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Review

Calcium sensitizers: What have we learned over the last 25 years?☆

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ABSTRACT

The use of inotropes for correcting hemodynamic dysfunction in patients with congestive heart failure has been described over many decades. Drugs such as cardiac glycosides, cathecolamines, phosphodiestherase inhibitors, and calcium sensitizers have been in turn proposed. However, the number of new chemical entities in this therapeutic field has been surprisingly low, and the current selection of drugs is limited. One of the paradigm shifts in the discovery for new inotropes was to focus on 'calcium sensitizers' instead of 'calcium mobilizers'. This was designed to lead to the development of safer inotropes, devoid of the complications that arise due to increased intracellular calcium levels. However, only three such calcium sensitizers have been fully developed over the latest 30 years. Moreover, two of these, levosimendan and pimobendan, have multiple molecular targets and other pharmacologic effects in addition to inotropy, such as peripheral vasodilation. More recently, omecamtiv mecarbil was described, which is believed to have a pure inotropy action that is devoid of pleiotropic effects. When the clinical data of these three calcium sensitizers are compared, it appears that the less pure inotropes have the cutting edge over the purer inotrope, due to additional effects during the treatment of a complex syndrome such as acute congested heart failure. This review aims to answer the question whether calcium sensitization *per se* is a sufficient strategy for bringing required clinical benefits to patients with heart failure. This review is dedicated to the memory of Heimo Haikala, a true and passionate innovator in this challenging field.

1. Historical background

In their classification of congestive heart failure, Forrester and Waters [1] recognized that two major hemodynamic dysfunctions can be manifested in this pathologic state: hypoperfusion (patient cold) and congestion (patient wet), either individually or in combination (patient wet and cold). In their seminal paper, Forrester and Waters [1] also indicated which of the treatments that were available at that time was of use according to the different hemodynamic profiles [1]. For patients with hypoperfusion and hypotension, inotropes were recommended (*albeit* with some caution). The definition of inotropy and inotropes (from Greek *in*-, fiber or sinew, plus-*trope*, turning or moving) in those years was closely linked to the regulation of cardiac contractile force *via* effects on ions [2], and especially on calcium which from 1883 was already considered a vital link in the process of contraction and relaxation [3].

The palette of inotropic drugs that were available in the clinic at the time of Forrester and Waters [1] was limited to digoxin, the peptide glucagon, and the cathecolamines (*i.e.*, isoproterenol, norepinephrine, dopamine). It was recognized that these inotropic agents have different pleiotropic hemodynamic effects, and differed predominantly in their effects on arterial pressure.

From the 1970's to the beginning of the 1980's, great efforts were made to develop new inotropic agents. The hemodynamic effects of dobutamine in man were described as early as 1973 [4], while the phosphodiesterase (PDE) inhibitor amrinone was first described in 1978 [5]. The first description of the cardiovascular properties of enoximone (originally MDL17,043) dates from 1982 [6], and one year later, the clinical effects of milrinone (originally WIN47203) were published [7].

All of these drugs, which were fully developed and became available in clinical practice, share a common feature, *i.e.* they increase contraction by mobilizing calcium. Although this is achieved by various mechanisms of action (Fig. 1), it makes these different drugs similar in terms of the reasons behind their inotropic effects. Indeed, they have recently been described collectively as the 'calcium mobilizers' [8].

This strategy of increasing contraction by increasing intracellular calcium handling, however, comes at a price:

☆ In memory of Heimo Haikala, PhD.

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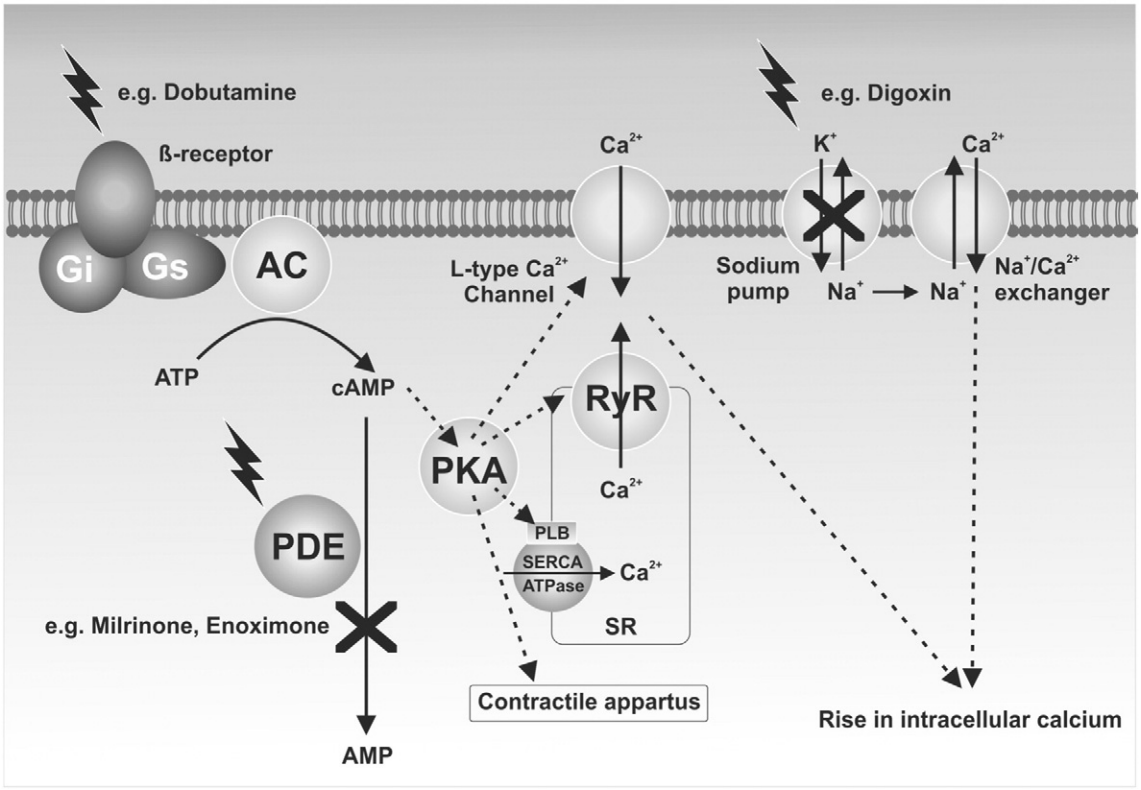

Fig. 1. Mechanisms by which calcium mobilizers increase intracellular calcium. AC, adenylate cyclase; PDE, phosphodiestherase; PKA, protein kinase A; RyR, ryanodine receptor; SERCA ATPase, sarcoplasmic endoplasmic ATP-ase; PLB, phospholamban; SR, sarcoplasmic reticulum.

(i) The increase in oxygen consumption in the myocardium that arises because of the increased need for re-internalization of calcium during diastole can lead to increased risk for ischemic patients; this may foster energy starvation in cardiac cells owing to increased ATP consumption in order to support an increased SERCA activity;
(ii) A further increase in oxygen demand is induced by the chronotropic effect induced by some of the calcium mobilizers (especially those which acts *via* an increase in intracellular cAMP level);
(iii) Drugs acting through modulation of cyclic AMP (*e.g.* cathecolamines, PDE inhibitors) also induce the phosphorylation of troponin I [9] and thus promote calcium desensitization of the contractile apparatus [10] leading to a less efficient contraction;
(iv) Disturbed intracellular calcium homeostasis can lead to ventricular arrhythmia [11] due to early and delayed afterdepolarizations, while unstable intracellular calcium dynamics can promote ventricular extrasystoles and increase the incidence of wave breaks during ventricular fibrillation [12];
(v) The increase in intracellular calcium has been associated with acceleration of myocardial remodeling, and with apoptosis [13];
(vi) Diastolic abnormalities, seen as impaired relaxation and increased diastolic wall stress, are also detrimental consequence of Ca^{2+} overload [14];
(vii) The overall worse prognosis in the mid-term to long-term, whereby the use of dobutamine and PDE inhibitors was specifically investigated in two focused meta-analyses by Tacon *et al.* [15] and by Nony *et al.* [16], respectively. Their conclusion was that these drugs do not provide any benefits in terms of patient survival.

In the 1980's, Solaro [17] and Rüegg [18] suggested that molecules that can sensitize the contractile apparatus to calcium would be better inotropes. The proposed definition of a calcium sensitizer since that time has been a molecule that modulates the contractile force without inducing any changes in the calcium transient. The expectations were that such molecules would not increase oxygen consumption, would not induce arrhythmia, would not have any detrimental effects as regards remodeling or apoptosis, and would not be associated with bad outcome when used in severely decompensated patients.

Also at that time, there was convincing evidence that the cardiac myofibrillar receptor that activates the actin–myosin interaction is troponin C [19]. It was thus straightforward to select troponin as a molecular target for the development of further calcium sensitizers. However, while many such molecules were tested starting from the early 1980's [17], very few underwent complete clinical development. Two

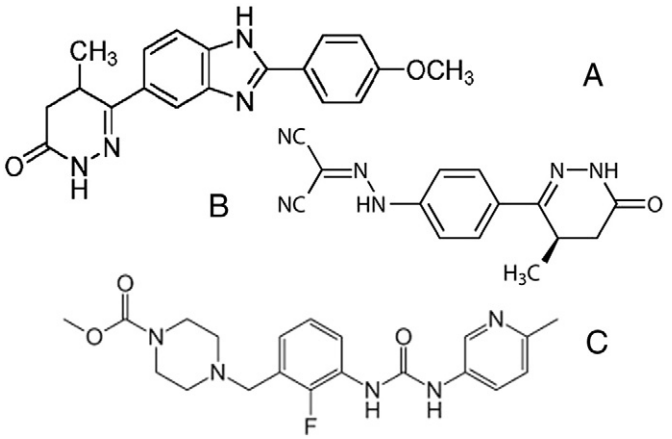

Fig. 2. Chemical structure of the 'calcium sensitizers' pimobendan (A), levosimendan (B) and omecamtiv mecarbil (C).