available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Calcium channel antagonists: Clinical uses—Past, present and future

David J. Triggle *

State University of New York, Buffalo, NY 14260, United States

ARTICLE INFO

Keywords:
Calcium channel antagonists
1,4-Dihydropyridines
Nifedipine
Verapamil
Diltiazem
Pain
Stroke
Contraception
Bone formation
Fertility' immune cells
T cells
Schistosomiasis

ABSTRACT

The calcium channel antagonists are a mature group of drugs directed at cardiovascular diseases including hypertension, angina, peripheral vascular disorders and some arrhythmic conditions. Their sites and mechanisms of actions have been well explored over the past two decades and their interactions at the α_1 subunit of L-type channels ($Ca_V1.1$–1.4) have made them valuable molecular tools for channel classification and localization. With the realization that other members of the voltage-gated calcium channel family exist – $Ca_V2.1$–2.3 and $Ca_V3.1$–3.3 – considerable effort has been directed to drug discovery at these channel types where therapeutic prospects exist for a variety of disorders including pain, epilepsy, affective disorders, neurodegenerative disorders, etc. In contrast to the situation with the L-type channel antagonists success in developing small molecule antagonists of therapeutic utility for these other channel types has thus far been lacking. The reasons for this are explored and potential new directions are indicated including male fertility, bone growth, immune disorders, cancer and schistosomiasis.

1. Calcium channel antagonists: past

The term ''calcium channel antagonists'' refers to a chemically, pharmacologically and therapeutically heterogeneous group of drugs prominent both as cardiovascular therapeutic agents and as molecular tools. The prototypical agents of this group are diltiazem (a benzothiazepinone), nifedipine (a 1,4-dihydropyridine) and verapamil (a phenylalkylamine). The cardiovascular activities of these drugs as antihypertensive, antianginal and selective antiarrhythmic agents are due to their interaction at one particular calcium mobilization process—calcium entry through a voltage-gated calcium channel of the L-type. Many studies have demonstrated that in accord with their chemical heterogeneity these agents interact at discrete receptor sites associated with a major subunit of the channel (Fig. 1). The properties of these drugs and the mechanisms by which they function have been extensively reviewed during the past 25 years [1–4].

Controversy remains as to the credit for the discovery of this class of agents, although it is clear that they were not designed as drugs that would block calcium channel function [5]. Principal credit should go to Albrecht Fleckenstein at the University of Freiburg whose work demonstrated that verapamil and prenylamine produced effective electromechanical uncoupling in the heart, that these effects mimicked those of calcium removal, and that this uncoupling could be overcome by increasing extracellular calcium concentrations [1]. Almost simultaneously, Godfraind and Polster in Belgium noted the effects of cinnarizine and flunarizine on excitation–contraction coupling in vascular smooth muscle and wrote,

* Tel.: +1 716 645 7315; fax: +1 716 645 3688.
E-mail address: Triggle@buffalo.edu.
0006-2952/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2007.01.016

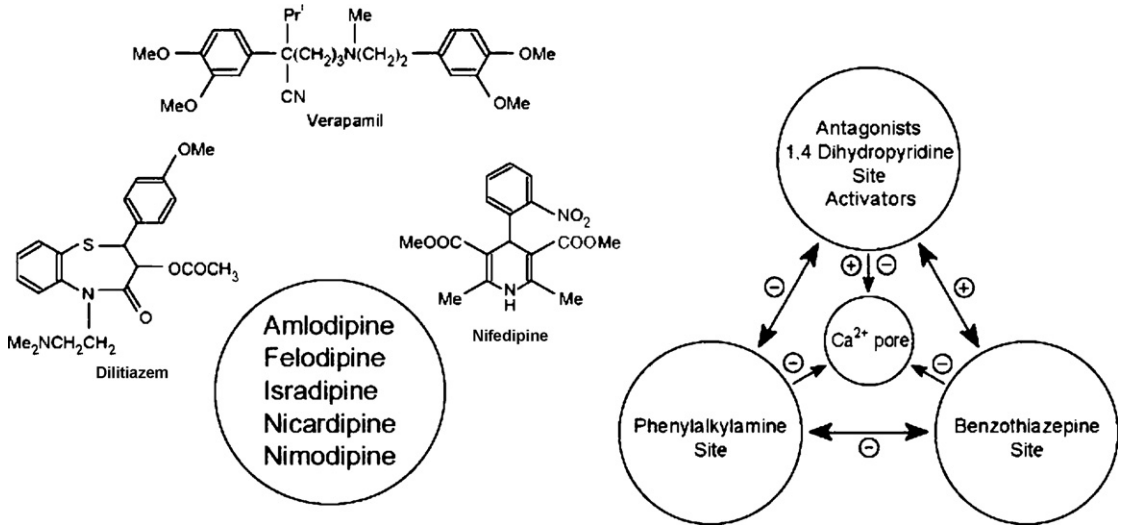
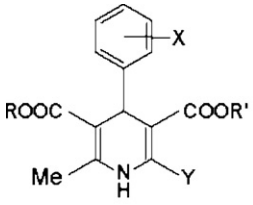


Fig. 1 – Ca^{2+} channel antagonist interactions at the L-type voltage-gated calcium channel. In this schematized representation the three major structural classes of drug are shown interacting at separate but allosterically linked receptor sites. The molecules depicted in the circle are second-generation 1,4-dihydropyridines and include the widely prescribed amlodipine (Norvasc™).

''la cinnarizine est un antagonist du calcium, au niveau de muscle vasculaire depolarise'' [6].

Following the introduction of these agents extensive work on second-generation drugs ensued. This led to the selective introduction of a number of agents of the 1,4-dihydropyridine class including amlodipine, benidipine, cilnidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nivadipine, nimodipine, nisoldipine, and nitrendipine ([3,4]; Fig. 2). Despite their close structural similarity to nifedipine and apparent ''me too'' status, these agents do differ in a number of important pharmacodynamic and pharmacokinetic properties, some of which are therapeutically significant, that are discussed in Section 3.

In the mid-1990s several cautionary notes were sounded concerning the safety of these agents (reviewed in [7]). These concerns included excess cardiovascular mortality [8], and increased risk of gastrointestinal bleeding and cancer [9,10]. A meta-analysis of trials of first-line antihypertensive agents indicated that hypertensive patients who had received calcium channel antagonists had a significantly increased risk of myocardial infarction relative to patients who had received β-blockers. Similarly, a cohort of elderly patients



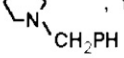
Amlodipine	X=2Cl; R=Me; R'=Et; Y=$CH_2OCH_2CH_2NH_2$
Benidipine	X=3NO_2; R=Me; R'=  ; Y=Me
Cilnidipine	X=3NO_2; R=$MeOCH_2CH_2$; R'=$CH_2CH{=}CH{\bullet}C_6H_5$(E); Y
Felodipine	X=2,3Cl_2; R=Me; R'=Et; Y=Me
Isradipine	X=  ; R=Me; R'=$CHMe_2$; Y=Me
Lacidipine	X=CH=CHCOOBu^t; R=Et; R'=Et; Y=Me
Lercanidipine	X=3NO_2; R=Me; R'=$CMe_2CH_2NMeCH_2CH_2CHPh_2$; Y=
Manidipine	X=3NO_2; R=Me; R'=CH_2CH_2N  $NCHPh_2$; Y=Me
Nicardipine	X=3NO_2; R=Me; R'=CH_2NMeCH_2Ph; Y=Me
Nifedipine	X=3NO_2; R=Me; R'=Me; Y=Me
Nilvadipine	X=3NO_2; R=Me; R'=$CHMe_2$; Y=Me
Nimodipine	X=3NO_2; R=$CHMe_2$; R'=CH_2CH_2OMe; Y=Me
Nisoldipine	X=2NO_2; R=Me; R'=CH_2CHMe_2; Y=Me
Nitrendipine	X=3NO_2; R=Me; R'=Et; Y=Me

Fig. 2 – 1,4-Dihydropyridine calcium channel antagonists.