The Role of ATP-Sensitive Potassium Channels in Neutrophil Migration and Plasma Exudation

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ABSTRACT

Neutrophil activation and migration during an inflammatory response is preceded or accompanied by plasma membrane electrical changes. Besides changes in calcium currents, neutrophils have a high permeability to potassium, mainly through potassium channels. However, the significance of potassium channels in neutrophil physiology is still unclear. Here, we show that the treatment of rats with the ATP-sensitive potassium channel blocker glibenclamide (4, 20, or 40 μmol/kg) dose dependently decreased carrageenan-, N-formyl-methionyl-leucyl-phenylalanine (fMLP)-, and lipopolysaccharide-induced neutrophil influx and fluid leakage into the interpleural space.

On the other hand, minoxidil (an ATP-sensitive potassium channel opener; 25, 50, and 100 μmol/kg) increased both neutrophil influx and fluid leakage induced by a submaximal dose of carrageenan. In addition, in vitro human neutrophil chemotaxis induced by leukotriene B₄ or fMLP (both 1 μM) was fully blocked by glibenclamide (10, 30, and 100 μM) or tetraethylammonium (a nonselective potassium channel blocker; 1, 3, and 10 mM). Thus, our results disclose the possibility that ATP-sensitive potassium channels may have a role in neutrophil migration and chemotaxis and plasma exudation in the inflammatory response.

Neutrophils are the most abundant polymorphonuclear leukocyte, constituting the main cell type involved in the nonimmune defense against pathogenic microorganisms. Although they have a protective effect, tissue damage observed in diseases such as rheumatoid arthritis, glomerulonephritis, immune vasculitis, and inflammatory bowel disease is also, at least in part, a consequence of neutrophil accumulation (Fauci et al., 1978; Holdsworth and Bellomo, 1984; Weissmann and Korchak, 1984; Chester et al., 1985; Wandall, 1985; Haynes, 1992). The neutrophil activation and migration during an inflammatory response result from a series of events, including up-regulation of cell surface integrin expression, adhesion to the endothelium, diapedesis, and transmigration. Neutrophils also release cytotoxic and proinflammatory mediators such as arachidonic acid metabolites, cytokines, superoxide anion, and nitric oxide (for a review see Chilvers et al., 2000).

The response of neutrophils to inflammatory mediators is preceded or accompanied by membrane depolarization and subsequent repolarization (Korchak and Weissmann, 1978; Mottola and Romeo, 1982) and hyperpolarization (Lazzari et al., 1990). These changes increase the release of Ca²⁺ from intracellular stores and stimulate the uptake of extracellular Ca²⁺ ions (Chandler and Kazilek, 1987); these effects are thought to be primary steps in neutrophil migration and have been correlated with locomotion and chemotaxis (Krause et al., 1990; Elferink and de Koster, 2000) and with the respiratory burst (Bei et al., 1998). Despite the overwhelming evidence indicating that membrane depolarization induces an excitable state in the majority of cell types, there are reports suggesting that in neutrophils membrane, depolarization may also function as an inhibitory signal (Di Virgilio et al., 1987). For instance, depolarization has been shown to blunt the oxidative burst (Martin et al., 1988). Subsequent studies have shown that initial increases in intracellular Ca²⁺ concentrations in response to N-formyl-methionyl-leucyl-phenylalanine (fMLP) occur together with membrane hyperpolarization dependent on intact potassium gradients and coincident with cytoplasmic acidification (Lazzari et al., 1990).

Neutrophils have a high permeability to potassium, and its efflux occurs mainly through potassium channels (Majander

ABBREVIATIONS: fMLP, N-formyl-methionyl-leucyl-phenylalanine; PBS, phosphate-buffered saline; TEA, tetraethylammonium; ANOVA, analysis of variance; MAP, mean arterial pressure; BSA, bovine serum albumin; TNF-α, tumor necrosis factor-α; LTB₄, leukotriene B₄; LPS, lipopolysaccharide; IFN-γ, interferon-γ.
and Wikström, 1989; Krause and Welch, 1990). Taking into account that ATP-sensitive potassium channel activity is involved in several physiological events such as insulin secretion and relaxation of vascular smooth muscle (for reviews, see Ashcroft and Gribble, 1999; Waldron and Cole, 1999) and that knowledge of the functional and physiological significance of this potassium channel in neutrophils is still relatively sparse, in this report we investigated the role of ATP-sensitive potassium channels in neutrophil migration induced by different chemotactic stimulus, using both in vivo and in vitro studies.

Materials and Methods

Animals

Male and female Wistar rats (3–4 months old, weighing 200–300 g) were employed in all experiments. Animals were housed on a 12-h light/dark cycle in a temperature-controlled room with free access to water and food. All procedures were approved by the Ethics Committee for Animal Use of the Universidade Federal de Santa Catarina, Brazil and are in accordance with the National Institutes of Health Animal Care Guidelines.

In Vivo Neutrophil Migration

Pleurisy was induced in anesthetized rats by intrapleural injection of the chemotactic agents carrageenan (300 μg/cavity), bacterial lipopolysaccharide (200 ng/cavity), or fMLP (100 nmol/cavity). All substances were dissolved in sterile Dulbecco’s phosphate-buffered saline (PBS; 137 mM NaCl, 2.7 mM KCl, 1.5 mM KH₂PO₄, 8.1 mM NaHPO₄, pH 7.4). The total volume injected was 100 μl. Control groups were injected intrapleurally with the same volume of PBS.

Collection of Exudates

Four hours after injection of chemoattractants, the animals were sacrificed with an overdose of pentobarbitone, and the thoracic cavity was opened and washed with 2 ml of PBS containing 1% EDTA. The volume of the exudate was measured and cell counts were performed by standard methods (Souza and Ferreira, 1985). The total cell count was made using samples diluted in Turk’s solution counted in a Neubauer chamber, and centrifuged slides (Cytospin 3; Shandon Southern Products, Atsmeo, UK), stained by the May–Grünewald–Giemsa method, were used for differential counts. Results are expressed as the number of neutrophils or total exudate (microliters) per cavity.

In Vivo Treatment with Potassium Channel Blockers

Previous experiments showed that doses of glibenclamide of 20 to 40 μmol/kg were necessary to achieve full inhibition of the intravenously hypotensive effects of the ATP-dependent potassium channel opener, cromakalim (10–100 nmol/kg; data not shown). Similar results were described by Gardiner et al. (1996). The dose of tetraethylammonium employed here was based on our previous work demonstrating that this dose range reversed in vivo nitric oxide-induced vascular hyporesponsiveness to vasoconstrictors in rats (Da Silva-Santos and Assreuy, 1999) and in the reports showing that tetraethylammonium (TEA) is effective in humans (Pickkers et al., 2001) and in the cat hindquarter vascular bed (Champion and Kadowitz, 1997). Therefore, the influence of potassium channel blockers on the development of pleurisy was examined through a single subcutaneous injection of glibenclamide (4, 20, or 40 μmol/kg) or tetraethylammonium (up to 250 μmol/kg), a selective ATP-sensitive potassium channel blocker and a nonselective potassium channel blocker, respectively. At least within this dose range, neither drug induced any visible side effects in the animals. These treatments were applied at the same time as the intrapleural injection of the inflammatory agents.

In Vivo Treatment with an ATP-Sensitive Potassium Channel Opener

To investigate the effects of an opener of ATP-sensitive potassium channels on neutrophil migration in response to carrageenan, different groups of animals were injected subcutaneously with minoxidil, an ATP-sensitive potassium channel opener (Leblanc et al., 1989) at doses of 25, 50, and 100 μmol/kg. Since minoxidil is a prodrug, the treatment consisted of three injections given 24 h, 12 h, and immediately before the inflammatory agent. A submaximal dose of carrageenan (100 μg) was used in this series of experiments to allow measurements of a possible potentiating effect of minoxidil. Thereafter, the animals were sacrificed and neutrophil counts were performed, and exudate volume was measured as described above.

Measurement of Glibenclamide, Tetraethylammonium, and Minoxidil Effects on Mean Arterial Blood Pressure

The animals were anesthetized with ketamine/xylazine (90:15 mg/kg i.m., supplemented at 45–60-min intervals), the right carotid artery was isolated, and a heparinized polyethylene catheter (PE 50) was inserted for the recording of mean arterial pressure (MAP). Data were recorded (at a 10-s sampling rate) with a Digi-Med (Louisville, KY) Blood Pressure Analyser system (model 190, NY) connected to Digi-Med System Integrator (model 200), software running on Windows 98 (Microsoft Corporation, Redmond, WA). After surgical procedures, a period of 30 min was allowed for blood pressure stabilization, and animals were then injected subcutaneously with glibenclamide (4, 20, and 40 μmol/kg), TEA (250 μmol/kg), or minoxidil (25, 50, and 100 μmol/kg). Besides evaluating the acute effects of minoxidil, animals treated for 2 days as described above also had their MAP assessed. The mean arterial blood pressure was recorded for 120 min following drug injections.

Determination of Blood Glucose Levels

Since the blockage of ATP-sensitive potassium channels with glibenclamide is clinically used as an oral hypoglycemic therapy, blood samples of animals were collected from the tail vein 4 h after glibenclamide treatment (4, 20, and 40 μmol/kg) for assessment of glucose levels. For this, we used a MediSense blood glucose sensor (Model Precision Q-ID; MediSense, Oxford, UK) with Precision Plus electrodes ( MediSense).

Blood Leukocyte Counts of Glibenclamide and Minoxidil-Treated Animals

To determine whether the treatment with the potassium channel blocker glibenclamide or the potassium channel opener minoxidil induced changes in neutrophil numbers, blood samples from animals treated with glibenclamide (4, 20, and 40 μmol/kg) or minoxidil (25, 50, and 100 μmol/kg) were subjected to total and differential leukocyte counts, as previously described.

In Vitro Neutrophil Migration Assay

Human Neutrophil Harvesting. Human neutrophils were isolated from heparinized venous blood of healthy donors using mono-poly-resolving medium (Flow Laboratories, McLean, VA) fractionation. Briefly, 3 ml of resolving medium was poured into a sterile 15-ml conical plastic tube and carefully overlaid with 3.5 ml of fresh, heparinized human venous blood. The tube was centrifuged at 300g for 30 min at room temperature. In the resulting centrifugate, red blood cells were pelleted at the bottom of the tube, whereas the first cell layer (which was discarded) below plasma was composed of mononuclear cells, and the second layer was composed of polymorphonuclear leukocytes. The isolated neutrophils (>95% purity; >99% viability assessed by trypan blue dye exclusion) were washed three times in RPMI 1640 medium and resuspended in the same medium containing 0.01% bovine serum albumin (BSA).

Pretreatment of Neutrophils. To test the effects of potassium channel blockers on in vitro migration, different samples of neutro-
phils (1 × 10⁶ cells/ml) were incubated for 30 min at 37°C and 5% CO₂ with either glibenclamide (10, 30, or 100 μM) or TEA (1, 3, or 10 mM) before the chemotaxis assay. Control samples were exposed to medium only. Cell viability, assessed by trypan blue dye exclusion, was >95% after exposure to potassium channel blockers and after chemotaxis assay.

Chemotaxis Assay. Briefly, we used a 48-well microchemotaxis plate (Neuro Probe Inc., Cabin John, MD) in which the chambers were separated by 5-μm pore-size polycarbonate-free polycarbonate membranes. Twenty-eight microliters of each chemottractant, diluted in RPMI 1640 medium containing 0.01% BSA were placed in the bottom chamber, and 50 μl of neutrophil suspension (10⁶ cells/ml), preincubated (for 30 min) with the potassium channel blocker, were added to the top chamber. Chemotactants (40 μl agents used were FMLP (1 μM) or leukotriene B₄ (1 μM), whereas the negative control was RPMI-BSA. Chambers were incubated for 1 h at 37°C and 5% CO₂. Subsequently, the filter was removed, fixed, and stained with a Diff-Quick stain kit (American Scientific Products, McGraw Park, IL). The number of neutrophils that had migrated to the lower side of the filter was counted in five random fields using a 100 × objective. Experiments were performed in triplicate for each variable and the means determined. The results are expressed as the number of neutrophils/field and are representative of three different experiments.

Determination of TNF-α Concentration in the Supernatant of Macrophages Treated with Glibenclamide and Tetraethylammonium and Stimulated with LPS/IFN-γ. The concentrations of TNF-α in the supernatant were measured by enzyme-linked immunosorbent assay based upon a previously described protocol (Tak-tak et al., 1991). Briefly, peritoneal macrophages were harvested from peritoneal cavities of animals injected 4 days before with 10 ml of thioglycollate (3% w/v) by washing the cavities with 10 ml of RPMI 1640 medium, pH 7.2. After quantification, the cells (2 × 10⁶/ml) were incubated with medium or LPS (100 ng/ml) plus IFN-γ (100 IU/ml) with (30 min before stimulus) or without glibenclamide (10, 30, and 100 μM) or TEA (1, 3, and 10 mM) for 24 h. After the incubation, the supernatants were collected and processed for TNF-α measurement. Microliter plates were coated overnight at 4°C with an immunoaffinity-purified polyclonal sheep antibody against TNF-α (2 μg/ml). After blocking the plates, rat recombinant TNF-α standards at various dilutions and the samples (100 μl) were added in duplicate and maintained at room temperature for 2 h. Sheep biotinylated immunoaffinity-purified polyclonal anti-TNF-α antibody at 1:1000 dilution was added, followed by incubation at room temperature for 1 h. Finally, 100 μl of avidin-horseradish peroxidase (1:5000 dilution) was added to each well; after 30 min, the plates were washed, and the color reagent o-phenylenediamine (40 μg/well) was added. After 15 min, the reaction was interrupted with H₂SO₄ (1 M), and the optical density was measured at 490 nm. The results were expressed as picograms of TNF-α per milliliter of the supernatant, comparing the optical density with a standard curve.

Compounds

Glibenclamide, TEA, minoxidil, leukotriene B₄ (LTB₄), FMLP, endotoxin (lipopolysaccharide from Escherichia coli serotype 0111-B4), were all purchased from Sigma (St. Louis, MO). Cell culture supplies were from Invitrogen (São Paulo, Brazil).

Statistical Analysis

Results are expressed as the mean ± S.E.M. (n = 6–10 for each group). Statistical comparisons were done by one-way analysis of variance (ANOVA) followed by Bonferroni's post hoc t test, where applicable. A value of P < 0.05 was considered statistically significant.

Results

Effects of Glibenclamide and Tetraethylammonium on Carrageenan-, Endotoxin- and FMLP-Induced Pleurisy. The total number of neutrophils found in the pleural cavity from control animals, which received only sterile PBS (vehicle) was 6.3 × 10⁶ ± 1.6 × 10⁶ per cavity (n = 23); these numbers were greatly increased after the intrapleural injection of carrageenan (Fig. 1A, closed bars), FMLP, or endotoxin (Fig. 2, closed bars). Subcutaneous administration of the ATP-sensitive potassium channel blocker glibenclamide (4, 20, and 40 μmol/kg) resulted in a dose-dependent decrease in both neutrophil migration (Fig. 1A) and fluid leakage to the interpleural space (Fig. 1B) induced by carrageenan. Maximal inhibitions were of the order of 45 and 80% for neutrophil influx and fluid leakage, respectively. On the other hand, neither neutrophil influx nor fluid leakage induced by carrageenan were affected by the nonselective potassium channel blocker TEA (250 μmol/kg; Fig. 1, hatched bars in A and B). A similar dose-dependent inhibitory effect of glibenclamide on neutrophil migration to the pleural cavity was observed using FMLP as the inflammatory stimulus (Fig. 2A). As with carrageenan, FMLP-induced fluid leakage was reduced by glibenclamide. For instance, glibenclamide at 20 and 40 μmol/kg reduced fluid leakage from 1380 ± 114 μl to 636 ± 80 μl and 710 ± 135 μl, respectively (P < 0.05). The inhibitory effect of glibenclamide was also observed when endotoxin was used as the chemottractant, although a clear dose-response effect was not observed (Fig. 2B). Endotoxin-induced fluid leakage was similarly reduced by glibenclamide treatment. Thus, the volume of exudate collected after the dose of 40 μmol/kg glibenclamide was 41 ± 18 μl whereas in control animals it was 291 ± 72 μl. As with carrageenan, TEA had no effects on neutrophil migration induced by FMLP (Fig. 2A, hatched bar) or by endotoxin (Fig. 2B, hatched bar).

Effects of Minoxidil on Carrageenan-Induced Pleurisy. Since systemic administration of the ATP-sensitive potassium channel blocker glibenclamide resulted in an inhibitory effect on the inflammatory responses to different agents, we sought to investigate whether the administration of minoxidil, an opener of ATP-sensitive potassium channels, would change carrageenan-induced neutrophil accumulation in the pleural cavity. Pretreatment with minoxidil (25, 50, and 100 μmol/kg) resulted in increased neutrophil and exudate accumulation in the pleural cavity induced by 100 μg of carrageenan (Fig. 3, A and B). Neutrophil counts in the pleural cavity of animals injected with minoxidil (100 μmol/
kg) in the absence of any chemotactrant did not differ from those of animals injected with PBS only (1.4 × 10⁵ ± 1.1 × 10⁵ and 1.8 × 10⁴ ± 0.9 × 10⁴ for PBS- and minoxidil-treated animals, respectively, n = 5).

**Effects of Glibenclamide, Tetraethylammonium, and Minoxidil on Mean Arterial Blood Pressure.** Control animals had basal MAP values of 102.4 ± 3.1 mm Hg. Subcutaneous injection of glibenclamide in anesthetized rats induced two different pressor effects on MAP. The first effect, which occurred 1 to 2 min after glibenclamide administration, was a decrease in MAP (9.3 ± 2.7, 13.4 ± 2.8, and 20.8 ± 3.1 mm Hg below control values for the doses of 4, 20, and 40 μmol/kg, respectively; n = 5–6 for each dose). This hypotensive effect was rapidly extinguished in a matter of 5 min. MAP values then increased (8.3 ± 4.2, 14.2 ± 3.1, and 23.4 ± 1.6 mm Hg above control values for the same doses), before returning to control levels over a period of 30 to 40 min and remaining unchanged during the rest of the experiment (120 min). Similar pressor effects of glibenclamide in rats have been previously described (Gardiner et al., 1999). On the other hand, tetraethylammonium (250 μmol/kg, s.c.; n = 6) caused only an increase in MAP (39.1 ± 3.4 mm Hg above control values), which fully subsided to control levels within 20 min. Pretreatment with minoxidil caused MAP to decrease (93.4 ± 4.2, 89.3 ± 2.3, and 85.4 ± 4.3 mm Hg, for the doses of 25, 50, and 100 μmol/kg, respectively, n = 6 for each group) relative to control animals (102.7 ± 4.2 mm Hg), in line with its use as an antihypertensive drug. The third dose of minoxidil (which was injected during the MAP recording) did not cause any additional changes during the 120-min period of evaluation.

**Effects of Glibenclamide and Tetraethylammonium on TNF-α Release by Rat Macrophages.** Neither glibenclamide (10, 30, and 100 μM) nor tetraethylammonium (1, 3, and 10 mM) had any effect on TNF-α release by rat macrophages stimulated in vitro with LPS/IFN-γ for 24 h (LPS/IFN-γ-stimulated macrophages 58.8 ± 2.2, plus 30 μM glibenclamide 55.4 ± 8.8, and plus 3 mM tetraethylammonium, 57.5 ± 2.3 pg/ml, respectively).

**Blood Glucose Levels.** In animals with free access to food, glibenclamide did not induce hypoglycemia. For instance, blood glucose levels measured 4 h after 4, 20, and 40 μmol/kg glibenclamide were 103 ± 1.95, 106 ± 8.0, and 100.4 ± 3.3 mg/dl, respectively, identical to control animals (103 ± 5.7 mg/dl). However, to confirm that glibenclamide was indeed inducing a hypoglycemia, a group of rats was injected with the drug (40 μmol/kg, s.c) and denied access to food for up to 4 h. In this group, glycemia was quickly reduced from 127.8 ± 1.8 mg/dl (before glibenclamide) to 78.8 ± 0.99 mg/dl (1 h after glibenclamide; n = 5) and remained ~40% below that of control animals for the subsequent 4 h.

**Blood Neutrophil Counts.** The number of neutrophils was unchanged by either glibenclamide or minoxidil. For instance, neutrophil counts in PBS-treated animals were 2.3 ± 0.21 × 10⁶ cells/ml (n = 6), whereas in glibenclamide-(40 μmol/kg) and minoxidil-treated animals (100 μmol/kg), they were 2.5 ± 0.21 and 2.4 ± 0.3 × 10⁶ cells/ml, respectively (n = 5-6 for each group). Numbers of eosinophils and mononuclear cells were similarly unchanged (data not shown).

**Effects of Glibenclamide and Tetraethylammonium on In Vitro Human Neutrophil Chemotaxis Induced by LTB₄ or fMLP.** We next evaluated the effects of potassium channel blockers on the ability of human neutrophils to migrate in vitro in microchambers. Pretreatment of neutrophils with either glibenclamide (10 to 100 μM) or tetraethylammonium (1 to 10 mM) for 30 min, dose dependently prevented both LTB₄ and fMLP-induced neutrophil chemotaxis. In fact, the highest concentration of either glibenclamide (100 μM) or tetraethylammonium (10 mM) completely inhibited neutrophil chemotaxis toward both chemotactants (Fig. 4, A and B, respectively). Neither glibenclamide nor TEA-induced neutrophil death or any apparent cytotoxic effect.

**Discussion**

In this study we have investigated the involvement of ATP-sensitive potassium channels in the neutrophil chemotactic response using both in vivo and in vitro approaches. Our results show that treatment of rats with the ATP-sensitive potassium channel blocker glibenclamide decreased the exudation and neutrophil influx into the pleural cavity induced by carrageenan, LPS, and fMLP. Conversely, minoxidil, an ATP-sensitive potassium channel opener, increased both the number of neutrophils and the volume of exudate found in the pleural cavity following the injection of carra-
of higher doses on in vivo neutrophil migration. Undesirable toxic effects of higher doses of 4-aminopyridine also appeared in the in vivo experiments. Alternative explanations for the lack of in vivo effect of TEA might be that this compound would be causing potassium channel-independent effects. As mentioned above, the possibility of potassium channel-independent effects shall be taken into account for glibenclamide as well. On the other hand, neither glibenclamide nor minoxidil induced any visible side effects in the animals.

Proinflammatory cytokines have a crucial role in the recruitment and activation of neutrophils (for a review see Dinarello, 1997). However, the possibility that changes in TNF-α production may have been responsible for the observed effects was ruled out since neither glibenclamide nor tetraethylammonium had any effect on TNF-α release by macrophages stimulated in vitro with LPS/IFN-γ. Although our in vivo findings could be explained by an effect of glibenclamide on other cell types (such as epithelial cells) besides the neutrophil, two observations indicate that, at least in its majority, glibenclamide effects indeed occur in the neutrophil. First, glibenclamide did not change TNF-α production (a powerful inducer of chemotaxon production by resident cells) by macrophages thus suggesting that its effects are not attributable to inhibition of cytokine release. Second, fMLP, which is a direct chemotaxin, had its in vivo and in vitro chemotactic effect inhibited by glibenclamide. Also, the described effects could not be attributed to changes in blood neutrophil numbers as neither glibenclamide nor minoxidil changed circulating neutrophil counts. It seems unlikely that changes in blood pressure could explain our results since glibenclamide (at least within the dose range employed here) had no significant effects on blood pressure by the time the inflammatory reaction was induced.

Insulin has been shown to have a potential anti-inflammatory activity, since it inhibits the expression of the proinflammatory adhesion molecule intercellular adhesion molecule-1 by endothelial cells (Aljad et al., 2000) and increases the expression of the mRNA for macrophage migration inhibitory factor (Sakaue et al., 1999). Glibenclamide is widely used as a hypoglycemicant (it increases pancreas insulin secretion; for a review see Ashcroft and Gribble, 1999), which explains the observed reduction in the glycemia of fasted rats. Since glibenclamide-treated animals with free access to food did not show any changes in glycemia, a potential role for blood glucose levels in our findings seems unlikely. However, at least in the in vivo setting, we cannot rule out an effect of insulin (which was released by glibenclamide in both situations) in decreasing neutrophil migration and exudation.

Although diabetes has been associated with a decrease in neutrophil migration toward a chemotactic stimulus (Pereira et al., 1987), Debczynski and Pietruska (1994) reported that the spontaneous migration and chemotaxis of leukocytes from diabetic patients is constitutively increased and that the use of oral hypoglycemics (such as glibenclamide) resulted in a decreased spontaneous migration rate. However, the mechanisms of the increased random migration and of the inhibitory effect of glibenclamide are still unknown. Potassium channels are involved in the regulation of a number of physiological processes and are, thus, a potential target for drug development. Pathological conditions currently treated with potassium channel effectors include diabetes mellitus type II, hypertension, and cardiac arrhythmias. The results
presented herein indicate that ATP-sensitive potassium channels may have an important role in inflammatory neutrophil migration. A better knowledge of the potassium channel involvement in neutrophil functions may thus provide new avenues for the treatment of inflammatory disorders.

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