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Short communication

K_{ATP} channels predominantly regulate conduit vessel tone in normoxic cat pulmonary arteries in vivo

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Abstract

Through our investigations of the intact pulmonary circulation, we aimed to find out whether K_{ATP} channels contribute to regulating basal vascular tone and to clarify which vascular segments dilate during K_{ATP} channel activation under basal tone conditions. Using an X-ray television system on anesthetized cat lungs, we measured internal diameter (ID) responses to two K_{ATP} channel inhibitors (glibenclamide and 4-morpholinecarboximidine-*N*-1-adamantyl-*N′*-cyclohexyl-hydrochloride (U-37883A)) and to an activator (levcromakalim) in normoxic pulmonary arteries. In conduit arteries (800–3000 μm ID), the inhibitors and activator induced larger ID constrictions (14–17%) and dilatations (29–32%), respectively. However, in resistance arteries (< 500 μm), the constriction response was negligible and the dilatation response relatively small (5–10%). The data suggest that K_{ATP} channels are active and capable of regulating basal vascular tone primarily within conduit pulmonary arteries even though these channels are present in all pulmonary arteries.

Keywords: KATP channel; Glibenchalmide; U-37883A; Levromakalim; Vascular tone, pulmonary; (Cat)

1. Introduction

The selective K_{ATP} channel inhibitor, glibenclamide, has no significant effect on either basal pulmonary vascular resistance in isolated perfused lungs or on basal tension of the pulmonary artery rings (Quayle et al., 1997; Reeve et al., 1997). It has therefore been suggested that K_{ATP} channels are not involved in regulating basal pulmonary vascular tone (Quayle et al., 1997; Reeve et al., 1997). However, this suggestion has not yet been verified for the intact pulmonary circulation controlled by neurohumoral factors which are capable of activating K_{ATP} channels (Edwards and Weston, 1993; Quayle et al., 1997).

On the other hand, K_{ATP} channel activators, such as cromakalim and levromakalim (Edwards and Weston, 1993), do significantly decrease basal pulmonary vascular resistance in both prefused and intact lungs (Hood et al., 1991; Minkes et al., 1991). They also cause membrane hyperpolarization and K^+ current activation in pulmonary artery myocytes (Clapp et al., 1993; Quayle et al., 1997). These effects are reversed by glibenclamide, suggesting that K_{ATP} channels are present and capable of modulating tone in the pulmonary vessels. However, the longitudinal distribution of the K_{ATP}-mediated vasodilatation through the in vivo pulmonary arteries with basal vascular tone has yet to be clarified.

To resolve these issues, we used an X-ray TV system (Shirai et al., 1986) on anesthetized cat lungs and directly measured the internal diameter (ID) changes caused by K_{ATP} channel inhibition or activation in the pulmonary arteries (100–3000 μm ID), which contain both the conduit (> ~ 500 μm) and resistance (< ~ 500 μm) segments (Kay, 1983).

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2. Materials and methods

Thirteen cats (2.8–3.2. kg body weight) anesthetized with pentobarbital sodium were used. The experimental procedure and angiography have been described in detail (Shirai et al., 1986). The procedures were approved by the ethical committee of National Cardiovascular Center Research Institute. The experiments were made in two groups. In group 1 ($n = 7$), the baseline angiogram was recorded first, and the angiogram with an injection of glibenclamide (20 mg/kg, i.v., $n = 4$) or 4-morpholinecarboximidine-*N*-1-adamantyl-*N*′-cyclohexyl-hydrochloride (U-37883A; 5 mg/kg, i.v., $n = 3$) (Quayle et al., 1997) was taken 20 or 10 min after the injection ended, respectively. In group 2 ($n = 6$), following the baseline angiogram, the angiograms with levcromakalim (1 and 20 μg/kg, i.v.) were taken 2–3 min after the injection ended. Our preliminary experiments showed that the doses of glibenclamide and U-37883A were able to cause maximal ID constriction and abolish the hypotensive effects of 20 μg/kg levcromakalim, which had been sufficient to maximally dilate the ID. In addition, there was no significant difference between the magnitudes of constriction with these K_{ATP} channel inhibitors. Following the method described in our previous study (Shirai et al., 1986), a random selection of many vascular sites for the ID measurement was made. The ID percentage change in response to a K_{ATP} channel inhibitor or activator was calculated at each measured vascular site. The measured sites were classified into four vascular groups with different ID sizes. By pooling the data from all the animals used in the experimental group 1 or 2, the mean value of the ID percentage change was calculated for each vascular group. All results are expressed as means ± S.E., and $P < 0.05$ was considered significant.

3. Results

Neither mean systemic arterial pressure nor mean pulmonary arterial pressure changed significantly 10–20 min following the glibenclamide and U-37883A injections. Levcromakalim, at a dose of 20 μg/kg, significantly decreased these pressures (from 115 ± 6 and 17 ± 1 up to 90 ± 7 and 14 ± 2 mm Hg, respectively). However, a dose of 1 μg/kg caused no decrease. Mean left atrial pressure remained unchanged in all protocols.

Glibenclamide and U-37883A injections induced large ID constrictions in the conduit arteries (14–17%) but only minimal (4%), or insignificant, constrictions in the resistance arteries (Fig. 1A). The levcromakalim injections significantly dilated the ID of all the pulmonary arteries observed (Fig. 1B). Both 1 and 20 μg/kg levcromakalim injections caused a similar ID response pattern which showed greater (29–32%) ID dilatations in the conduit arteries and smaller (5–10%) ID dilatations in the resistance arteries.

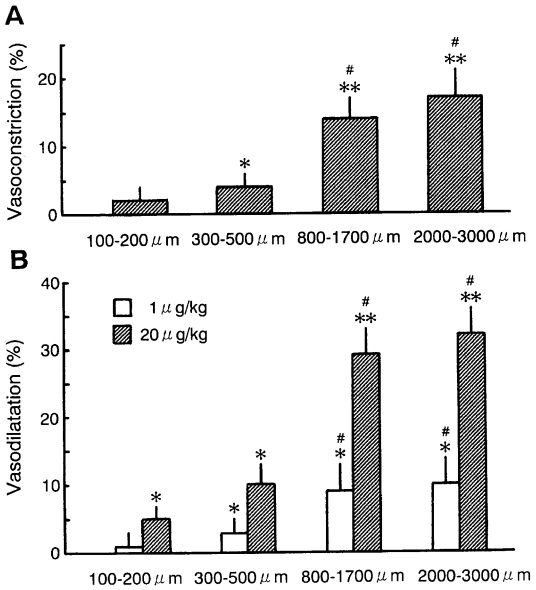

Fig. 1. (A) Mean value of internal diameter (ID) percentage decreases in response to K_{ATP} channel inhibitors, glibenclamide and U-37883A, is shown in each of the following four vascular groups; resistance arteries at the intra-acinar level (100–200 μm ID) and pre-acinar level (300–500 μm), and conduit arteries at the segmental level (800–1700 μm) and lobar level (2000–3000 μm). Numbers of measured sites in these four vascular groups were 106, 95, 71, and 39, respectively. (B) Mean value of ID percentage increases in response to a K_{ATP} channel activator, levcromakalim (1 or 20 μg/kg), is shown in each of the above-mentioned four vascular groups. Numbers of measured sites in these vascular groups were 92, 83, 64 and 35, respectively. Data are means ± S.E. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. baseline (Student's paired *t*-test). $^{\#}P < 0.01$ vs. 100–200 and 300–500 μm resistance artery groups (analysis of variance with Scheffe's test).

4. Discussion

Pressure–flow studies in isolated perfused lungs have found that glibenclamide causes no significant change in pulmonary vascular resistance and suggested no regulatory role of K_{ATP} channels in basal pulmonary vascular tone (Quayle et al., 1997; Reeve et al., 1997). However, our direct ID measurements have clearly revealed that the conduit arteries constrict significantly during K_{ATP} channel inhibition although there are only slight, or insignificant, constrictions in the resistance arteries (Fig. 1A). These results suggest that, within the intact pulmonary circulation, K_{ATP} channels do contribute to reducing basal vascular tone and do so primarily at the conduit segments rather than the resistance segments. This is consistent with the previous suggestion that K_{ATP} channels may contribute to setting the resting membrane potential in smooth muscle cells isolated from the rabbit main pulmonary artery (Clapp and Gurney, 1992; Reeve et al., 1997). Moreover, such a

non-uniform distribution of the K_{ATP} channel inhibitor-induced vasoconstriction may explain the previous and present findings that there is no significant change in pulmonary arterial pressure and left atrial pressure in response to this inhibitor, if it is assumed that the change in pulmonary pressure–flow relation primarily reflects the resistance segment response.

It has been shown that glibenclamide does not affect the pressor response during moderate hypoxia but does markedly inhibit reversal of the hypoxic pressor response (the secondary vasodilatation) during severe hypoxia in isolated perfused ferret lungs (Wiener et al., 1991). These results suggest that during severe, but not moderate, hypoxia K_{ATP} channels modulate hypoxic vasoconstriction which is primarily induced in the resistance pulmonary arteries (Shirai et al., 1986). Moreover, when this and our current data are considered together, it is possible to suggest that K_{ATP} channels are opening under both normoxic and hypoxic conditions in the conduit segments but only under severe hypoxia conditions in the resistance segments.

Levcromakalim injections predominantly dilated the conduit-artery ID more than the resistance-artery ID (Fig. 1B). On the other hand, levcromakalim injections at the high dose (20 μg/kg) simultaneously caused pulmonary arterial pressure reductions of about 3 mm Hg. Moreover, a previous study has shown that cromakalim injections (30–300 μg/kg, i.v.) increase cardiac output in anesthetized cats (Minkes et al., 1991). It is therefore possible that the local pressure- and flow-sensing mechanisms (Bevan and Laher, 1991) had some influence on the levcromakalim-induced ID response pattern. However, the low dose (1 μg/kg) of levcromakalim also caused a similar ID dilatation pattern (Fig. 1B) but without any significant blood pressure changes. Furthermore, in preliminary experiments, we found that this ID dilatation pattern is also observed at 10–15 s after 20 μg/kg levcromakalin injection, a stage at which the local pressure- and flow-mediated vasomotor responses can be considered to be barely established (Folkow, 1989; Smiesko et al., 1989; Koller and Kaley, 1990) and therefore, make only minor contributions to the ID response resulting from levcromakalim injection. These data suggest that the possibility of their influence is small and that pulmonary arterial K_{ATP} channel activation predominantly dilates the conduit arteries under basal tone conditions. It is of interest to note that calcitonin gene-related peptide, nitric oxide, and atrial natriuretic peptide, which can activate K_{ATP} channels (Quayle et al., 1997), induced similar pulmonary vasodilatation patterns in anesthetized cats (Shirai et al., 1993, 1997, 1999). K_{ATP} channels may act as a common point of integration for several different vasodilators which are capable of activating these channels (Edwards and Weston, 1993; Quayle et al., 1997) to regulate vascular tone in the in vivo normoxic pulmonary arteries, particularly the conduit segments.

It has been shown that cromakalim (30–300 μg/kg) causes only small decreases in cat pulmonary arterial perfusion pressure under resting tone conditions (Minkes et al., 1991). This is consistent with the present finding that levcromakalim induces small ID dilatations in the resistance segments. Under high tone conditions, however, cromakalim caused significant dose-related decreases in pulmonary arterial pressure (Minkes et al., 1991). This suggests that the effect of these K_{ATP} channel activators on the resistance segments is augmented under high tone conditions. Indeed, it has been demonstrated that levcromakalim and cromakalim can abolish hypoxic vasoconstriction in isolated rat pulmonary resistance vessels (Zhang and Morice, 1994) as well as in isolated perfused ferret lungs (Wiener et al., 1991).

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