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JA SYMPOSIUM

Functional roles of ATP-sensitive potassium channel as related to anesthesia

Takashi Kawano

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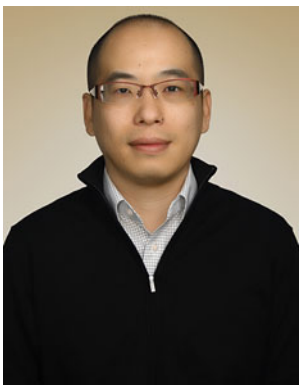

T. Kawano

Adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels are regulated by intracellular ATP and are, therefore, considered to link cellular metabolism with membrane excitability [1–3]. Functional K_{ATP} channels are widely distributed in metabolically active tissues, such as pancreas, brain, peripheral nervous system, and cardiovascular system. Recent electrophysiological and molecular genetic studies of K_{ATP} channels have provided insights into the roles of these channels in physiological and pathophysiological processes, such as insulin secretion, cell protection, vasodilation, and neuropathic pain [1, 3, 4]. K_{ATP} channels are the target for many pharmacological agents, including sulfonylureas and a group of structurally unrelated K^+-channel openers [5]. In addition, studies now suggest that volatile and intravenously administered anesthetics may influence K_{ATP}-channel activity in an anesthetic-dependent manner [6]. Therefore, a great deal of interest has focused on the influence of anesthetics on K_{ATP}-channel activities.

T. Kawano (✉)
Department of Anesthesiology and Critical Care Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan
e-mail: takashika@kochi-u.ac.jp

Molecular structure and biophysical properties of K_{ATP} channels

K_{ATP} channels comprise octamers composed of four pore-forming, inward-rectifier (Kir6.x) subunits that coassemble with four regulatory sulfonylurea receptor (SUR) subunits [7]. The Kir6.x subunits belong to the family of inwardly rectifying potassium channels (Kir) and determine the inward rectification, ATP sensitivity, and unitary (single-channel) conductance of the K_{ATP} channel. On the other hand, SUR subunits belong to the ATP-binding-cassette superfamily and confer responsiveness to K_{ATP}-channel openers and sulfonylureas. Coexpression of SUR1 and Kir6.2 results in formation of pancreatic β-cell-type and neuronal-type K_{ATP} channels, whereas that of SUR2A and Kir6.2 and SUR2B and Kir6.1 results in formation of cardiac-type and vascular smooth-muscle-type K_{ATP} channels, respectively [1–3, 7].

Native K_{ATP} channels show tissue-specific responses to K_{ATP}-channel openers and sulfonylureas [3]. Similarly, different types of cloned K_{ATP} channels show different ATP sensitivity and pharmacologic properties (Table 1). Such differences in tissue-specific biophysical properties of K_{ATP} channels are attributable to the different molecular compositions of the Kir6.x and SUR subunits [3, 7].

Pancreatic K_{ATP} channel

The pancreatic K_{ATP} channels play a pivotal role in glucose-stimulated insulin secretion in the following manner:

Table 1 Biophysical properties of adenosine triphosphate potassium (K_{ATP}) channels in pancreas, heart, vascular smooth-muscle cell (VSMC), and neuronal cell

	Pancreas (SUR1/Kir6.2)	Heart (SUR2A/Kir6.2)	VSMC (SUR2B/Kir6.1)	Neuronal cell (SUR2B/Kir6.1)
Activation by ATP free	(+ + +)	(+ + +)	(+ ~ 0)	(+ + +)
Sulfonylurea				
Glibenclamide	(− − −)	(−)	(− −)	(− − −)
Tolbutamide	(− − −)	(− ~ 0)	(− ~ 0)	(− − −)
K_{ATP}-channel opener				
Diazoxide	(+ + +)	(0)	(+ + +)	(+ + +)
Pinacidil	(+)	(+ + +)	(+ + +)	(+)
Nicorandil	(0)	(+)	(+++)	(+)

SUR sulfonylurea receptor, *Kir6.2, Kir6.1* pore-forming, inward-rectifier subunits

(+), activation; (0), no effect; (−), inhibition

glucose-induced closure of K_{ATP} channels causes depolarization of β-cell membrane, which, in turn, triggers the opening of voltage-gated calcium (Ca^{2+}) channels, thereby inducing Ca^{2+}-influx and stimulating insulin exocytosis [1]. Sulfonylureas (glibenclamide, tolbutamide, glyburide, etc.), induce closure of K_{ATP} channels and stimulate insulin secretion and are widely prescribed for treating type 2 diabetes [1]. Volatile anesthetics can impair insulin secretion and glucose utilization; however, the underlying mechanism remains unclear [8, 9]. In a study performed in rats, Zuurbier et al. [10] reported that glibenclamide administration prevented isoflurane-induced hyperglycemia and restored insulin secretion. Furthermore, using an in vivo rabbit model, we demonstrated that inhalation of 1.0 minimum alveolar concentration (MAC) isoflurane inhibits glibenclamide-induced insulin secretion during the late phase of an intravenously administered glucose tolerance test (IVGTT) [11]. Furthermore, patch-clamp experiments showed that isoflurane significantly decreases ATP sensitivity of pancreatic K_{ATP} channels in the presence of 10 mM glucose, resulting in the opening of these channels in pancreatic β cells [12]. These results indicate that the isoflurane-induced inhibition of insulin secretion from pancreatic β cells is mediated by isoflurane-induced activation of K_{ATP} channels in these cells.

In contrast, propofol, an intravenously administered anesthetic, did not affect glucose-induced insulin secretion from isolated rat pancreatic islet cells; similar results were also observed in an in vivo IVGTT study [12]. The frequently used combination of propofol and opioids also does not impair glucose homeostasis in rats [10]. Clinically relevant concentrations of propofol had no effect on pancreatic K_{ATP}-channel activity in different patch-clamp configurations [12]. Therefore, the different effects of isoflurane and propofol on insulin release may be caused by the difference in K_{ATP}-channel sensitivity in pancreatic β cells.

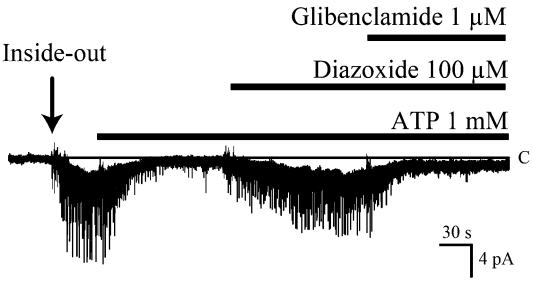

Fig. 1 Representative example of the adenosine triphosphate potassium (K_{ATP}) currents from isolated rat ventricular myocytes in inside-out patch clamp configuration. Membrane potential was clamped at −50 mV. Upon excising patches into an ATP-free solution, channels developed marked activation that was inhibited by 1 mM ATP. The periods of drug treatment are marked with *horizontal bars*. *C* closed state

Cardiac K_{ATP} channel (sarcolemmal channel)

Under normal physiological conditions, sarcolemmal K_{ATP} channels in cardiomyocytes usually exist in a closed state. However, during metabolic stress conditions such as ischemia or hypoxia, the channels become active [6]. In addition, these channels are activated by K_{ATP}-channel openers (Fig. 1). The opening of K_{ATP} channels results in an enhanced outward repolarizing flow of K^+ ions and cell-membrane hyperpolarization. Consequently, the action potential duration is shortened, and the voltage-dependent Ca^{2+} current and contractility are decreased, thereby leading to energy sparing. Thus, K_{ATP}-channel activation is considered to exert a protective effect during myocardial ischemia [6].

Interestingly, numerous animal experiments have shown that preischemic exposure to volatile anesthetics attenuates the deleterious effects of myocardial ischemia and reperfusion injury [13]. Furthermore, several clinical observations have revealed that inhalation of volatile anesthetics improves ischemic outcomes [14, 15]. These properties

have been attributed to anesthetic preconditioning; although the precise mechanisms underlying activation of cardiac sarcolemmal K_{ATP} channels remain unclear, several studies suggest it may contribute to anesthetic preconditioning [6, 13]. Electrophysiological experiments have shown that isoflurane may activate K_{ATP} channels at a moderately acidic intracellular pH of 6.8 [16] or facilitate the opening of channels via the activation of protein kinase C [17]. In contrast, our previous patch-clamp experiments indicated that high supraclinical concentrations of propofol directly inhibited the cardiac K_{ATP}-channel activity [18, 19]. Ketamine also inhibits recombinant cardiac K_{ATP}-channel activity in a concentration-dependent manner [20]. These results indicate that anesthetics given i.v., unlike volatile anesthetics, might impair the endogenous-organ protective mechanisms mediated by K_{ATP} channels.

Vascular K_{ATP} channel

In vascular smooth muscle cells, opening of the K_{ATP} channels leads to membrane hyperpolarization, decreased intracellular Ca^{2+} concentrations, and vasodilatation [2, 3]. Recent physiological studies conducted on mice lacking K_{ATP}-channel subunits further elucidated the roles of vascular K_{ATP} channels [3]. In particular, mice deficient in Kir6.1 and SUR2 showed impaired vascular smooth-muscle function that manifested as episodic coronary artery vasospasm and resulted in high rates of sudden death. Therefore, vascular K_{ATP} channels are critical for vascular tonus regulation, especially in the coronary artery, in response to hypoxia and ischemia. In vivo studies on canines show that vascular K_{ATP}-channel activation is also involved in coronary vasodilatation induced by volatile anesthetics [21]. Furthermore, we reported electrophysiological experiments in rats, which revealed isoflurane-induced K_{ATP}-channel activation via direct phosphorylation of a cyclic adenosine monophosphate (cAMP)-dependent protein kinase (protein kinase A) [22]. These results indicated that isoflurane-induced coronary vasodilatation is mediated by vascular K_{ATP}-channel opening. However, we also reported that both acute hyperglycemia [23] and aging [24] impair the isoflurane-induced vascular K_{ATP}-channel activation, possibly contributing to increased myocardial ischemic injury in patients with perioperative hyperglycemia and/or those of advanced age.

Neuronal K_{ATP} channel

K_{ATP}-channel activation in the brain result in K^+ efflux, leading to membrane hyperpolarization, decreased excitability, attenuation of transmitter release, and protection from cell death [1, 2]. K_{ATP} channels also act as transducers and effectors of neuronal preconditioning. Similar to cardiomyocytes, volatile anesthetics afford neuroprotection against cerebral ischemia via neuronal K_{ATP}-channel activation [25]. In addition to functional K_{ATP} channels in the CNS, we identified these channels in rat primary afferent neurons dissociated from the dorsal root ganglia (DRG) [4, 26–28]. Immunohistochemistry and electrophysiological experiments from cell-free membrane recording indicate that peripheral sensory neuronal K_{ATP} channels are composed of SUR1/Kir6.2 or SUR2/Kir6.2 subunits [27]. Our tests on cell-attached patches further showed that the basal K_{ATP} channel opening in large DRG neurons decreased in hyperalgesic rats but not in the animals that did not develop hyperalgesia following axotomy [4, 27]. This selective reduction of K_{ATP} channel opening suggests that loss of current through these channels contributes to the pathogenesis of neuropathic pain. In addition, peripheral K_{ATP}-channel opening partly contributes to the analgesic effects mediated by morphine [29]. Thus, K_{ATP} channels in the primary afferent neurons warrant further investigation as putative therapeutic targets in peripheral neuropathic pain treatment.

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