Iptakalim: A novel multi-utility potassium channel opener

Pranav Sikka, Seema Kapoor[1], V. K. Bindra[2], Manish Saini, K. K. Saxena

Department of Pharmacology, LLRM Medical College, Meerut,[1]Departments of Oral Pathology and Microbiology, ITS –CDSR, Murad Nagar, Ghaziabad,[2]Department of Medicine, IDST, Meerut, Uttar Pradesh, India

Hypertension is a multifactorial disorder, and effective blood pressure control is not achieved in most individuals. According to the most recent report of the American Heart Association, for 2010, the estimated direct and indirect financial burden for managing hypertension is estimated to be $76.6 billion. Overall, almost 75% of adults with cardiovascular diseases/ comorbidities have hypertension, which is associated with a shorter overall life expectancy.[1] Alarmingly, rates of prehypertension and hypertension are increasing among children and adolescents due, in part, to the obesity epidemic we currently face. There is also the problem of an aging population and the growing rates of diabetes and obesity in adults, all factors that are associated with high blood pressure.[2] Thus, the need is great for novel drugs that target the various contributing causes of hypertension and the processes leading to end organ damage.

Iptakalim (IPT), chemically 2, 3–dimethyl-N-(1-methylethyl)-2-butanamine hydrochloride, is novel adenosine triphosphate–sensitive potassium (K_{ATP}) channel opener. K_{ATP} channels are composed of discrete pore-forming inward rectifier subunits (Kir6.1s) and regulatory sulphonylurea subunits (SUR).[3] IPT shows high selectivity for cardiac K_{ATP} (SUR2A/Kir6.2) and vascular K_{ATP} (SUR2B/Kir6.1 or SUR6B/Kir6.2). Because of this high selectivity, IPT does not exhibit the adverse side effects associated with the older nonspecific K^+ channel openers, which limit their use to the treatment of severe or refractory hypertension. IPT produces arteriolar and small artery vasodilatation, with no significant effect on capacitance vessels or large arteries. Vasodilatation is induced by causing cellular hyperpolarization via the opening of K^+ channels, which in turn decreases the opening probability of L-type Ca^{2+} channels. Of particular note, IPT is very effective in lowering the blood pressure of hypertensive humans but not of those with normal blood pressure.[4]

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Endothelin-1 (ET-1) is a potent vasoconstrictor and comitogen/proliferation factor for vascular smooth muscle. Wang *et al*. (2005) have shown that IPT reduces ET-1–induced arterial contraction and decreases ET-induced hypertension in rats.[5] They hypothesized that activation of endothelial K_{ATP} channels might result in protection against endothelial dysfunction. The mechanism behind endothelial dysfunction, an early risk factor for cardiovascular disease and hypertension, includes reduced nitric oxide (NO) generation and increased ET-1 generation. Wang *et al*. (2007) first reported that the K_{ATP} channel opener, IPT, promotes NO synthase (NOS) activity and NO release; inhibits ET-1 synthesis, and suppresses ET-1 and endothelin converting enzyme (ECE) mRNA expression.[6] Also, Zhao and Wang (2011) have suggested that IPT, via opening K_{ATP} channels, enhances the endothelial chemerin/ChemR23 axis and NO production and thus improves endothelial function.[7]

Gao *et al*. (2009) showed that IPT possesses antihypertrophic properties, preventing the progression of left ventricular hypertrophy (LVH) to heart failure induced by pressure overload. Additionally, IPT reduces myocardial and perivascular fibrosis as well as mRNA expression of two important molecular markers of heart failure, viz, atrial natriuretic peptide and B-type natriuretic peptide. The results

Address for correspondence: Pranav Sikka, Department of Pharamacology, LLRM Medical College, Meerut, Uttar Pradesh, India.
E-mail: drpranavsikka@yahoo.com

suggest that IPT's effects on hypertrophy induced by pressure overload occurs through maintenance of the balance between the NO and endothelin signaling systems.[8]

Changes in K^+ channel function may represent a universal mechanism by which Ca^{2+} signals are targeted toward the activation of gene expression and cell growth.[9] Furthermore, activation of K^+ channels can induce apoptosis in vascular smooth muscle cells (SMCs) in proliferative conditions of vessels.[10] Thus, K_{ATP} channels can be potential targets to regulate proliferative vascular disorders in diseases such as pulmonary hypertension.[11] Pan *et al*. (2010) and Zhu *et al*. (2008) have shown that IPT inhibits the ET-1-induced proliferation of human pulmonary arterial smooth muscle cells (PASMCs).[4,12]

A study in the spontaneous hypertensive rat (SHR) model by Xue *et al*. (2005) indicated that IPT not only effectively reduces blood pressure but also ameliorates the pathological changes in the glomerular filtration membrane and the glomerular and renal interstitia, reverses renal arteriolar remodeling, decreases proteinuria, and improves renal function. Furthermore, long-term antihypertensive therapy with IPT decreases the circulating and intrarenal concentrations of ET-1 and transforming growth factor (TGF)-β1; downregulates the elevated expression of ET-1, ECE-1, and TGF-β1 mRNA; and corrects the matrix metalloproteinase-9 (MMP-9)/MMP tissue inhibitor-1 (TIMP-1) imbalance; all of which is evidence of the renoprotective effect of IPT.[13] IPT is also a potential alternative antihypertensive in cases where angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists are either ineffective or contraindicated.

Because the K_{ATP} channels are widely distributed throughout the mammalian brain[14,15] and are found in the neural circuits that are implicated in the pathophysiology of schizophrenia, IPT might broadly impact brain functions by opening these K_{ATP} channels and modulating glutamate and dopamine release when the brain is under stress. Sun and colleagues (2009) who are the pioneers in exploring the antipsychotic activity of IPT, found that the drug is effective in reducing both amphetamine- and phencyclidine-induced locomotor activity, as well as in suppressing avoidance responding, a behavioral profile shared with all currently used antipsychotics.[16,17] Neuroanatomically, IPT also exhibits an antipsychotic profile. It dose-dependently increases c-Fos expression in the nucleus accumbens, medial prefrontal cortex, and lateral septal nucleus, but not in the dorsolateral striatum. All these findings are consistent with the behavioral and molecular profiles of antipsychotics. IPT, by opening K_{ATP} channels located on the ventral tegmental area (VTA) dopamine neurons, inhibits dopamine and glutamate release[18,19] and attenuates the behavioral and c-Fos expression effects induced by amphetamine, phencyclidine, or conditioned stimulus. Hence, it can be concluded that IPT is a potential antipsychotic drug, with distinct mechanisms of action.[20]

Tests in a variety of *in vivo* and *in vitro* ischemia and Parkinson disease models indicate that IPT also has neuroprotective effects.[21–24] Furthermore, IPT has potential in the prevention of drug addiction because it inhibits cocaine challenge–induced enhancement of dopamine release in the rat nucleus accumbens.[25]

Although, IPT opens up new avenues in medicine, large randomized controlled trials are required to establish its efficacy.

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