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DISCOVERY AND DEVELOPMENT OF CALCIUM CHANNEL BLOCKERS

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ABSTRACT

In the mid-1960s, experimental work on molecules under screening as coronary dilators allowed the discovery of the mechanism of calcium entry blockade by drugs later named calcium channel blockers. This paper summarizes scientific research on these small molecules interacting directly with L-type voltage-operated calcium channels. It also reports on experimental approaches translated into understanding of their therapeutic actions. The importance of calcium in muscle contraction was discovered by Sidney Ringer who reported this fact in 1883. Interest in the intracellular role of calcium arose 60 years later out of Kamada (Japan) and Heibrunn (USA) experiments in the early 1940s. Studies on pharmacology of calcium function were initiated in the mid 1960s and their therapeutic applications globally occurred in the the 1980s. The first part of this report deals with basic pharmacology in the cardiovascular system particularly in isolated arteries. In the section entitled from calcium antagonists to calcium channel blockers, it is recalled that drugs of a series of diphenylpiperazines screened *in vivo* on coronary bed precontracted by angiotensin were initially named calcium antagonists on the basis of their effect in depolarized arteries contracted by calcium. Studies on arteries contracted by catecholamines showed that the vasorelaxation resulted from blockade of calcium entry. Radiochemical and electrophysiological studies performed with dihydropyridines allowed their cellular targets to be identified with L-type voltage-operated calcium channels. The modulated receptor theory helped the understanding of their variation in affinity dependent on arterial cell membrane potential and promoted the terminology calcium channel blocker (CCB) of which the various chemical families are introduced in the paper. In the section entitled tissue selectivity of CCBs, it is shown that characteristics of the drug, properties of the tissue, and of the stimuli are important factors of their action. The high sensitivity of hypertensive animals is explained by the partial depolarization of their arteries. It is noted that they are arteriolar dilators and that they cannot be simply considered as vasodilators. The second part of this report provides key information about clinical usefulness of CCBs. A section is devoted to the controversy on their safety closed by the Allhat trial (2002). Sections are dedicated to their effect in cardiac ischemia, in cardiac arrhythmias, in atherosclerosis, in hypertension, and its complications. CCBs appear as the most commonly used for the treatment of cardiovascular diseases. As far as hypertension is concerned, globally the prevalence in adults aged 25 years and over was around 40% in 2008. Usefulness of CCBs is discussed on the basis of large clinical trials. At therapeutic dosage, they reduce the elevated blood pressure of hypertensive patients but don't change blood pressure of normotensive subjects, as was observed in animals. Those active on both L- and T-type channels are efficient in nephropathy. Alteration of cognitive function is a complication of hypertension recognized nowadays as eventually leading to dementia. This question is discussed together with the efficacy of CCBs in cognitive pathology. In the section entitled beyond the cardiovascular system, CCBs actions in migraine, neuropathic pain, and subarachnoid hemorrhage are reported. The final conclusions refer to long-term effects discovered in experimental animals that have not yet been clearly reported as being important in human pharmacotherapy.

KEYWORDS: calcium channel blockers, voltage operated calcium channels, cardiovascular diseases, hypertension, stroke, dementia, cardiac arrhythmia.

INTRODUCTION

In 1883, from a series of experiments on isolated heart, Ringer reported that calcium is required for the maintenance of cellular activity. In 1901, Stiles extended this observation to smooth muscle contraction. Sixty years later, Kamada in Japan and Heilbrunn in the United States discovered the role of intracellular calcium for muscle contraction. It is nowadays recognized that calcium is involved in a wide range of cellular processes being generally considered the ubiquitous second messenger.

In the 1960s, experimental work on molecules under screening for coronary dilatation allowed the discovery

of the mechanism of calcium entry blockade by drugs later named as calcium channel blockers.[1] Those drugs are now among the most commonly used agents for the treatment of cardiovascular diseases. The present paper summarizes research on small molecules interacting directly with calcium channels, also considering their therapeutic action effective in cardiovascular diseases and in neurological pathologies and their availability for medical use.

In the early sixties, many drugs have been screened either by imitation or by blockade of a typical effect of identified neurotransmitters. This was before the advent of combinatorial chemistry. The chemical structure of the neurotransmitter usually served as initial leading compound for a serial iterative processes of synthesis followed by biological assay. This serial synthesis was a rate-limiting procedure when compared to the current combinatorial chemistry allowing the preparation of many compounds in one time. The bioassay was as simple as possible often avoiding the use of dose effect curves. Structural starting points were natural compounds, dyes or chemical entities already known for other purposes. Usually compounds obtained were termed on the basis of the lead neurotransmitter. For instance, in the group of adrenaline, they were qualified as sympathomimetics or sympatholytics. Nowadays since the deciphering of the genetic code the number of potential targets increased tremendously. In the case of G-protein coupled receptors, there are at least 800 genes representing about 4% of total human genes. Their classification is provided by NC-IUPHAR a Committee of IUPHAR, the international Union of Basic and Clinical Pharmacology.

Coming back to the early sixties, a drug discovery program was started by various pharmaceutical companies targeted coronary circulation in order to discover coronary dilators for the treatment of angina pectoris. This was initiated by Janssen Pharmaceutica with diphenylmethylpiperazines including lidoflazine, cinnarizine, flunarizine, and by Knoll AG with phenylalkylamines including verapamil, D600.[2] Bayer AG followed with dihydropyridines: nifedipine, nimodipine, nisoldipine, and Tanabe with the benzothiazepine diltiazem. Later Sandoz with isradipine, Pfizer with amlodipine, and others followed with other dihydropyridines.

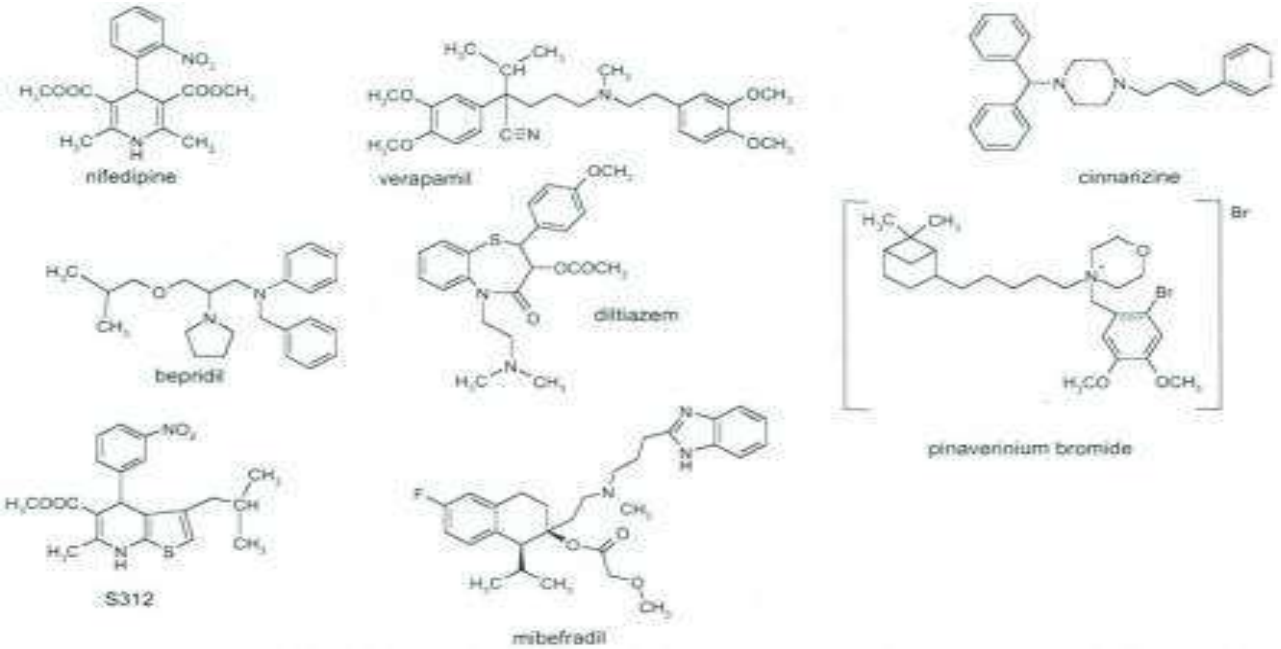

Figure 1: Chemical structures of the major families of Calcium Channel Blockers as represented by their lead compounds.

FROM CALCIUM ANTAGONISTS TO CALCIUM CHANNEL BLOCKERS

The first drugs we studied were obtained from Belgian and French Pharmaceutical Companies. In Paul Jannsen's laboratory, Jagenau and Schaper had examined in dog the action of a series of diphenylmethylpiprazines on coronary arteries contracted by angiotensin. Lidoflazine had been selected from this series for clinical studies in patients suffering from angina pectoris. The pharmacological action of lidoflazine has been studied by Godfraind et al. on the guinea pig isolated ileum stimulated by angiotensin and other agonists.[4-5] Collected estimates of pA_2 and pAh values show similarity of values of pA_2 and pAh with regard to various agonists studied. Lidoflazine[3], behaving as an insurmountable antagonist of similar potency for various agonists activating their specific receptors, was hypothesized to act by blocking a mechanism common to those activated receptors. The working hypothesis implied that this common mechanism involved calcium translocation. This hypothesis was based on Edman and Schild's findings that calcium is required in the bathing

fluid to obtain a contraction of the Rat uterus in response to acetylcholine. On the basis of the calcium hypothesis, Godfraind and Colleagues designed experiments to examine the activity of depolarized Rat aorta contracted by 10 mM $CaCl_2$ and exposed to increasing concentrations of lidoflazine and of other drugs acting similarly. They observed that the calcium-evoked contraction was dose-dependently reduced by lidoflazine, cinnarizine, and chlorpromazine. Furthermore, the antagonist action on Ca^{2+} contraction in various arteries was overcome by increasing Ca^{2+}concentration in the perfusion fluid. On the basis of these observations Godfraind and Colleagues concluded that those drugs were acting as calcium antagonists, Further experiments with cinnarizine better determined the nature of this antagonism. As illustrated in Figure Figure2,2, calcium dose-effect curves were performed in depolarized rabbit mesenteric artery in the absence of cinnarizine and 90 min after its addition to the medium. At the lowest concentration of cinnarizine there was a displacement to the right of the calcium dose-effect curve, but at higher concentration, the antagonism was insurmountable. Such observations have been extended to other non-competitive antagonists such as chlorpromazine, papaverine, and several dihydropyridines. The dose-effect curves drawn from these experiments were similar to those obtained in agonist-antagonist studies and it supported the denomination calcium antagonist but it didn't provide indication on the mechanism of this action. Albrecht Fleckenstein and his Colleagues coincidentally made use of the term calcium antagonist in their study on the inhibitory effect of verapamil on electromechanical coupling in mammalian myocardium.

The action of calcium channel blockers in cardiac ischemia

Early clinical studies of CCBs in ischemic heart disease

Ischemic Heart Disease affects the supply of blood to the heart. Blood vessels might be blocked due to deposition of cholesterol in their walls. This reduces the supply of oxygen and nutrients to the heart muscles. This may eventually lead to destruction of an area of heart tissue, inducing a heart attack. Ischemic heart disease is the most common cause of death in many countries around the world. Causal factors including hypertension have been listed above. The clinical aspects of ischemic heart disease are usually expressed by Angina Pectoris, an acute chest pain attributed to chronic stable effort angina, to vasospastic angina, to unstable angina, and acute myocardial infarction. Heart failure might follow a resulting weakness of the heart muscle.[6-8]

Calcium channel blockers in cardiac arrhythmias

In slow response tissues such as sinoatrial and atrioventricular nodes, non-dihydropyridine CCBs (nd-CCBs) do block Ca current that generate slowly propagating action potentials, this action displays antiarrhythmic effects. Acute myocardial infarction may convert fast conducting tissue such as ventricular myocardium and Purkinje fibers into slow response tissue. In ischemic areas, ionic changes cause partial depolarization in resting cells supporting slow Ca currents and leading to conduction blocks. Such blocks play a crucial role in the development of reentrant pathways. These processes are involved in the incidence of premature beats and ventricular tachycardia. In 1971 verapamil that was known to inhibit arrhythmia induced by ouabain, was used to reduce the ventricular rate in atrial fibrillation. It has been later ranged in class IV antiarrhythmics. Its action is due to interaction with intracellular binding sites different from the dihydropyridine receptor. Verapamil and diltiazem *in vivo* are powerful antiarrhythmic agents.[9] Dihydropyridines usually evoke reflex tachycardia resulting from increase in sympathetic tone, masking their slight negative chronotropic effect.[10] Verapamil and diltiazem are recommended in supraventricular tachycardia. Intravenous verapamil produces the conversion of reentrant supraventricular tachycardia, diltiazem being less effective and. Intravenous injection of verapamil and diltiazem in atrial fibrillation results in reduction of the ventricular response an effect confirmed in the Verapamil plus antiarrhythmic drugs trial. However, in the presence of anomalous bundle, verapamil, and diltiazem are contraindicated and the ESC guidelines recommend a treatment by catheter ablation for the management of atrial fibrillation.

Calcium channel blockers in hypertension and HT complications

According to 2016 reports of WHO and of Medscape, globally, the overall prevalence of raised blood pressure in adults aged 25 and over was around 40% in 2008. The number of hypertensive adults worldwide was estimated to 1.1 billion in 2015 with a disparity among countries, the prevalence being lowest in wealthy countries. This could be explained by diet and drug treatment control. In view of disability or death due to complications, such as cardiac ischemia, kidney insufficiency, stroke and dementia, it is mandatory to evaluate the efficacy of medications.[10-13]

CONCLUSIONS

In the various sections of this paper dedicated to history, facts reported by a large number of authors have been put forward. They do enlighten the global cooperative activity of the basic and clinical biomedical community to analysis of the potential of CCBs for treating a large spectrum of diseases from angina pectoris to various forms of dementia. There are some experimental discoveries that haven't been accounted for in this Review. They have been covered elsewhere under the topic “long-term effects”, which comprises antioxidant effects, vascular remodeling actions, gene expression and function of major autacoids including angiotensin. It is hypothesized that such long-term effects are involved in the therapeutic action of CCBs, an action that could not only been due to reduction of vascular tone controlling

the level of blood pressure but also to BP independent actions. Authors of large RCTs reported above favor this assumption. On the basis of electrophysiological experimentation, the hypothesis cannot be ruled out that in addition to blockade of $Ca_v1.2$, blockade of other voltage-operated channels could be of importance for therapy. However, as well as for long-term effects, robust demonstration needs to be supported by clinical data. Much hope is provided by ongoing translational research and by Big Data analysis in the future of Medicines development.

Author contributions

The author confirms being the sole contributor of this work and approved it for publication.

REFERENCES

1. Abernethy D. R., Schwartz J. B. (1999). Calcium-antagonist drugs. N. Engl. J. Med., 341: 1447–1457. 10.1056/NEJM199911043411907 [PubMed] [CrossRef]
2. Alps B. J. (1992). Drugs acting on calcium channels: potential treatment for ischaemic stroke. Br. J. Clin. Pharmacol., 34: 199–206. 10.1111/j.1365-2125.1992.tb04125.x [PMC free article] [PubMed] [CrossRef]
3. Angelico P., Guarneri L., Leonardi A., Testa R. (1999). Vascular-selective effect of lercanidipine and other 1,4-dihydropyridines in isolated rabbit tissues. J. Pharm. Pharmacol., 51: 709–714. 10.1211/0022357991772844 [PubMed] [CrossRef]
4. Arribas S. M., Costa R., Salomone S., Morel N., Godfraind T., McGrath J. C. (1999). Functional reduction and associated cellular rearrangement in SHRSP rat basilar arteries are affected by salt load and calcium antagonist treatment. J. Cereb. Blood Flow Metab., 19: 517–527. 10.1097/00004647-199905000-00006 [PubMed] [CrossRef]
5. Arunlakshana O., Schild H. O. (1959). Some quantitative uses of drug antagonists. Br. J. Pharmacol. Chemother., 14: 48–58. 10.1111/j.1476-5381.1959.tb00928.x [PMC free article] [PubMed] [CrossRef]
6. Atkinson J., Capdeville C. (1990). Hypertension, Antihypertensive Treatment and Cerebrovascular Disease. Southborough, MA: TransMedica Europe Limited.
7. Balligand J. L., Godfraind T. (1994). Effect of nisoldipine on contractions evoked by endothelin-1 in human isolated distal and proximal coronary arteries and veins. J. Cardiovasc. Pharmacol., 24: 618–625. 10.1097/00005344-199410000-00013 [PubMed] [CrossRef]
8. Balligand J. L., Kelly R. A., Marsden P. A., Smith T. W., Michel T. (1993). Control of cardiac muscle cell function by an endogenous nitric oxide signaling system. Proc. Natl. Acad. Sci. U.S.A. 90: 347–351. 10.1073/pnas.90.1.347 [PMC free article] [PubMed] [CrossRef]
9. Bean B. P. (1984). Nitrendipine block of cardiac calcium channels: high-affinity binding to the inactivated state. Proc. Natl. Acad. Sci. U.S.A. 81: 6388–6392. 10.1073/pnas.81.20.6388 [PMC free article] [PubMed] [CrossRef]
10. Bean B. P., Sturek M., Puga A., Hermsmeyer K. (1986). Calcium channels in muscle cells isolated from rat mesenteric arteries: modulation by dihydropyridine drugs. Circ. Res., 59: 229–235. 10.1161/01.RES.59.2.229 [PubMed] [CrossRef]
11. Bentahila S., Atkinson J., Capdeville C. (1991). Protective effects of antihypertensive treatment with isradipine on the consequences of cerebral ischaemia in the spontaneously hypertensive rat. J. Hypertens., 9: 121–129. 10.1097/00004872-199102000-00004 [PubMed] [CrossRef]
12. Berdeaux A., Drieu La Rochelle C., Richard V. (1990). Calcium Antagonists and the Coronary Circulation. Southborough, MA: TransMedica Europe Limited.
13. Bolt G. R., Saxena P. R. (1984). Acute systemic and regional hemodynamic effects of felodipine, a new calcium antagonist, in conscious renal hypertensive rabbits. J. Cardiovasc. Pharmacol., 6: 707–712. 10.1097/00005344-198407000-00025 [PubMed] [CrossRef]