The ATP-sensitive K+ channel mediates hypotension in endotoxemia and hypoxic lactic acidosis in dog.

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Research Article

Endotoxemia causes hypotension characterized by vasodilation and resistance to vasopressor agents. The molecular mechanisms responsible for these changes are unclear. The ATP-regulated K+ (K+ATP) channel has recently been found to be an important modulator of vascular smooth muscle tone which may transduce local metabolic changes into alterations of vascular flow. We report here that in endotoxic hypotension, the sulfonylurea glyburide, a specific inhibitor for the K+ATP channel, caused vasoconstriction and restoration of blood pressure. Glyburide also induced vasoconstriction and restoration of blood pressure in the vasodilatory hypotension caused by hypoxic lactic acidosis, while it was ineffective in the hypotension induced by sodium nitroprusside. Thus, vasodilation and hypotension in septic shock are, at least in part, due to activation of the K+ATP channel in vascular smooth muscle, and anaerobic metabolism with acidosis is a sufficient stimulus for channel activation. Because anaerobic metabolism and acidosis are common features in shock of any etiology, sulfonylureas may be effective therapeutic agents in the treatment of shock.

The ATP-Sensitive K^+ Channel Mediates Hypotension in Endotoxemia and Hypoxic Lactic Acidosis in Dog

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Abstract

Endotoxemia causes hypotension characterized by vasodilation and resistance to vasopressor agents. The molecular mechanisms responsible for these changes are unclear. The ATP-regulated K^+ (K^+_{ATP}) channel has recently been found to be an important modulator of vascular smooth muscle tone which may transduce local metabolic changes into alterations of vascular flow. We report here that in endotoxic hypotension, the sulfonylurea glyburide, a specific inhibitor for the K^+_{ATP} channel, caused vasoconstriction and restoration of blood pressure. Glyburide also induced vasoconstriction and restoration of blood pressure in the vasodilatory hypotension caused by hypoxic lactic acidosis, while it was ineffective in the hypotension induced by sodium nitroprusside. Thus, vasodilation and hypotension in septic shock are, at least in part, due to activation of the K^+_{ATP} channel in vascular smooth muscle, and anaerobic metabolism with acidosis is a sufficient stimulus for channel activation. Because anaerobic metabolism and acidosis are common features in shock of any etiology, sulfonylureas may be effective therapeutic agents in the treatment of shock. (*J. Clin. Invest.* 1992. 89:2071–2074.) Key words: shock • vascular smooth muscle • sulfonylurea

Introduction

Septic shock, a response to bacterial products such as endotoxin, is a syndrome of cardiovascular collapse and multiple organ failure (1). The hallmark of septic shock is severe hypotension due to vasodilation and reduced systemic vascular resistance (2, 3). The hypotension of sepsis is partially mediated by endothelium-derived relaxing factor (4, 5) which is released by tumor necrosis factor (5). Although inhibitors of these (4–7) and other (8, 9) agents have potential value in the treatment of septic shock, it remains a frequently fatal disorder (1). Recently, the ATP-sensitive potassium channel (K^+_{ATP} channel) has been identified as an important modulator of arterial vascular smooth muscle tone (10). Opening of this channel hyperpolarizes vascular smooth muscle and reduces Ca^{2+} entry through voltage-gated Ca^{2+} channels, thereby inducing relaxation. The K^+_{ATP} channel is activated by decreased intracellular ATP (11, 12) by cytosolic acidosis (13, 14), and increased cytosolic lactate (15) conditions that may present in septic shock, which is characterized by inadequate tissue oxygenation (16, 17), anaerobic metabolism, and lactic acidosis (18, 19). Thus, we examined the role of K^+_{ATP} channel activation in the hypotension of sepsis by means of an animal model (4) for septic shock. In an effort to define sufficient stimuli for this activation, we also examined the role of the K^+_{ATP} channel in the vasodilatory shock of hypoxic lactic acidosis and in the hypotension induced by sodium nitroprusside.

Methods

Experimental preparation. The experiments were performed on 15 male mongrel dogs, 3 yr old and weighing 19±2 kg (mean±SEM), which were fed a normal chow diet. Anesthesia was induced with intravenous pentobarbital (30 mg/kg) and was maintained with periodic administrations. After cannulation of the trachea, the dogs were mechanically ventilated to obtain normal arterial blood pH before experimental manipulations. Through a femoral artery, a catheter was introduced into the aorta for arterial blood collections and arterial pressure measurements via a transducer and a polygraph recorder (both from Grass Instruments Co., Quincy, MA). Via the right jugular vein, a Swan-Ganz catheter was placed in the pulmonary artery and cardiac output was measured by the thermodilution technique. Systemic vascular resistance was estimated by dividing mean arterial pressure by cardiac output, and was expressed in arbitrary units.

Endotoxic shock model. Polysaccharide (*Escherichia coli* B:27; Sigma Chemical Co., St. Louis, MO) was administered via the intravenous central line at a dose of 40 μg/kg. The dose of endotoxin was repeated after 30 min of initial administration if arterial pressure remained above 90 mmHg. After mean arterial pressure declined to less than 60 mmHg, cardiac output was measured and arterial blood samples were taken for determination of blood gases, pH, lactate, and glucose. Within minutes of these "endotoxin" measurements, glyburide (Sigma Chemical Co.) was administered. Glyburide (1 mg/ml in saline) was administered through a single injection at a dose of 0.15 mg/kg (20, 21). "Glyburide" measurements were made during the peak response after glyburide administration.

Hypoxic lactic acidosis model. Dogs were initially ventilated with 100% O_2, and minute ventilation was adjusted to obtain a normal arterial blood pH. After 15 min, the ventilation gas was changed to 7% O_2/93% N_2 (22). After arterial pressure declined to less than 60 mmHg, cardiac output was measured, and arterial blood samples were drawn to measure blood gases, pH, arterial lactate, and glucose. Within minutes of these "hypoxic" measurements, glyburide was administered intravenously as a bolus at a dose of 0.15 mg/kg body wt. When glipizide (Pfizer, Groton, CT) replaced glyburide in this protocol, its dose was 1.5 mg/kg. Glyburide measurements were made during peak response.

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All results are expressed as mean±SEM. Data were analyzed by paired *t* test. Differences were termed significant if the *t* value exceeded the 5% level.

Results

We induced endotoxic shock in dogs by the intravenous administration of *E. coli* lipopolysaccharide (4). After 30–90 minutes, mean arterial pressure fell by 53% because of decreases in both systemic vascular resistance and cardiac output (Table I). To determine the role of the K^+_{ATP} channel in the decrease in pressure, we next administered the sulfonylurea glyburide. Glyburide is a specific and potent inhibitor of the K^+_{ATP} channel in the pancreatic islet cell, and in skeletal, cardiac, and vascular smooth muscle (23–26). A single intravenous dose of glyburide resulted in a rapid increase in arterial pressure starting within 2 min and reaching a plateau at 6 min (+67%, Table I). An illustrative arterial pressure response from a single dog is shown in Fig. 1 *a*. Arterial pressure remained elevated during 20 min and thereafter declined in some animals. As cardiac output was unchanged by glyburide, the rise in arterial pressure induced by this drug was caused by an increase in systemic vascular resistance (+109%, Table I), most likely the result of systemic vasoconstriction. The increase in arterial pressure was not associated with a significant change in arterial pH, or in concentrations of lactate or glucose. Administration of the same volume of diluent (~ 3 ml) with no glyburide did not increase arterial pressure.

Glyburide had no effect on blood pressure when administered in the absence of endotoxin (not shown), suggesting that vascular K^+_{ATP} channel activity is low in the basal state. Because the vasomotor effects of sulfonylureas do not require the presence of endothelium (27, 28), our results suggest that glyburide increased vascular resistance and blood pressure in endotoxemia by inhibiting the K^+_{ATP} channel of vascular smooth muscle. Needless to add, these experiments do not exclude the possibility that an effect of glyburide on the endothelium could contribute to the vasoconstriction.

The endothelium-derived relaxing factor, nitric oxide (29) or its thiol adduct (30), contributes to the hypotension caused by endotoxin (4) or tumor necrosis factor (5) by activating soluble guanylate cyclase. Moreover, the endothelium-derived relaxing factor hyperpolarizes vascular smooth muscle from many vascular segments (31), and this effect is partially blocked with glyburide (10). To determine whether activation of the K^+_{ATP} channel in endotoxemia could have been a result of the endothelium-derived relaxing factor, we administered a continuous intravenous infusion of the nitric oxide generator nitroprusside to a dog (32) to obtain a stable mean arterial pressure of 65 mmHg. There was no decrease in arterial pH or increase in lactate concentration during the hypotension. The administration of glyburide at a dose (0.15 mg/kg) which markedly increased arterial pressure in endotoxemia had only a minor effect on pressure (+5 mmHg) during infusion of nitroprusside. This indicates that nitric oxide hypotension does not require activation of the K^+_{ATP} channel and thus suggests that K^+_{ATP} channel activation in endotoxemia is not because of the endothelium-derived relaxing factor. However, vascular beds have been identified in which an endothelium-derived hyperpolarization factor (EDHF)[1] was elicited independently from nitric oxide (33). This raises the possibility that despite the lack of effect of glyburide on sodium nitroprusside hypotension, activation of the K^+_{ATP} channel in sepsis could be endothelium-dependent by an as yet unidentified EDHF. An intriguing possibility is that endotoxin could release this EDHF.

Table I. Effect of Glyburide in Endotoxic Shock

	Baseline	Endotoxin	Glyburide
AP (mmHg)	116±4	54±2‡	90±9‡
CO (liters/min)	3.82±1.02	2.25±0.24	2.10±1.10
SVR	36±11	23±2	48±20‡
pO_2 (mmHg)	86±10	84±19	92±26
pH	7.37±0.01	7.22±0.02*	7.20±0.01
pCO_2 (mmHg)	35±3	38±1	40±1
Lactate (mM)	1.0±0.2	4.1±0.6*	5.3±1.0
Glucose (mM)	5.3±0.5	8.6±3.7	6.6±3.7

AP, arterial pressure; CO, cardiac output; SVR, systemic vascular resistance (expressed in arbitrary units). $n = 4$, except baseline CO and SVR, where $n = 3$. Values are mean±SEM. * $P < 0.01$ and ‡ $P < 0.05$ in comparison to the corresponding value of the previous column.

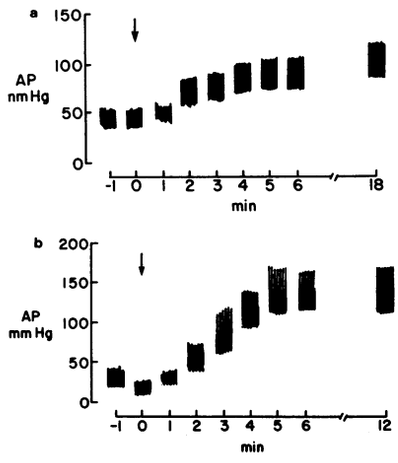

Figure 1. Effect of glyburide on arterial pressure in (*a*) endotoxemia and (*b*) hypoxic lactic acidosis. (*a*) A dog was given polysaccharide (40 μg/kg) intravenously, as described in Methods. When arterial pressure fell to 50 mmHg, glyburide (0.15 mg/kg) was administered intravenously at the arrow. (*b*) A dog was ventilated with a 7% O_2/93% N_2 gas mixture to induce hypoxic lactic acidosis. When blood pressure fell to 20 mmHg, glyburide (0.15 mg/kg) was given intravenously at the arrow. Pressure tracings are from 6-s intervals at the times indicated.

Probably because of inadequate tissue oxygenation (16, 17), endotoxemia increased anaerobic metabolism and caused lactic acidosis (see Table I). Although extracellular pH fell only 0.15 pH units, cytoplasmic pH should have been lower. Thus, a decrease in ATP (11, 12) and/or cytoplasmic acidosis (13, 14) and as an increase cell lactate (15) could have activated the vascular smooth muscle K^+_{ATP} channel, causing vasorelaxation and hypotension. To determine whether anaerobic metabolism and acidosis can activate the K^+_{ATP} channel independently from other actions of lipopolysaccharide, we investigated the effect of K^+_{ATP} channel inhibitors on the shock of hypoxic lactic acidosis.

Dogs were ventilated first with 100% O_2 with a minute ventilation to obtain normal arterial blood pH. After a control period, the ventilation gas mixture was changed to 93% N_2/7% O_2 (22), which resulted in marked hypoxia (Table II). After 30–90 min of hypoxia, the animals developed lactic acidosis and hypotension which were of similar magnitude to those observed in endotoxemia (Table II). The fall in arterial pressure

1. *Abbreviations used in this paper:* EDHF, endothelium-derived hyperpolarization factor.

Table II. Effect of Glyburide in Hypoxic Lactic Acidosis

	Baseline	Hypoxia	Glyburide
	100% O_2	7% O_2/93% N_2	7% O_2/93% N_2
AP (mm Hg)	127±8	54±11*	102±10‡
CO (liters/min)	3.30±0.60	3.78±0.40	4.30±0.42*
SVR	42±5	13±3*	22±3‡
pO_2 (mmHg)	406±58	19±2*	22±2
pH	7.37±0.03	7.21±0.03*	7.16±0.01
pCO_2 (mmHg)	37±1.2	37±1.3	38±2.5
Lactate (mM)	1.0±0.2	4.9±2.4‡	6.6±2.5
Glucose (mM)	5.9±0.6	9.6±0.8	12.0±2.3

Abbreviations as in Table I. $n = 6$. Values are mean±SEM. * $P < 0.01$ and ‡ $P < 0.05$ in comparison to the corresponding value of the previous column.

(−57%) was caused by a marked decline in systemic vascular resistance (−69%, Table II).

The subsequent intravenous administration of a single dose of glyburide resulted in a rapid increase in arterial pressure starting within 2 min and reaching a plateau at 5 min. Arterial pressure increased an average of 48 mmHg (+89%, Table II). 15–20 min after glyburide, arterial pressure started to decline towards control. An illustrative arterial pressure response from a single dog is shown in Fig. 1 *b*.

The arterial pressure rise induced by glyburide was caused by an increase in systemic vascular resistance and a smaller increase in cardiac output (+69% and +14%, respectively; Table II). This indicates that hypoxic lactic acidosis induces hypotension largely by activation of the K^+_{ATP} channel in vascular smooth muscle. A similar mechanism was shown to be responsible for the hypoxic dilation of coronary arteries (34). The rise in cardiac output induced by glyburide could be because of the blockade of K^+_{ATP} channels in the venous capacitance vessels, thus increasing cardiac return.

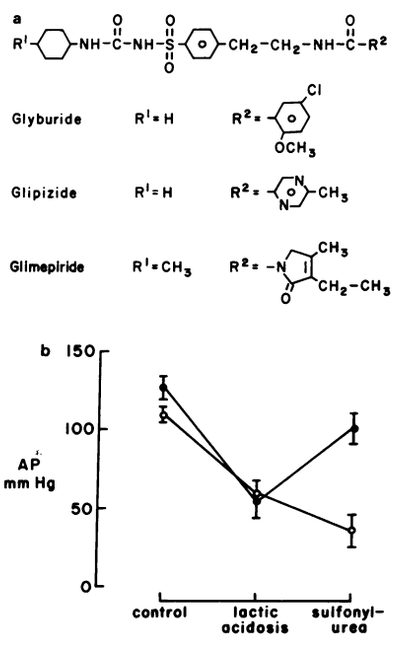

Figure 2. (*a*) Structures of hypoglycemic sulfonylureas. (*b*) Effect of glyburide and glimepiride on arterial pressure (AP) during hypotensive hypoxic lactic acidosis. Effect of an intravenous dose of glyburide (0.15 mg/kg) or glimepiride (0.15 mg/kg) on mean arterial pressure (AP) during hypotensive hypoxic lactic acidosis. Data from the dogs receiving glyburide are those shown in Table II. Experiments in which glimepiride was administered were identical to those in which glyburide was used. Values are mean±SEM. Glimepiride (*open circles*) $n = 4$; glyburide (*closed circles*), $n = 6$.

In order to exclude an idiosyncratic action by glyburide, we examined the effect of two other hypoglycemic sulfonylureas, glipizide (23) and glimepiride (35), on the hypotension of hypoxic lactic acidosis. Each drug was given at a dose equivalent to that of glyburide on the basis of the relative potency against pancreatic islet cell K^+_{ATP} channels (23, 35). Glipizide increased arterial pressure and systemic vascular resistance (not shown) in a manner similar to that of glyburide, its close structural congener (Fig. 2 *a*). However, the structurally dissimilar glimepiride showed little effect on arterial pressure (Fig. 2 *b*). In an animal without a pressure response to glimepiride, subsequent treatment with glyburide increased arterial pressure and vascular resistance. A threefold higher dose of glimepiride did increase arterial pressure by 5 mmHg. Because glimepiride is nearly equipotent with glyburide in its hypoglycemic action in dogs (35), these results suggest that the side chain modifications in glimepiride have disproportionately reduced its affinity for the vascular smooth muscle isoform of the K^+_{ATP} channel. Pharmacologically distinct forms of the channel have been demonstrated in pancreatic islet cell, cardiac myocyte, and a variety of vascular beds (36, 37).

Discussion

These results indicate that the hypotension and fall in peripheral vascular resistance of septic shock are, at least in great part, due to activation of the K^+_{ATP} channel in vascular smooth muscle. Moreover, while endotoxic shock has a myriad of mediators (1, 4, 7, 8) which could activate the K^+_{ATP} channel, our results suggest that anaerobic metabolism and lactic acidosis are sufficient stimuli for channel activation.

It is of interest that inadequate tissue oxygenation with anaerobic metabolism and lactic acidosis are features common to shock of any etiology (18), and it appears likely that activation of K^+_{ATP} channels is a general mechanism involved in the hypotension of shock. For example, severe hypovolemia is initially associated with systemic vasoconstriction, but as tissue hypoxia persists, lactic acidosis develops and systemic vascular resistance falls (38, 39), suggesting activation of the K^+_{ATP} channel. Similarly, lactic acidosis frequently complicates cardiogenic shock (40, 41), a condition in which despite a low cardiac output, vascular resistance is often times not increased (41). Activation of the channel could also account for the frequently observed poor vasopressor response to catecholamines seen in advanced shock (42), since hyperpolarization of vascular smooth muscle prevents the effect of catecholamines to facilitate Ca^{2+} entry into the cell (43). Septic shock alone is the leading cause of death in intensive care units, and intractable hypotension frequently leads to death (1). The finding that the K^+_{ATP} channel of vascular smooth muscle contributes to the hypotension of endotoxemia and of hypoxic lactic acidosis suggests that sulfonylurea blockers of this channel constitute a class of agents with potential therapeutic value in shock.

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