ION CHANNELS AND DRUG DEVELOPMENT
FOCUS ON POTASSIUM CHANNELS AND THEIR MODULATORS

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Summary. *Ion channel modulation has recently become an attractive target for experimental and clinical research in a never ending quest for drug development. Following the decades of domination of calcium channel blockers, currently the focus is on potassium channels and their modulators; this is one of the most rapidly developing field of research. Because potassium channels have an important role in maintaining the membrane potential in all tissues and in shaping the action potential in the heart, potassium channel modulators are expected to provide better therapies primarily in cardiology (acute coronary syndromes, arrhythmias) but also in other branches of medicine.*

Key words: *K^+ channels, K^+ channel blockers, K^+ channel openers, therapeutic potential*

Introduction

Basic physiological regulatory functions of neuro-transmitters and hormones are believed to be mediated by receptors. Receptor concept has been used over the last 80 years since the work od Ehrlich and Langley, appeared to be very fruitful in drug development, and may be regarded as a mainstay of modern pharmacotherapy. However, receptors do not function independently but directly or indirectly modulate certain ion channels.

The ubiquitous presence of ion channels also suggests their importance in maintaining cellular integrity and function. Ion channels as a biological mechanism exploit ionic gradients between the cytosolic side and the extracellular space to transfer essential ions such as Na^+, K^+, Ca^{++} and Cl^- from one to the other side of excitable membranes and maintain vital cellular processes. Our understanding of the part they play in health and disease has been growing since 1952 and the work of Hodgkin and Huxley who studied ion channels in giant squid axons and provided the basis of the current knowledge of voltage-gated ion channels (1).

Abnormalities of ion channels are believed to be implicated in the pathogenesis of a number of diseases. Hyperkalemic periodic paralysis arisis from a defective voltage activated sodium channel in skeletal muscle, some forme of erectile dysfunction seem to be due to abnormalities of calcium dependent potassium channels in the cavernous smooth muscle cells, cystic fibrosis arises from a genetic abnormalities in chloride ion function, in diabetes mellitus a disfunction of ATP-dependent potassium channels and their coupling to opening of the voltage sensitive calcium channels, and recently evidence has begun to emerge of the role of ion channels in many aspects of cell biology including cell cycle, apoptosis and cancer development (2).

Ion channels are usually classified by the principal ion they carry (sodium-Na^+, potassium-K^+, calcium-Ca^{++} or chloride-Cl^-) and the mechanism by which they are opened or closed. Functioning independently or in close association with some receptor types, ion channels have been for a couple of decades attractive targets for pharmacological manipulation and drug development. Na^+ channel blockers: lidocaine, procainamide, disopiramide etc, are used for decades as local anestetics or I class antiarrhythmic agents. Ca^{++} channel blockers: verapamil, diltiazem, nifedipine etc have become during the last 20 years major cardiovascular drugs used in hypertension and ischemic heart disease. Cl^- channel modulators: barbiturates, benzodiazepines, hydantoines etc are used to treat a number of diseases and conditions induced by hyperactivity of the CNS. Finally, during the last decade the focus is on modulation of the K^+ channels. Currently, the therapeutic use of K^+ channel modulators is scarce, mainly as vasodilators and antihypertensive agents, however the fast growing field of research is promising a development of new therapeutic agents for cardiovascular and other diseases.

Potassium channels

Potassium (K^+) channels are the most abundant class of ion channels; at least 16 types and many more subtypes have been described so far (Table 1), and their physiological functions are still far from being fully

understud. However, some of them are well known such as their key role in the maintenance of resting membrane potential and repolarization of the action potential in the heart, smooth muscle and endocrine glands (pancreatic β-cells).

Table 1. Main types and subtypes of potassium channels (3,4,5)

Voltage sensitive
Delayed rectifier - K_V
Inward rectifier - K_{IR}
Transient outward rectifier - K_A
Ligand sensitive
Calcium activated K+ channels
Large conductance channel - BK_{Ca}
Intermediate conductance channel - IK_{Ca}
Small conductance channel - SK_{Ca}
Metabolically gated K+ channels
ATP-sensitive K+ channel - K_{ATP}
Arachidonic acid/fatty acid modulated K+ channel - K_{AA}
Acetylcholine-activated K+ channel - K_{ACh}

Fast growing research in pharmacology of K^+ channels has been made possible by discoveries of numerous specific ligands (apamin, charybdotoxin, dendrotoxin etc) for their activation and block, by introduction of new electrophysiological techniques (voltage clamp, patch clamp), and particularly by the development of recombinant DNA technologies enabling the cloning of many of the known K^+ channels. The most recent classification of K^+ channels from 1996, shown in Table 1, was made according to the main mechanism of activation or opening of the channels. Activation of voltage-sensitive channels is regulated by changes in the membrane potential, and of the ligand-sensitive channels by a number of ligands: calcium ions, ATP, neurotransmitters and G-protein (5,6,7).

Modulation of potassium channels

A number of naturally occurring and synthetic compounds have been identified that modulate opening and closing of ATP-dependent K^+, the family of K^+ channels which has been most thoroughly studied.

Endogenous modulation

ATP-sensitive K^+ channels are regulated by intracellular concentrations of ATP, which has a very high affinity for the channel. At high ATP levels the channel is closed and when the concentrations becomes lower the channel opens. Therefore, a low ATP concentration, e.g. during ischemia, will lead to hyperpolarization and the cell becomes less excitable, whereas higher ATP concentrations will cause the closing of the channel with subsequent depolarization. Thus, these channels link membrane potential to the bioenergetic situation of the cell (8). It is important to recall that the K^+ gradient in excitable cells is opposite to that of Ca^{++}, since the cytosolic K^+ concentration is high (150 mM), and the extracellular is low (4-6 mM). Consequently, selective opening of K^+ channeles leads

to loss of intracellular positive charges which, in turn, is followed by cellular hyperpolarization and a fall of cytosolic Ca^{++} concentration. These changes will reduce cellular contractility at the myocardial and vascular level (9).

Adenosine is also an endogenous modulator acting via A_1 receptors in the heart and via A_2 receptors in the coronary arteries to open K_{ATP} channels. Other endogenous ligands, such as NO, EDHF (endothelium derived hyperpolarizing factor), VIP (vasoactive intestinal peptide), prostacyclin and CGRP (calcitonin gene related peptide) have been also shown to relax vascular smooth muscle by opening K^+ channels (10).

Exogenous modulation

Potassium channels function could be modulated by a number of naturally occurring or synthetic substances which block or open the channels and therefore have unequivocal therapeutic potential.

Blocking agents

K^+ channel blocking agents belong to chemically quite different classes: from inorganic cations, quaternary ammonium compounds, aminopyridines, sulfonylurea derivatives, class III antiarrhythmic drugs and naturally occurring toxins, as shown in Table 2.

Inorganic cations, aminopyridines, quaternary ammonium compounds and the toxins are used predominantly as experimental agents. Their potency and specificity is very variable.

Quaternary ammonium compounds are most widely used potassium channel blockers, however they are nonselective and block voltage-dependent as well as ligand-dependent channels.

Aminopyridines are more selective and more potent then the quaternary ammonium compounds, preferentially blocking voltage-dependent K^+ in different tissues, and to a certain degree they bloock K_{ATP} channels. The result is a proconvulsant action on the skeletal muscle, increase in the resting tension and contractility in the vascular and non-vascular smooth muscle, and increased neurotransmitter release from the sympathetic neurons (9,10).

Naturally occurring toxins are derived from exotic plants, scorpion and snake venoms. They are more selective, and therefore very useful experimental agents for identification of various subtypes of K^+ channels.

Apamin - a peptide derived from the venom of European honey bee, is probably the most selective of all K^+ channel blockers, particularly for the SK_{Ca} (Ca^{++}-activated K^+ channels).

Charybdotoxin - derived from the venom of an Israeli scorpion - is commonly regarded as a selective blockers of BK_{Ca}.

Leiurotoxin - derived from the same venom - has an apamine-like activity.

Noxiustoxin is also derived from a scorpion venom, and has a charybdotoxin-like activity.

Dendrotoxin - derived from the green mamba snake - is a neurotoxin and central convulsant selective for

voltage-dependent channels (K_V).

Table 2. Potassium channel modulators （7）

Blocking agents	Openers
Aminopyridines	*Drugs*
4-aminopyridine, 3,4	Diazoxide
diaminopyridine	Minoxidil
Inorganic cations	Cromakalim
Li, Cs, Ba, Hg i Zn	Levcromakalim
	Bimakalim
Quaterary ammonium	Pinacidl
compounds	Aprikalim
tetraethylammonium-TEA	Nicorandil
Naturally occurring toxins	
apamin, charybdotoxin,	
noxiustoxin, dendrotoxin,	
iberiotoxin, leiurotoxin,	
conotoxin,	
strychnin, falloidin, capsaicin	
etc.	
Sufonyl urea derivatives	
glibenclamide, tolbutamide	
etc.	
Class III antiarrhythic drugs	*Endogenous ligands*
amiodaron, brethylium,	ATP, adenosine, prostacyclin,
bethanidine, clofilium, sotalol,	somatostatin,
ibutilide, dofetilide etc.	VIP, CGRP, EDHF, NO

Conotoxin - derived from a marine snail venom - is also selective for K_V.

Strychnine - an alkaloid derived from a Brasilian plant - a central convulsant blocks primarily K_V, and in addition the Na^+ channels. Its action on the vascular smooth muscle is more complex, a mixture of K^+ channel blocking and opening effects.

Phalloidine - an alkalioid from a death-cap mushroom - is one of the most potent blockers of K_V so far described.

Capsaicin - the active component of hot peppers - blocks K_V in sensory neurons but its action is nonselective, since the Na^+ and Ca^{++} channels are blocked by the same or even lower concentration of capsaicin. Therefore, it is unlikely that K^+ channel blockade is of primary importance for the excitation and subsequent desensitization of nociceptive fibres by capsaicin (9).

Sulphonylurea derivatives (glibenclamide and others) are very selective blockers of the K_{ATP} in the pancreatic β-cells, and also in the myocardium. They reduce the K^+ permeability in these cells, depolarize the membrane and allow an increase Ca^{++} entry and insulin secretion. In the heart, glibenclamide might be effective in supressing ischemia-induced arrhythmias.

Class III antiarrhythmic drugs: sotalol, amiodarone, clofillium etc are known to prolong the duration of action potential by retarding repolarization due to the block of K_V and outward K^+ current activated during the plateau phase of the action potential. However, in addition to blocking K^+ channels, most of them also block beta receptors (sotalol) or the other types of ion channels and adrenoceptors (amiodaron).

D-Sotalol was the first of the "pure" K^+ channel blockers used in a clinical outcome trial, planned to prolong survival in postinfarction patents with arrhythmias and heart failure. However, the international study SWORD (Survival With Oral d-Sotalol) was prematurely terminated due to the excess in mortality in patients treated with d-sotalol as compared to placebo (11). It was a serious blow to the concept of the "pure" K^+ channel blockers as successful drugs for ventricular arrhythmias in high risk patients.

Newer class III antiarrhythmics are in many cases more potent structural analogues of the above prototype compounds, which have been shown to increase action potential duration by blocking K^+ channels. A number of them is in various phases of clinical investigation planned to reduce incidence of the sudden cardiac death and improve survival.

Theoretically, alterations in ventricular repolarization during myocardial ischemia may lead to ventricular fibrillation and sudden cardiac death. The delayed rectifying current I_K (largely responsible for repolarization) consists of two components: I_{Ks}, a slowly activating current that is enhanced by sympathetic hyperactivity and I_{Kr}, a rapidly activating current insensitive to sympathetic stimulation. Since sympathetic stimulation increases the propensity for ventricular fibrillation, drugs that selectively block I_{Ks} may be more effective in preventing these arrhythmias.

The agents under investigation were found to affect the I_K differently: some of them the rapid component, the slow component or both (12,13).

Ibutilide is already approved for intravenous use in patients with atrial fibrillation. It should be mentioned here that ibutilide has a unique dual blocking properties, affecting both Na^+ and K^+ channels; in the later in primarily blocks the I_{Kr}.

Dofetilide selectively blocks K^+ channels and the I_{Kr} component of the repolarizing current. It has been found effective in a broad range of tachyarrhythmias when used intravenously for rapid termination of atrial fibrillation and flutter, or orally in maintaining normal synus rhythm in patients with atrial fibrillation and flutter. In the study known by acronym DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide), in patient with myocardial infarction and congestive heart failure, treatment with dofetilide was neutral with respect to all cause mortality compared to placebo, but was effective in converting patients with atrial fibrillation to synus rhythm and safely maintained synus rhythm in 75 % of patients during 1 year.

Ambasilide and azimilide are nonselective blockers of the I_K, and were shown to block both I_{Kr} and I_{Ks}, and they are expected to be more effective than dofesilide in preventing sudden cardiac death; the results of clinical trials which are under way are awaited with great expectations. Successful completion of such trials would provide a decisive support to the present antiarrhythmic strategy in prevention of sudden death.

Chromanol 293B is a highly selective blocker of the

I_{Ks} in human and guinea-pig ventricles able to block the dofetilide-insensitive part of the repolarizing current. It is currently a valuable tool for assesing the potential of I_{Ks} blocker to treat arrhythmias [Reported on 13th European Congress of Cardiology, Vienna 1998].

A disadvantage of the use of class III antiarrhythmic agents is that prolongation of cardiac repolarization can have proarrhythmic effects including the induction of potentially fatal polymorphic ventricular tachycardia, mostly torsade de pointes in association with QT-prolongation. The concerns whether the antiarrhythmic drugs can survive survival trials? are based on negative experience with a number of clinical trials including the SWORD with d-sotalol, and sound quite realistic (14).

Potassium channel openers - PCOs

Potassium channel opening has become a new drug principle in cardiovascular medicine offering significant treatment possibilities in acute coronary syndromes, cardio-protection, heart failure and hypertension (15). Several old vasodilators (diazoxide, minoxidil, hydralazine) have been shown to owe ther action to opening K^+ channels, and a series of new substances have been developed and approved or included in various phases of preclinical and clinical investigation (Table 2).

Chemical structure

Chemical structures of PCOs varies considerably: diazoxide is a benzothiadiazine derivative, minoxidil is a pyrimidine, cromakalim, levcromakalim, bimakalim are penzopyran derivatives, aprikalim and its active enantiomer are thioformamides, pinacidil and its analog P1705 are cyanoguanidines, whereas nicorandil is a complex compound containing a nitrate moiety.

The first drug recognized as a PCO was nicorandil in 1984, but later it became evident that nicorandil is a hybrid molecule acting as a PCO and a nitrate-like compound.

Cromakalim was the first PCO developed as a specific synthetic PCO and its mechanism of action was reported in 1986. It is a mixture of enantiomers, with biological activity residing in the (-)-3S,4R form, which is known by the generic name levcromakalim; other enantiomers are much less potent.

Mechanism of action

Although chemically very much different, the PCOs share a common site and mechanism of action: they open the K_{ATP} in pancreatic, cardiovascular and other tissues. Glibenclamide is commonly used experimentally as a very selective antagonist of K_{ATP} to detect actions of drugs or endogenous ligands which involve K_{ATP} opening. Concentrations of glibenclamide in nM range are sufficient to block the pancreatic K_{ATP} channels whereas µM concentrations are required to block cardiovascular K_{ATP} channels. Generally, K^+ channels in the vascular and non-vascular smooth muscle are 10-100 times more sensitive to PCOs than those in the heart (16). Therefore, K_{ATP} is not a single

distinct type of channel but rather a family of several K_{ATP} subtypes with important tissue-dependent diferences in sensitivity to pharmacologic modulation.
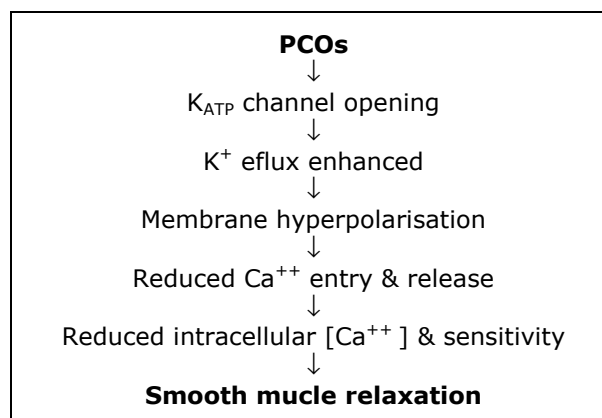

Fig. 1. Sequence of events involved in smooth muscle relaxation induced by potassium channel opening. (Adapted from ref. 15).

Pharmacodynamic profile

Vascular smooth muscle relaxation

The PCOs are potent arterial vasodilators in various vascular beds: systemic as well as pulmonary or coronary circulation. Smooth muscle relaxation results from a common sequence of events, as shown in Fig 1. Vasorelaxant effects of PCOs was shown in a number of laboratories including ours (9,10, 17, 18, 19, 20, 21, 22). These drugs have been shown to relax contractions of various arteries: aorta, coronary, pulmonary, renal, mesenteric, uterine and others including the human internal mammary artery, induced by moderately raised extracellular K^+ concentrations (20-30 mM) and by a series of agonists. However, the PCOs did not influence contractions induced by high (40-120 mM K^+). Glibenclamide in low µM concentrations has been found to competitively antagonize their effects. The effects of cromakalim and levcromakalim have been shown to entirely depend on the opening of K_{ATP} channels, whereas the effects pinacidil appeared to be more complex, and to include another component resembling calcium antagonists.

Coronary vasodilation has been shown in the presence of PCOs in vitro and in vivo. In some hemodynamic studies coronary vasodilation was preferential, produced in doses having no effect on the blood pressure. Cromakalim, pinacidil and nicorandil dilate large epicardial arteries as well as small coronary resistance arteries in vivo. The effect of cromakalim and pinacidil in vivo was shown to be partly endothelium-dependent, whereas the effect of nicorandil has included an additional nitrate component (15).

Hemodynamic studies in animals and humans have shown that PCOs decrease blood pressure in a dose-dependent manner in normotensives and hypertensives. Heart rate was usualy unaffected or slightly increased in

anesthetized animals but markedly increased in conscious rats with normal operating autonomic nervous system.

Regional blood flow in cerebral, renal, mesenteric and skeletal musle vascular beds was much less affected than in the coronary circulation. Despite their potent coronary vasodilator effect, the PCOs have not been found to produce coronary steel in contrast to calcium antagonists. Thus, the regional blood flow profile is quantitatively and qualitatively different from that of the calcium antagonists (which are potent coronary, cerebral and skeletal muscle vasodilators) and ACE inhibitors (which preferentially dilate the renal and skeletal muscle beds) (23).

Relaxation of non-vascular smooth muscle

Currently, the focus in research in this area is on vascular smoth muscle and the heart, however there are numerous reports of the general smooth muscle relaxing action od the PCOs on any smooth muscle tested: bronchial, intestinal, urinary bladder, uterus etc (3).

Anti-ischemic effect on the heart - Preconditioning

Since the original work of Murry and colleagues in 1986 in which they showed dog hearts protection by preceding short cycles of sublethal ischemia and intermittent reperfusion (24), ischaemic preconditioning has been demonstrated in every animal tested and has become recognized as the most potent and reproducible mode of cardioprotection known to date. A preconditioned heart when exposed to a prolonged and potentially lethal ischaemic stress followed by reperfusion, has a markedly reduced infarct size, reduced ultrastructural damage, higher ATP reserves, beter functional recovery and fewer arrhythmic events (25).

Numerous animal experiments with: pinacidil, cromakalim, bimakalim, nicorandil etc, have demonstrated their immitating effects of physiological preconditioning and they are expected to act synergistically in preservation of myocardial energy and reduce the tissue damage (26,27). Whether their effects are direct (on the myocardium) or indirect (on vasculature) remains to be detected. Cardioprotection appears to be the final step in the cascade of events triggereg by the K_{ATP} channel opening, shown in Fig 2. The concept of cardioprotection may gain significance by agents developed in the future, with greater binding to the myocardium and the coronaries, without affecting smooth muscle activity at other sites (28).

Cellular mechanisms underlying this adaptive process have been studied thoroughly during the recent years. Adenosine, bradykinin, opioids and noradrenaline have ben identified as triggers of the preconditioning mechanism, and their substitution for the short ischaemic insult mimics the protection afforded by preconditioning. In contrast, administration of respective antagonists prior to, or simultaneous with, the preconditioning ischaemia abolishes the protective

effects. The triggers activate a cascade of events to finally activate the effector protein. It has been suggested that K_{ATP} channel might be one of the potential candidates for the effector proteins. The evidence supporting a role for K_{ATP} channels comes from studies where the blocking of these channels has abolished the protective effects of preconditioning, while pharmacological activation of these channels mimics this protection (29).
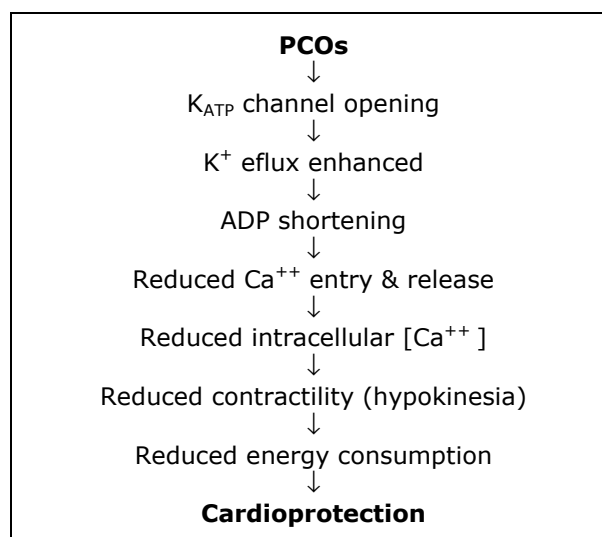
Fig. 2. Sequence of events involved in cardioprotective effects induced by potassium channel opening. ADP = action potential duration.(Adapted from ref. 15).

In humans, cardioprotective effects of preconditioning seems to parallel that found in animals, and important role has been demonstrated for adenosine and K_{ATP} channels. To be effective the preconditioning stimulus must be administered prior to the prolonged, potentially lethal insult. Therefore, patients with unstable angina, due to a high risk of progression to myocardial infarction, form a well defined group who might benefit from pretreatment with agents that trigger or enhance the myocardial preconditioning. Nicorandil is already approved for use in patients with vasospastic and effort angina, and therefore one of the first agents to be tried in unstable angina. Preliminary results are already available, and they show that oral treatment with nicorandil significantly reduce the incidence of arrhythmic events and episodes of transient myocardial ischemia (30). Thefore, the stage is set for development of new agents and their more regular use in selected patients (31).

Electrophysiologic effects on the heart

Most studies in vitro with nicorandil, pinacidil and cromakalim reported a major shortening of the action potential duration. This situation introduces discontinuities in refractoriness between normal and ischemic cardiac tissue, and represents a well known source of reentrant arrhythmias. The effect was antagonized by

sulfonylureas, supporting the involvement of K_{ATP} channels.

In humans, nicorandil was not found to alter the action potential duration or intracardiac conduction, which may be due to the fact that the therapeutic doses in humans are much lower than the concentrations applied in most experiments in vitro. On the other hand, there are very few electrophysiological data reported in studies dealing with the cardioprotection in animals. Therefore, it remains controversial whether PCOs prevent or induce arrhythmias (3).

Therapeutic use and potential

Currently, PCOs are approved only for use in cardiovascular medicine, in hypertension and coronary heart disease. Hypertension is the most important indication for the PCOs since they are so potent arterial vasodilators. However, their status has not been well defined.

Diazoxide has many drawbacks and now has little or no place in the treatment of hypertension; hyperglycemia is the limiting side effect.

Minoxidil is a very potent drug, but its use should be reserved for severe forms of hypertension when other agents fail; its use is hampered by side effects such as cardiotoxicity, reflex sympathetic stimulation requiring concommitant use of beta blockers and diuretics, and by hirsutism.

Hydralazine had a long reputation of a directly acting vasodilator and anti-hypertensive drug, but has been recetly shown to open BK_{Ca} channels. Its use is declining due to the inferior benefit/risk ratio as compared to modern antihypertensives; particularly limiting side effect is the lupus-like syndrome.

Pinacidil has been approved in several European countries, and is most widely used of all "pure" PCOs. It can be used in the treatment of mild to moderate hypertension as monotherapy, but the reflex increases in heart rate favour the coadministration of a beta blocker. Pinacidil was shown to be as effective as prazosin, hydralazine, methyldopa and captopril. Side effect profile is as commonly observed with potent vasodilators: headache, flushing, edema and weight gain, rhinitis, palpitations and diziness. At present it should not be recommended as a first-line antihypertensive treatment because the long-term experience is lacking.

Cromakalim underwent initial studies in hypertension and coronary heart disease but its development was terminated in favour of its active isomer levcromkalim which is now in clinical trials in Japan and the United States.

Nicorandil has no place in the treatment of hypertension, but is approved in many countries worldwide including Yugoslavia for the treatment of angina pectoris. It is as active as the other commonly used antianginal drugs including beta blockers, nitrates and calcium antagonists, in terms of reducing symptoms. Tolerance was not observed in long term trials with treatment periods up to 12 weeks. Systemic blood pressure and heart rate were almost unchanged during nicorandil use. Headache is the principal side effect, mostly in the beginning of therapy; flushing, palpitations, edema, aggravation of anginal symptoms have also been noted (3). No outcome trials have been reported so far.

In noncardiovascular medicine the therapeutic potential of PCOs spans a broad array of indications: asthma, irritable bowel syndrome, irritable bladder syndrome, premature labor and possibly depression. However, very few clinical data have been published with the current PCOs, and the potential new drugs are in early phases of development. Increased potency coupled with tissue selectivity will be required for their clinical acceptance.

Conclusion

Potassium channels constitute a most abundant family of membrane proteins involved in maintaining very important biological functions. Their modulation is becoming a very attractive target for drug development. The availability of organic molecules that block or open K^+ channels is widening the field for pharmacological treatment of cardiovascular and other diseases. Research in this area has been growing fast in recent years, particularly since the channel cloning technology has become available.

Many K^+ channel blocking agents have been either synthesized or discovered in the nature as important experimental tools for identification of the channels. Some of them have been in use for a long time and their channel blocking effects recognized more recently. In the quest for a successful antiarrhythmic drug new molecules have been developed as a "pure" K^+ channel blocking agents devoid of other receptor or channel blocking properties.

Potassium channel opening has become a new drug principle with a therapeutic potential spaning an array from primarily cardiovascular to other diseases. Several PCOs have already been approved for clinical use, however in the future they are expected to be clinically successful only if new molecules are developed with increased tissue specificity coupled with greater potency. Great expectations are connected with the use of PCOs as adjuncts for preconditioning in patients with acute coronary syndromes.

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JONSKI KANALI I RAZVOJ LEKOVA
KALIJUMSKI KANALI I NJIHOVI MODULATORI

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Kratak sadržaj: *Modulacija jonskih kanala je od skora postala moderni pristup za eksperimentalna i klinična istraživanja u neprekidnom traganju za boljim lekovima. Posle decenija u kojima su dominirali blokatori kalcijumskih kanala (antagonisti kalcijuma), sada su u žiži interesovanja kalijumski kanali i njihovi modulatori; u ovoj oblasti se ostvaruje najbrži tempo istraživanja. S obzirom da kalijumski kanali imaju važnu ulogu u održavanju membranskog*

potencijala u svim tkivima i da učestvuju u oblikovanju akcionog potencijala u srcu, od modulatora kalijumskih kanala se očekuje da se među njima nađu bolji terapijski agensi pre svega za bolesti srca (akutni koronarni sindromi, aritmije) kod kojih je mortalitet i dalje visok, ali i u drugim oblastima medicine u kojima terapija ne zadovoljava.

Ključne reči: *K^+ kanali, blokatori K^+ kanala, otvarači K^+ kanala, terapijski potencijal*