INTRODUCTION

CALCIUM ANTAGONISTS

Historically, the development of slow-channel blockers dates back to the early 1960s, at which time some German scientists observed that prenylamine, a newly developed coronary dilator, and verapamil, another phenylalkylamine with coronary dilating properties, exerted negative inotropic effects on isolated cat and rabbit myocardium and also depressed cardiac performance in the canine heart lung preparation. They differ from classic vasodilators, because drugs such as nitroglycerine and papaverine with potent smooth-muscle relaxing properties depress cardiac muscle only at high concentration (Saini, 1984).

Prenylamine and verapamil were shown experimentally to act in the same way as Ringer's calcium free infusion i.e. they mimicked the cardiac effects of calcium deficiency. Subsequently, it was shown that the pharmacological basis of action of verapamil and nifedipine was to inhibit calcium entery into cardiac cells and smooth muscles. The term calcium antagonists was introduced in 1969 for agents that prevented the entery of calcium

from the extracellular fluid into the cell via postulated pores or channels. Hence these drugs were also called calcium entery blockers or calcium channel blockers (Lewis, 1982).

Within the last several years the list of agents which have been classified as "calcium channel blockers" has grown from essentially three-nifedipine, verapamil and diltiazem - to well over a hundered, including a number of nifedipine analogues, as well as careverine, lidoflazine, FR 7534 and cinnarizine (Weishaar, 1984).

It is probably a historic accident that the calcium channel blockers were developed as cardiovascular drugs (Katz et al., 1984).

Jones (1985) reported that calcium not only have an important role in muscle contraction, but it also mediates endocytosis and exocytosis, cellular mobility, movement of chromosomes prior to cell division and possibly the division process itself. It also has an influence on the metabolism of glycogen, blood coagulation and haemostasis and the release of neurotransmitter.

CLASSIFICATION OF CALCIUM CHANNEL BLOCKERS

Fleckenstein (1970) originally classed some of the substances listed in Table (1) as "calcium antagonists" on the basis of two requirements:

a) The predominent characteristic of these substances is their ability of inhibit the slow Ca^{++} current; and

b) This inhibition could be overcome by adding Ca^{++}.

The continued unqualified use of the term "calcium antagonists" requires reappraisal because of its lack of specificity with respect to the exact site and precise mode of drug action; as "calcium antagonism" can be expressed at a variety of sites, including the cell membrane, the myofibrills, the sarcoplasmic reticulum and the mitochondria. When used in therapeutic concentration, however, the drugs expressed their "calcium antagonistic" properties at only one site, the cell membrane. Even at the cell membrane there are other ways in which substances can interfere with transmembrane Ca^{++} movements - apart from the entery of Ca^{++} through the voltage-activated "channels".

Possibly, therefore, there is some merit in considering drugs of the type shown in Table (1) as being a subgroup of a much larger group of drugs which, may be better called "Ca^{++} entery blockers" or Ca^{++} entery antagonists". This group of drugs - "The Ca^{++} entery blockers" or "Ca^{++} entery antagonists" would include any drug which impedes the inward movement of Ca^{++}, irrespective of the route of entery.

Nayler (1982) reported that the known routes of Ca^{++} entery into cardiac and smooth muscle cells include by passive diffusion, in exchange for Na^{+}, in exchange for K^{+}, and through the voltage-activated, ion selective channels (Fig. 1). Therefore, as far as cardiac and smooth muscle cells are concerned, it is possible that four different sub-groups of Ca^{++} entery blockers (or antagonists) will ultimately become available. However, the drugs which are currently available are specific only for the sub-group that antagonizes the influx of Ca^{++} through the voltage-activated, ion selective channels.

Subclassification:

Substances which inhibit slow channel transport can be conveniently subdivided into two major subgroups, on

the basis of their chemistry. Thus, there are the inorganic (cobalt & lanthanum) and the organic inhibitors. The organic inhibitors can be further subdivided into three main classes, on the basis of their tissue specificity. According to this scheme drugs which predominantly affect slow channel activity in the myocardium (e.g. verapamil), can be classed as having strong class I activity. Class II could include those drugs which are most effective in blocking slow channel transport in vascular smooth muscle (e.g. Nifedipine). Class III would include slow channel transport in pacemaker, nodal and conducting tissue of the heart (e.g. verapamil). These relative activities are summarized in Table (2).

Class II drugs can be further subdivided into at least three subgroups (Fig. 2). For example, the effect of diltiazem on the slow channels is more marked in the smooth muscle cells of the coronary than peripheral vasculature. Nimodipine acts preferentially on slow channel transport in the cerebral vessels. By contrast lidoflazine is more potent on the peripheral blood vessels (Nayler, 1982).

McFaden (1981) proposed a classification of Ca^{++} antagonists into two groups: those that block centery of calcium ions into the cell, and those that affect the intracellular sites of calcium actions. Some examples of the first are nifedipine, verapamil, diltiazem, perhexiline,methoxyverapamil, benzyclane and phenyamine. The aminoindenenes and mechinarone seem to have their primary action at intracellular sites.

During the last several years, however, this group of agents has been classified into several subgroups, including the calcium channel blockers and the so-called "intracellular Ca^{++} antagonists". This latter subgroup is believed to include the "calmodulin inhibitors" such as W-7 and R 24571, as well as several other ill-defined agents (Weishaar, 1984).

Table (1): Substances classed as Ca^{++} antagonists

Verapamil.

Methoxyverapamil (D600).

Prenylamine.

Nifedipine.

Lidoflazine.

Nimodipine.

Diltiazem.

Depridil.

Caroverine.

Niludipine.

Fendiline.

(After Nayler, 1982).

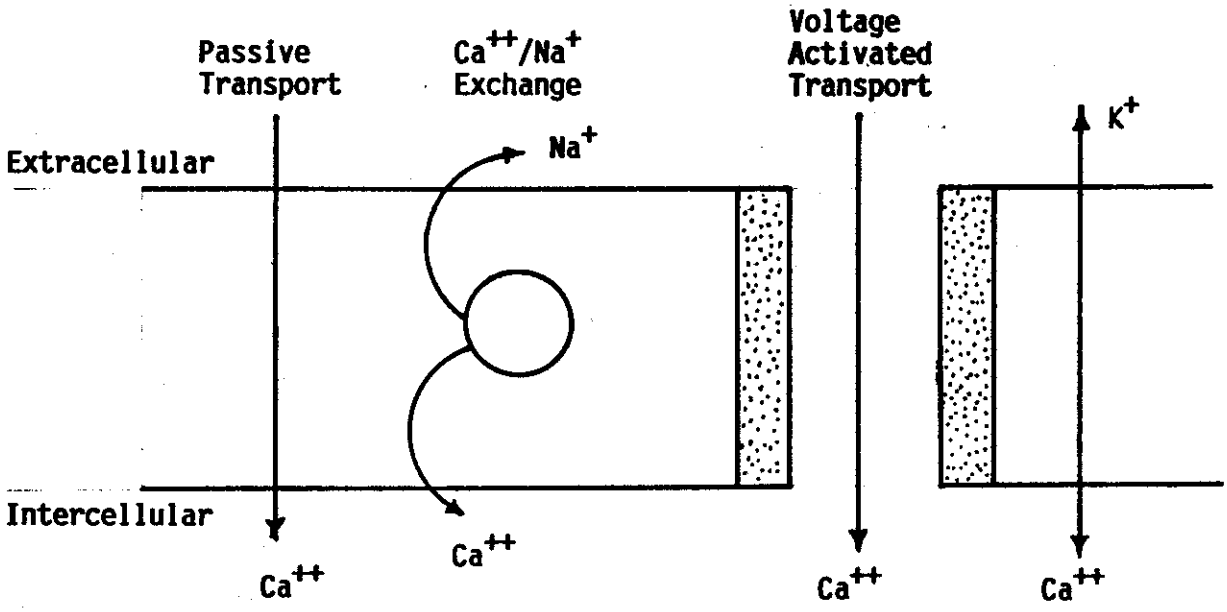

Fig. (1): Schematic representation of possible routes of Ca^{++} entry into a myocardial cell (After Nayler, 1982).

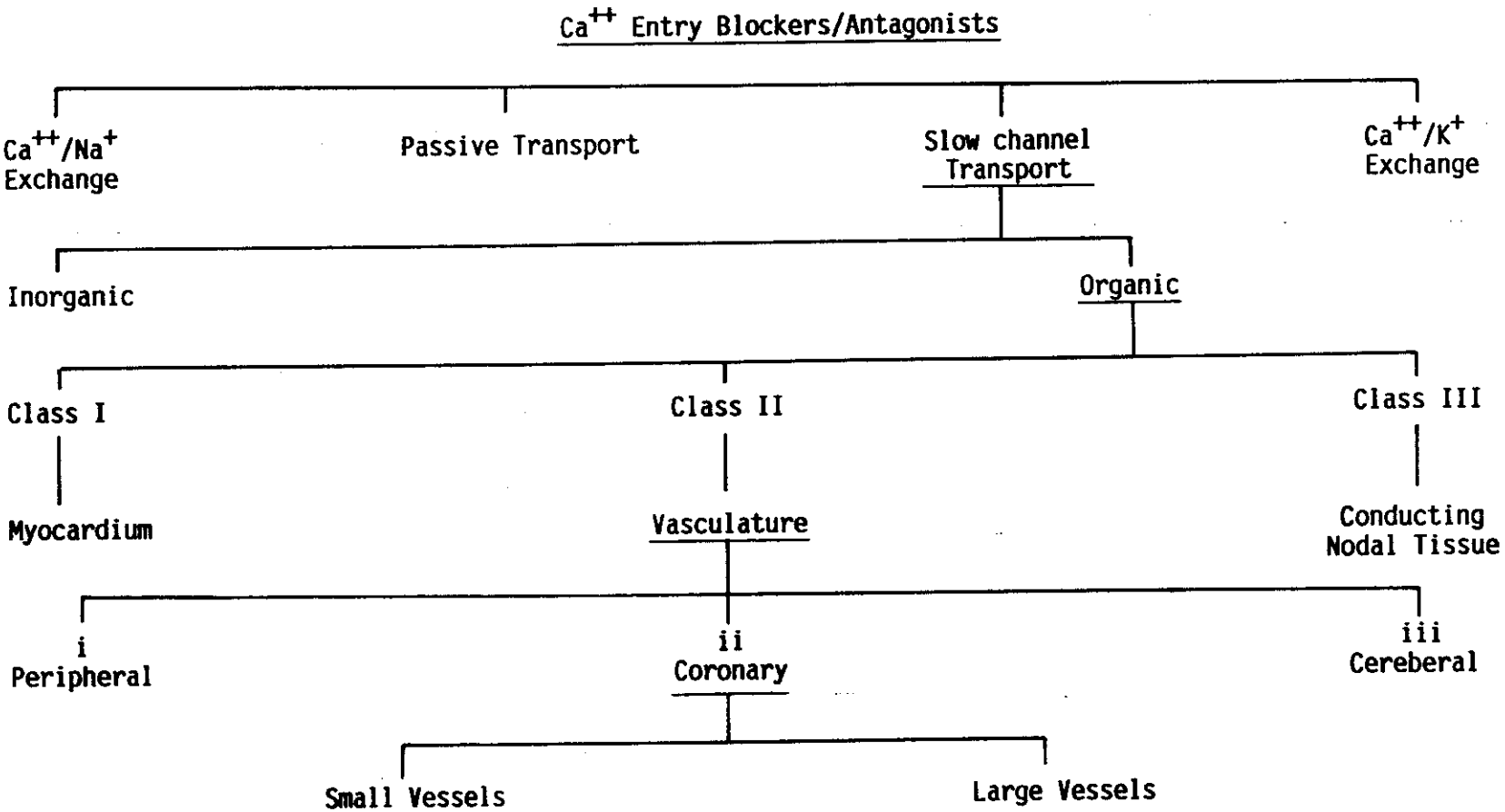

Fig. (2): Proposed subdivision of Ca^{++} entery blocking drugs (After Nayler, 1982).

Table (2): Subdivision of slow channel inhibitors.

Class	Slow channel inhibitor			
	Verapamil	Nifedipine	Diltiazem	Lidoflazine
I	Strong	Weak	Weak	Absent
II	Weak	Strong	Strong	Strong
III	Strong	Absent	Weak	Absent

(After Nayler, 1982).