2/SUR1) expressed in HEK293 cells. The effect of the drug is voltage independent, rapidly reversible, is observed only when haloperidol is added to the external side of the membrane, and is modulated by [K\textsuperscript{+}]\textsubscript{o}. The inhibitory effect is mediated via the Kir6.2 subunit of the K\textsubscript{ATP} channel.

Haloperidol is a hydrophobic compound (Froemming et al., 1989) and can therefore freely diffuse through the plasma membrane. In our experiments, haloperidol was only able to block the channel when applied to the extracellular solution. A possible explanation for this finding is that when applied intracellularly, any haloperidol that crosses the membrane is rapidly diluted by the bulk extracellular solution before it has time to bind to its binding site.

Our experiments indicate that external potassium ions modulate channel inhibition by haloperidol. The mechanism of this effect was not explored but theoretically could involve a reduction in haloperidol binding (either by direct competition or via an allosteric effect), interference with the transduction mechanism by which haloperidol binding results in closure of the channel, or, if the drug interacts preferentially with a particular gating state, an effect of external potassium ions on gating. It has been shown that the binding of open channel blockers, including haloperidol, to voltage-gated potassium channels are reduced at higher [K\textsuperscript{+}]\textsubscript{o} (Kuo, 1998; Jo et al.).

<table>
<thead>
<tr>
<th>$[\text{K}^+]_o$ (mM)</th>
<th>Mean open time (ns)</th>
<th>Mean short closed time (ns)</th>
<th>Mean long closed time (ns)</th>
<th>Mean burst duration (ms)</th>
<th>Open probability ($P_o$)</th>
<th>$I$ (pA, at −70mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.62 ± 0.12</td>
<td>0.58 ± 0.02</td>
<td>109.7 ± 17.3</td>
<td>11.1 ± 4.5</td>
<td>0.20 ± 0.13</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>10 µM haloperidol</td>
<td>1.47 ± 0.20</td>
<td>0.57 ± 0.03</td>
<td><strong>176.9 ± 35.8</strong></td>
<td><strong>9.1 ± 2.7</strong></td>
<td><strong>0.15 ± 0.11</strong></td>
<td><strong>4.4 ± 0.1</strong></td>
</tr>
</tbody>
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*P < 0.05, paired Student’s t-test.

Table 1: Outside-out analysis of haloperidol effect on K\textsubscript{ATP} channels in pancreatic β cells
2000; Shuba et al., 2001). The detailed mechanism is still not clear, but it has been proposed that external potassium ions compete with the open channel blocker imipramine for binding to the external pore region of the A-type potassium channel in rat hippocampal neurons (Kuo, 1998). Single-channel analysis of K\textsubscript{ATP} channels showed that haloperidol is not an open channel blocker but [K\textsuperscript{+}]\textsubscript{o} still can hinder its binding to the channel. It has also been confirmed by the X-ray crystallography that potassium ions are bound close to the external mouth of the pore (Zhou et al., 2001; Kuo et al., 2003), and it is possible that these potassium ions and channel blockers might compete for the same binding site. A similar interaction might explain how the elevated [K\textsuperscript{+}]\textsubscript{o} solutions (e.g. Kobayashi et al., 2000), which may possibly lead to underestimation of the safety margin of these compounds as is the case for haloperidol (Redfern et al., 2003).

Our results indicate that the effect of haloperidol is mediated via Kir6.2, probably by direct binding of the drug to the protein. In this respect, haloperidol resembles the imidazoline phenotolamine (Proks & Ashcroft, 1997), which also appears to interact directly with Kir6.2. Kir6.2 also serves as the pore-forming subunit of the K\textsubscript{ATP} channel in other islet cells (x and δ cells; Göpel et al., 2000), in the L cells of the gut which secrete the insulin incretin GLP-1 (Gribble et al., 2003), in many neurons, and in cardiac and skeletal muscle (Inagaki et al., 1995). Muscle K\textsubscript{ATP} channels are mostly closed under resting conditions and open only in response to ischemia. However, K\textsubscript{ATP} channels in islet cells and L cells are involved in the release of hormones that modulate insulin secretion. Likewise, K\textsubscript{ATP} channels in ventromedial hypothalamic neurons appear to be involved in the counter-regulatory response to glucose (Miki et al., 2001), and those of the substantia nigra may be involved in movement control (Roeppe et al., 1999). Since Kir6.2 is the binding site for haloperidol, it might exert unspecific side effects by inhibiting different K\textsubscript{ATP} channels in a wide range of tissues.

An important question is whether the inhibitory effect of haloperidol on the K\textsubscript{ATP} channel is clinically relevant. There are several arguments against this possibility. First, the peak plasma concentration found in patients during treatment for schizophrenia is about 10–100 nM (Froemming et al., 1989), which is an order of magnitude lower than the IC\textsubscript{50} for K\textsubscript{ATP} channel inhibition. However, at least in brain, haloperidol rapidly accumulates to higher concentration (>200 nM; Kornhuber et al., 1999) and this could block a significant fraction of K\textsubscript{ATP} channels. Second, not all D2 antagonists which precipitate DM block K\textsubscript{ATP} channels with the same affinity. For example, sulpiride alters glucose homeostasis in rats (Baptista, 1999), but our studies indicate it has little inhibitory effect on K\textsubscript{ATP} channels, even at high concentration. Third, studies have shown that haloperidol can either reduce insulin secretion (Hermansen, 1978) or have no effect (El-Denshary et al., 1982), but an increase in secretion (which is expected if the drug blocks K\textsubscript{ATP} channels) has not been reported. It is possible that haloperidol blocks Ca\textsuperscript{2+} currents in β cells, as it does in other tissues, which leads to a reduction in insulin secretion, glucose intolerance, and diabetes. Further studies are needed to resolve this question.

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