The Heart and Drug Therapy

AstraZeneca is proud to sponsor this NATURE Insight on the Heart. The company has a longstanding scientific interest in creating better drugs in this area. The available drugs for heart disease were mostly developed around the middle of the last century; no new antiarrhythmic drugs have been developed in the last 30-50 years. The same is true for the thrombo-embolic area (except for the new anti-platelet agents). AstraZeneca has a long-term interest in cardiovascular research with registered compounds such as propranolol, metoprolol, atenolol, lisinopril, candesartan, felodipin and compounds in late clinical development such as the superstatin Crestor and the oral, direct-acting thrombin inhibitor Exanta. We will continue to have a strong program in this area of heart and drug therapy with special interest in the lipid-lowering, antiarrhythmic, antihypertensive and thrombo-embolic areas.

AstraZeneca's interest in antiarrhythmic agents:

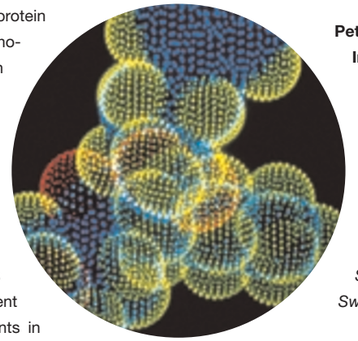
Although cardiac arrhythmias are a major health problem in society, efficient and safe pharmacological treatments are still lacking. In the1980s, the Cardiac Arrhythmia Suppression Trials (CAST) highlighted the proarrhythmic risk and inefficacy of class I (sodium channel blocking) antiarrhythmic agents in patients at relatively low risk for sudden death. These studies resulted in an increased interest in class III (action potential prolonging) antiarrhythmic agents. However, even though efficacy has been proven for different class III agents, they, like class I agents, have been shown to be proarrhythmic and the initial optimism for them has waned. Clearly medical need is great – this is probably true for ventricular arrhythmias, and is certainly true for supra-ventricular tachyarrhythmias, including both acute termination and prophylaxis against recurrence of atrial fibrillation or atrial flutter.

Knowledge about the physiology, structure and molecular biology of cardiac ion channels/ion transporters has grown substantially in recent times. The fruitful combination of electrophysiological techniques with state-of-the art molecular biology and genetics has not only advanced our understanding of basic cardiac physiology, but also started to provide insights into the pathophysiology of cardiac rhythm disorders. It has become increasingly clear that cardiac arrhythmias can themselves cause drastic changes in electrical, structural and functional properties and that these changes directly promote the maintenance of the arrhythmia.

The rapid progress in this field holds the promise of providing a detailed understanding of the basic determinants of different cardiac arrhythmias in the very near future. It may then be possible to target the development of the arrhythmia substrate (i.e. upstream therapy), rather than modulating its result. Progress in molecular biology and genetics might facilitate prerequisites for more individualised therapy. For example, through genetic screening, it may be possible to identify patients at risk for unwanted side effects or those that will benefit most from a specific therapy. AstraZeneca is at the forefront of using these new approaches to find an effective and, perhaps even more important, safe pharmacological treatment for atrial fibrillation and flutter.

AstraZeneca's interest in vascular disease prevention:

Cardiovascular disease remains the leading cause of death despite the number of drugs with different mechanisms of action used in the clinical setting. Arteriosclerosis in coronary arteries underlying myocardial infarction is a complex trait arising from the interaction of multiple susceptibility genes with a range of environmental factors. Biological remodelling processes in combination with metabolic dysfunction, e.g. insulin resistance and dyslipidemia, cause a set of different plaque architectures in the vessel wall. This ranges from large, fibrotic, stable lesions to lipid-rich unstable plaques, the latter being more prone to rupture and so to causing a thrombotic event. Lipoprotein retention and modification, reverse cholesterol transport, matrix deposition and vascular wall inflammation are all examples of local processes in the athero-sclerotic plaque that could be of benefit in treating the disease. Recently it has been elegantly demonstrated by magnetic resonance imaging that lipid lowering treatment with statins decreases the amount of lipids present in the plaque. Technical achievements in non-invasive imaging will enable monitoring of local events in the plaque and make it more attractive to explore antiatherosclerotic therapies in parallel with the more established lipid lowering approaches. AstraZeneca has efficacious lipid-modulating compounds in clinical development and is exploring possible local target mechanisms in the vessel wall. The symptoms of acute plaque rupture and/or erosion with the subsequent exposure of thrombogenic surfaces and formation of thrombi can be prevented by antithrombotic therapies. AstraZeneca has a commitment to and a leading position in the development of more effective and safer antithrombotic drugs focusing on several mechanisms of the coagulation cascade. The impressive advances in drug discovery and the basic science of cardiac disease will most likely over the next decade translate into significant impact on the clinical therapeutic opportunities available for treatment of cardiovascular diseases.



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