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Activators of Cation Channels: Potential in Treatment of Channelopathies

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LQTS long QT syndrome

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Abstract:

Cation channels are membrane proteins that provide controlled pathways for ion passage through cellular membrane. They play important roles in physiological processes such as secretory transduction, control of ion homeostasis, cell volume, vesicle cycling and electrical control of excitable tissues. In a variety of channelopathies ion channel function is reduced and activators of cation channels are promising candidates to regain channel function in acquired or inherited channelopathies. Shortage in cation channel activators prevents testing of efficiency of activators in a variety of indications. This shortage might result from the relative incapability of modern drug screening methods but increasing knowledge about cation channel activator binding and action might enable us in the future to use *in silico* guided drug design of channel modulators. New compounds like the HERG channel activator RPR260243 will enable us to increase our understanding in cation channel modulation and to test the concept of channel activation as a clinically relevant principle in treatment of channelopathies.

Ion channels are integral membrane proteins that provide controlled pathways for ion passage through cellular membrane. Cation selective channels play important roles in physiological processes such as secretory transduction, control of ion homeostasis, cell volume, vesicle cycling and electrical control of excitable tissues. The importance of cation channels is also amplified by the fact that many therapeutic drugs mediate their effects by targeting these proteins. Potassium selective channels are the most genetically diverse of all cation channels. Starting with the first cloned potassium selective ion channel from *Drosophila*, Shaker, more than one hundred potassium channels have been identified. The number of functionally distinct channels in native tissues is further increased by heteromultimeric assembly of potassium channel α -subunits with other α - and β -subunits and other modifications such as alternative splicing of mRNAs, glycosylation and phosphorylation. In the light of the broad range of physiological roles of cation channels it is not surprising that channel impairment result in a variety of pathophysiological conditions. Channels might loose or gain function as a result of mutations in the promotor or coding region of a gene.. Likewise, functional impairment of channel function might result from regulatory derangements or by autoantibodies. The diseases based on altered ion channel function are called channelopathies and include Bartter's syndrome type 2 (KCNJ1, Kir1.1 or RomK, (Derst *et al.*, 1997)) persistent hyperinsulinaemic hypoglycaemia of infancy (Kir 6.2 and Sur, (Nestorowicz *et al.*, 1996;Thomas *et al.*, 1995)) and episodic ataxia type 1 (KCNQ1 or Kv1.1, (Adelman *et al.*, 1995)).

Inherited long QT syndrome (iLQTS) is a disorder which can occur by mutations in the coding region of the cardiac Na^+ -channel (SCN5A, LQT syndrome 3) (Wang *et al.*, 1995) or Ankyrin-B (LQTS4) (Mohler *et al.*, 2003). However, in most cases of LQTS, the potassium channel α -subunits KCNQ1 (LQTS1) and HERG (human ether-a-go-go-related gene, LQTS2) or their β -subunits (KCNE1, 2; LQT 5, 6) are affected. A second group of patients develops LQTS as response to clinically used drugs. This type of LQTS is called acquired LQTS (aLQTS) or drug-induced LQTS and is far more common than the inherited forms of LQTS. Drugs associated with increased risk of aLQTS include antiarrhythmics (Amiodarone, Disopyramide, Dofetilide, Ibutilide, Procainamide, Quinidine, Sotalol), antibiotics (Clarithromyzine, Erythromyzine, Sparfloxazine), psychoactive drugs (Chlorpromazine, Droperidol, Haloperidol, Levomethadyl, Mesoridazine, Methadone, Pimozide, Thioridazine), antimalaria drugs

(Halofantrine, Chloroquine) and others. A more complete list of drugs with risk of prolonging the QT interval and inducing torsade-de-pointes arrhythmias are available at <http://www.torsades.org/medical-pros/drug-lists/drug-lists.htm#>. Most of the listed drugs are highly potent HERG blockers and some are comparably weak KCNQ1/KCNE1-blockers. The iLQTS associated KCNQ1/KCNE1 and HERG/KCNE2 channel mutations cause a decrease in net repolarizing current I_K by reducing potassium currents through "dominant negative" or "loss of function" mechanisms whereas the aLQTS is the result of I_K -blockade. In both cases the reduced repolarizing I_K results in lengthened action potentials, reduced repolarization reserve, increased Ca^{2+} -inflow, likelihood of early after depolarisations and prolongation of the QT interval on the electrocardiogram (ECG). These alterations predispose affected individuals to syncope, seizures, aborted cardiac arrests and sometimes sudden cardiac death. However, block of I_{Kr} or I_{Ks} could be beneficial under special conditions and highly selective blockade of HERG/KCNE2- or KCNQ1/KCNE1-channels were formerly considered as promising antiarrhythmic approaches and several companies developed selective blockers (Gerlach, 2003; Lee *et al.*, 2003). Indeed, one of the most effective antiarrhythmic drugs, Amiodarone, has several targets including HERG/KCNE2-channels. The block of HERG channels is regarded a severe problem for pharmaceutical compounds intended for clinical trials. Therefore, testing for HERG blockade has become an integral part of drug development and safety pharmacology. Treatment for inherited LQTS includes high thoracic left sympathectomy and implantation of cardioverter-defibrillators (Schwartz *et al.*, 2000). These invasive therapies are cost intensive and not favored by patients for obvious reasons. The primary drug therapy of LQTS is the blockade of β -adrenergic receptors. β -blocker therapy was shown to be beneficial in symptomatic LQTS patients (Schwartz *et al.*, 1975; WARD, 1964). However, in about 20-35% of LQTS patients β -blockers are not effective (Ackerman, 1998; Moss *et al.*, 2000). These high risk patients continue to have breakthrough cardiac events like aborted cardiac arrest, syncope and even sudden death. The failure rate of β -blocker therapy might be higher in patients carrying mutations in the potassium channel genes KCNQ1 and HERG than in SCN5A as indicated by a recent study on 28 genotyped patients (Chatrath *et al.*, 2004). While the known therapies have considerably reduced mortality in inherited LQTS there is a well recognized need for improved treatments of iLQTS. The aLQTS forces to discontinue drug application and prevents usage of

certain drugs in predisposed patients. The situation is complicated because the aLQTS might not always be apparent. During aLQTS and iLQTS a drug activating I_K is supposed to be beneficial.

HERG channels somehow act as “magnets” for small hydrophobic drugs with aromatic ring systems. For some time it remained elusive why so many drugs bind to and block the HERG channel. Then, four years ago Mitcheson et al. (Mitcheson *et al.*, 2000) determined the putative binding site of the high potent blockers MK-499, Terfenadine and Cisapride. The main determinants for the “sticky” binding site for highly potent blockers are aromatic residues pointing towards the central cavity. These aromatic residues form hydrophobic and/or pi-stacking interactions with lipophilic and aromatic constituents of drug molecules (Chen *et al.*, 2002). Knowing that many clinically relevant drugs contain aromatic ring systems and are lipophilic to enable membrane passage the high incidence of interactions of the HERG/KCNE2 channels with drugs becomes understandable. Currently, several academic groups and companies are trying to combine pharmacophore models of HERG blockers with structural constraints for the HERG channel derived from homology to the bacterial channels KcsA and MthK (Bains *et al.*, 2004) with the goal to generate in silico tools for the prediction of potential HERG blocking reagents. In any case, for acute aLQTS a drug counteracting the I_{Kr} block would be very desirable.

Channelopathies most often result from a loss of channel function. It would be an attractive approach to activate channels to regain channel function. Channel activation could arise from augmented currents without marked alterations of kinetics or in the case of gating modifiers as a result of faster activation, slower deactivation, altered voltage-dependence or a combination of these mechanisms. To test the potential clinical benefit of this approach, specific activator compounds would be needed. In most cases, the lack of activator molecules has made testing this hypothesis impossible. Only a few highly potent cation channel activators are known. Several of these activators like 1-EBIO, Stibenes and Fernemates are not specific and of relatively low potency. Examples include a variety of K_{ATP} -channel agonists (BMS-180448, Cromakalim, Celikalim, Diazoxide, JTV-506, KR-30450, Lemakalim, Levosimendan, Minoxidil sulfate, Nicorandil, P1075, Pinacidil, Rilmakalim, SKP-450, WAY-133537, Y 26763, ZD6169, ZM-244085), seven classes of Ca^{2+} -activated K^+ -channel (BK and SK) activators (BMS-204352, Chlorzoxazone, DHS-I, 1-EBIO/DC-EBIO, maxiKdiol, NS304/analog, BRL-55834), two KCNQ2-5 activators (BMS-204352/MaxiPost, Retigabine), one KCNK-activator (Riluzole), 3

KCNQ1/KCNE1 activators (Fernemates, R-L3, Stibenes), one GIRK channel activators (Flupirtine), one sodium channel activator (BDF 9148/analogues) and several L-type Ca-channel activators of dihydropyridine type (Bay K 8644, FPL 64176). The K_{ATP} -channel activators are indicated in hypertension and to stimulate hair regrowth. Possible further indications might be asthma and hyperactive bladder disorders. (S)-(-)Bay K 8644 remained a tool for basic research but was recently tested for its potential in verapamil intoxication (Magdalan, 2003). The KCNQ2-5 channels form the classical M-channels and the activators Retigabine and BMS-204352 might have a future for the treatment of incontinence or epilepsy. BK-channel activators could become important in treatment of stroke, hypertension and overactive bladder disorders (Malysz *et al.*, 2004). The activation of KCNK channels by Riluzole exerts significant anti-seizure properties (Borowicz *et al.*, 2004). Other possible indications for specific channel openers are reviewed (Cooper & Jan, 1999; Lawson & Dunne, 2001). Thus, cation channel activators are very rare but hold a broad variety of potential applications.

The Pharmaceutical industry searches for ion channel modulators using high capacity screening methods and huge compound libraries. Robust assays can easily screen 10,000 compounds per day on a single target. However, only a few cation channel activator lead structures have been reported. Why is it so difficult to discover activators? A glimpse of an idea arises when studying data on interactions of cation channel activators with their binding site on the channel. The variety of K_{ATP} -channel activators might arise from the fact that all K_{ATP} -channel activators bind to one of two binding sites in the sulfonylurea subunit of the channel and that this subunit provides a relatively easy accessible drug target. In the case of the other activators very little is known about their binding sites. (S)-(-)Bay K 8644 is believed to interact with the S5-S6 pore module and probably the III/IV interface of L-type Ca-channels (Yamaguchi *et al.*, 2003; Zhorov *et al.*, 2001). Last year we identified the binding site of an activator for a voltage-dependent potassium channel. Alanine-scanning methods combined with 3D-modelling techniques were used to determine the putative binding site of a benzodiazepine R-L3 that activates KCNQ1 channels (Seeböhm *et al.*, 2003b). The binding site is located deep in the potassium channel protein among pore helix, S5, S6 and possibly S4. Theoretically, this position and the small size of the binding pocket might not allow even closely related chemicals to enter and bind to this position. If substances have to bind to binding sites deep inside channel proteins as suggested for BAY K 8644 and R-L3, then even minor structural changes in the activator

molecules could disrupt correct binding and the chemical optimisation process might be highly challenging.

Often activators are found by accident when screening for compounds intended for other targets. Possibly there is a technical problem unaddressed by modern screening techniques: Pharmaceutical companies screen for lead structures. Then they modify these leads to explore the structure in detail to find the molecule with the best combination of EC₅₀, bioavailability, selectivity and drug stability. This concept works well for binding sites on the surface or in large cavities. An example is the search for small molecule cation channel blockers for which the preferential binding site is the large central cavity of cation channels. Thus, in the conventional screen lead structures and analogs binding to surface accessible binding sites are preferentially identified. It is therefore not surprising that activators are often found randomly when working with compounds intended for distinct targets but not by systematic screens for channel activators. The screening methods used to identify channel blockers are possibly not well suited for the identification of activators. Most commonly voltage dependent-fluorescence and cell based assays with potassium depolarisations are used to identify channel blockers. The assays might identify blockers of K⁺-permeation easily, but it is questionable if they are sensitive enough to identify the effects of a gating modifying activator like RPR260243 or R-L3. Thus, classical screening methods might not be very effective in the development of activators. Alternative screening methods such as automated patch clamp or automated TEVC should help, but these methods are relatively slow (100-500 compounds per day, (Xu *et al.*, 2001)). Gathering of structural data and functional modification of channel features by drugs could allow us in future to use computer aided approaches for putative channel activators. Such in silico approach could be combined with the relatively slow electrophysiologic screening methods.

In this issue of Molecular Pharmacology, Kang *et al.* (Kang *et al.*, 2004) report the initial characterisation of the first known HERG channel activator, RPR260243. They find that RPR260243 markedly slows HERG deactivation in single cells and functionally counteracts blockade by Dofetilide in retrograde perfused hearts (Langendoff heart). Six years ago the only high potent selective KCNQ1/KCNE1 activator R-L3 known today was published (Salata *et al.*, 1998). R-L3 also shortens action potential duration, suppresses early afterdepolarisations in ventricular myocytes isolated from hypertrophied rabbit hearts, reverses action potential lengthening and suppresses early afterdepolarizations in rabbit myocytes treated with the I_{Kr}

(HERG)-blocker Dofetilide mimicking LQTS (Xu *et al.*, 2002). These studies provided the first hint that activation of cardiac I_{Kr} and I_{Ks} could be beneficial in LQTS. Like RPR260243, R-L3 has also the potential to activate most of the LQTS associated mutant channels. However, one mutation disrupted the activating effect probably by disrupting the R-L3 binding site (Seeböhm *et al.*, 2003a). Increasing resting membrane stabilization by K_{ATP} -channel opening was proposed to be beneficial in LQTS (Shimizu & Antzelevitch, 2000; Tan *et al.*, 1999) and therefore activation of K^+ -channels in LQTS might be a therapeutic principle. Activators can increase channel currents by increasing open probability or by propagation of membrane insertion by affecting channel trafficking. Compounds acting by these mechanisms do not change macroscopic gating of channels. RPR260243 markedly slows HERG channel deactivation thereby increasing net HERG currents. The compound seems to increase the energy barrier for open state to closed state transitions. These slowing of deactivation identify RPR260243 as a gating modifier. The effect of RPR260243 on HERG channel deactivation is comparable to the effect of R-L3 on KCNQ1 channels. Maybe the binding sites share similarity. Analysis of the binding site and the effects of the drug in vivo could be the next steps in the study of this new compound. RPR260243 provides us with a new tool for the exploration of gating modifier action and could prove to be clinically relevant.

In summary, activators of cation channels are promising candidates to regain channel function in acquired or inherited channelopathies. However, a shortage in cation channel activators prevents testing of efficiency of activators in a variety of indications. This shortage might result from the relative incapability of modern drug screening methods. An increased knowledge about cation channel activator binding and action might enable us to use in silico guided drug design of channel modulators. The new RPR260243 will enable us to increase our understanding in cation channel modulation and to test the concept of I_{Kr} -activation as a clinically relevant principle in cardiac repolarisation disorders.

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References

- Ackerman, M. J. (1998). The long QT syndrome: ion channel diseases of the heart. *Mayo Clin.Proc.* **73**, 250-269.
- Adelman, J. P., Bond, C. T., Pessia, M., & Maylie, J. (1995). Episodic ataxia results from voltage-dependent potassium channels with altered functions. *Neuron* **15**, 1449-1454.
- Bains, W., Basman, A., & White, C. (2004). HERG binding specificity and binding site structure: evidence from a fragment-based evolutionary computing SAR study. *Prog.Biophys.Mol Biol* **86**, 205-233.
- Borowicz, K. K., Rwiader, M., Drelewska, E., & Czuczwar, S. J. (2004). Interactions between riluzole and conventional antiepileptic drugs - a comparison of results obtained in the subthreshold method and isobolographic analysis. *J Neural Transm.* **111**, 1511-1522.
- Chatrath, R., Bell, C. M., & Ackerman, M. J. (2004). Beta-blocker therapy failures in symptomatic probands with genotyped long-QT syndrome. *Pediatr.Cardiol.* **25**, 459-465.
- Chen, J., Seeböhm, G., & Sanguinetti, M. C. (2002). Position of aromatic residues in the S6 domain, not inactivation, dictates cisapride sensitivity of HERG and eag potassium channels. *Proc.Natl.Acad.Sci.U.S.A* **99**, 12461-12466.
- Cooper, E. C. & Jan, L. Y. (1999). Ion channel genes and human neurological disease: recent progress, prospects, and challenges. *Proc.Natl.Acad.Sci.U.S.A* **96**, 4759-4766.
- Derst, C., Konrad, M., Kockerling, A., Karolyi, L., Deschenes, G., Daut, J., Karschin, A., & Seyberth, H. W. (1997). Mutations in the ROMK gene in antenatal Bartter syndrome are associated with impaired K⁺ channel function. *Biochem Biophys.Res.Commun.* **230**, 641-645.
- Gerlach, U. (2003). Blockers of the slowly delayed rectifier potassium IKs channel: potential antiarrhythmic agents. *Curr.Med Chem.Cardiovasc.Hematol.Agents* **1**, 243-252.
- Kang, J., Chen, X. L., Wang, H., Ji, J., Cheng, H., Incardona, J., Reynolds, W., Viviani, F., Tabart, M., & Rampe, D. (2004). Discovery of a Small Molecule Activator of the Human Ether-a-go-go-Related Gene (HERG) Cardiac K⁺ Channel. *Mol Pharmacol.*

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Lawson, K. & Dunne, M. J. (2001). Peripheral channelopathies as targets for potassium channel openers. *Expert.Opin.Investig.Drugs* **10**, 1345-1359.

Lee, K., Park, J. Y., Ryu, P. D., Kwon, L. S., & Kim, H. Y. (2003). IKr channel blockers: novel antiarrhythmic agents. *Curr.Med Chem.Cardiovasc.Hematol.Agents* **1**, 203-223.

Magdalan, J. (2003). New treatment methods in verapamil poisoning: experimental studies. *Pol.J Pharmacol.* **55**, 425-432.

Malysz, J., Buckner, S. A., Daza, A. V., Milicic, I., Perez-Medrano, A., & Gopalakrishnan, M. (2004). Functional characterization of large conductance calcium-activated K⁺ channel openers in bladder and vascular smooth muscle. *Naunyn Schmiedebergs Arch Pharmacol.* **369**, 481-489.

Mitcheson, J. S., Chen, J., Lin, M., Culberson, C., & Sanguinetti, M. C. (2000). A structural basis for drug-induced long QT syndrome. *Proc.Natl.Acad.Sci.U.S.A* **97**, 12329-12333.

Mohler, P. J., Schott, J. J., Gramolini, A. O., Dilly, K. W., Guatimosim, S., duBell, W. H., Song, L. S., Haurogne, K., Kyndt, F., Ali, M. E., Rogers, T. B., Lederer, W. J., Escande, D., Le Marec, H., & Bennett, V. (2003). Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* **421**, 634-639.

Moss, A. J., Zareba, W., Hall, W. J., Schwartz, P. J., Crampton, R. S., Benhorin, J., Vincent, G. M., Locati, E. H., Priori, S. G., Napolitano, C., Medina, A., Zhang, L., Robinson, J. L., Timothy, K., Towbin, J. A., & Andrews, M. L. (2000). Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* **101**, 616-623.

Nestorowicz, A., Wilson, B. A., Schoor, K. P., Inoue, H., Glaser, B., Landau, H., Stanley, C. A., Thornton, P. S., Clement, J. P., Bryan, J., Aguilar-Bryan, L., & Permutt, M. A. (1996). Mutations in the sulfonylurea receptor gene are associated with familial hyperinsulinism in Ashkenazi Jews. *Hum Mol Genet* **5**, 1813-1822.

Salata, J. J., Jurkiewicz, N. K., Wang, J., Evans, B. E., Orme, H. T., & Sanguinetti, M. C. (1998). A novel benzodiazepine that activates cardiac slow delayed rectifier K⁺ currents. *Mol Pharmacol.* **54**, 220-230.

Schwartz, P. J., Periti, M., & Malliani, A. (1975). The long Q-T syndrome. *Am Heart J* **89**, 378-390.

MOLPHARM/2004/010173

Schwartz, P. J., Priori, S. G., Dumaine, R., Napolitano, C., Antzelevitch, C., Stramba-Badiale, M., Richard, T. A., Berti, M. R., & Bloise, R. (2000). A molecular link between the sudden infant death syndrome and the long-QT syndrome. *N.Engl.J Med* **343**, 262-267.

Seeböhm, G., Pusch, M., Chen, J., & Sanguinetti, M. C. (2003a). Pharmacological activation of normal and arrhythmia-associated mutant KCNQ1 potassium channels. *Circ.Res.* **93**, 941-947.

Seeböhm, G., Pusch, M., Chen, J., & Sanguinetti, M. C. (2003b). Pharmacological activation of normal and arrhythmia-associated mutant KCNQ1 potassium channels. *Circ.Res.* **93**, 941-947.

Shimizu, W. & Antzelevitch, C. (2000). Effects of a K(+) channel opener to reduce transmural dispersion of repolarization and prevent torsade de pointes in LQT1, LQT2, and LQT3 models of the long-QT syndrome. *Circulation* **102**, 706-712.

Tan, H. L., Alings, M., Van Olden, R. W., & Wilde, A. A. (1999). Long-term (subacute) potassium treatment in congenital HERG-related long QT syndrome (LQTS2). *J Cardiovasc.Electrophysiol.* **10**, 229-233.

Thomas, P. M., Cote, G. J., Wohllk, N., Haddad, B., Mathew, P. M., Rabl, W., Aguilar-Bryan, L., Gagel, R. F., & Bryan, J. (1995). Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. *Science* **268**, 426-429.

Wang, Q., Shen, J., Splawski, I., Atkinson, D., Li, Z., Robinson, J. L., Moss, A. J., Towbin, J. A., & Keating, M. T. (1995). SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* **80**, 805-811.

WARD, O. C. (1964). A NEW FAMILIAL CARDIAC SYNDROME IN CHILDREN. *J Ir.Med Assoc.* **54**, 103-106.

Xu, J., Wang, X., Ensign, B., Li, M., Wu, L., Guia, A., & Xu, J. (2001). Ion-channel assay technologies: quo vadis? *Drug Discov.Today* **6**, 1278-1287.

Xu, X., Salata, J. J., Wang, J., Wu, Y., Yan, G. X., Liu, T., Marinchak, R. A., & Kowey, P. R. (2002). Increasing I(Ks) corrects abnormal repolarization in rabbit models of acquired LQT2 and ventricular hypertrophy. *Am J Physiol Heart Circ.Physiol* **283**, H664-H670.

Yamaguchi, S., Zhorov, B. S., Yoshioka, K., Nagao, T., Ichijo, H., & Adachi-Akahane, S. (2003). Key roles of Phe1112 and Ser1115 in the pore-forming IIIS5-S6 linker of L-type Ca²⁺

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channel α_1C subunit (CaV 1.2) in binding of dihydropyridines and action of Ca^{2+} channel agonists. *Mol Pharmacol.* **64**, 235-248.

Zhorov, B. S., Folkman, E. V., & Ananthanarayanan, V. S. (2001). Homology model of dihydropyridine receptor: implications for L-type Ca^{2+} channel modulation by agonists and antagonists. *Arch Biochem Biophys.* **393**, 22-41.

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Legends to Figures

Figure 1

Structure of potassium channel activators. Cation channel activators are small lipophilic molecules.