Editorial

Anti-β₁AR antibodies in dilated cardiomyopathy: Are these a new class of receptor agonists?

Terence E. Hébert*  

Department of Pharmacology and Therapeutics, Faculty of Medicine, 13th floor, Room 1303, McIntyre Medical Sciences Building, 3655 Promenade Sir William Osler, Montreal, QC, Canada H3G 1Y6

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See article by Tutor et al. [9] (pages 51–60) in this issue.

1. Introduction

Under physiological conditions, the β₁-adrenergic receptor (β₁AR) is the predominant βAR responsible for inotropic, chronotropic and lusitropic responses in the myocardium via the classical Gs/adenylyl cyclase/PKA pathway (reviewed in [1–3]). However, during the development of heart failure, sustained β₁AR signalling may also lead to a number of adverse effects including cardiomyocyte hypertrophy and eventually apoptosis. It has become clear in recent years that alterations in the ERK and other MAP kinase signalling cascades play critical and complicated roles in the development of cardiac hypertrophy and the progression towards heart failure [4]. It is also clear that β-adrenergic receptors are key regulators of MAP kinase signalling, especially in the context of heart disease [5]. In a series of interesting papers, Martin Lohse and his colleagues have demonstrated a causal role in disease progression for autoimmune anti-β₁AR antibodies found in patients with dilated cardiomyopathy (DCM, [6–8]). In an article in this issue of Cardiovascular Research, Tutor et al. [9] demonstrate a novel link between all of these observations by showing that anti-β₁AR antibodies from several patients with DCM, but not control sera from healthy donors or sera from DCM patients that do not produce anti-β₁AR, can activate the ERK signalling pathway in a manner distinct from receptor ligands. Their study has significant implications for basic receptor biology as well as the role of these antibodies in modulating βAR function in DCM.

2. Anti-receptor antibodies and ERK signalling

One of the first surprises in the study was that anti-β₁AR antibodies from a number of different DCM patients stimulated ERK1/2 as potently as isoproterenol and with similar kinetics. The same results were obtained in receptor-transfected HEK 293 cells, the HL-1 cardiomyocyte cell line (which expresses the receptor endogenously) and in acutely isolated neonatal myocytes. In all cases, the responses were sensitive to the β₁AR blocker CGP 20712A. Another interesting finding was that isoproterenol and the anti-β₁AR antibodies used different signalling pathways to activate ERK1/2. Although there were some commonalities in that neither response was pertussis toxin-sensitive and both were blocked by the PKA inhibitor H-89, indicating a role for the Gs/adenyl cyclase/PKA cascade, the response to the anti-β₁AR antibodies was inhibited by the src antagonist PP2 but not by mono-dansylcadaverine, a blocker of endocytosis and subsequent receptor internalization. The converse was true for isoproterenol-mediated ERK activation.

The most striking observation in the study is that the localization and likely the putative cellular targets for ERK1/2 also differed between isoproterenol- and anti-β₁AR antibody-stimulated cells. Isoproterenol stimulation resulted in a predominately cytosolic pattern of phospho-ERK accumulation, while stimulation with the anti-β₁AR antibodies led to an...
accumulation of phospho-ERK in the nucleus [9]. A number of studies have shown that the targets of ERK signalling critically depend on where the ERK is localized physically in the cell [10–13]. Interestingly, dual stimulation led to accumulation of phospho-ERK in both cytosolic and nuclear compartments. It would have been interesting in the case of isoproterenol to see if this was due to the β₁AR alone, since isoproterenol also stimulates the β₂AR.

3. Interactions between anti-receptor antibodies and ligands

The distinct signalling pathways and subcellular localizations of phospho-ERK engendered by the different means of receptor activation may alter significantly the outcome of activating the same populations of receptor. Recent experiments suggest that G-protein-coupled receptor signalling pathways can be functionally compartmentalized such that different agonists acting at the same receptor may have different potencies depending on which effector pathway is being assayed (see [14,15] for review). This “agonist trafficking” or “stimulus trafficking” challenges the classical pharmacological definition of efficacy, which posits that agonist potency is independent of effector output. It has been suggested that receptors can exist in distinct states that differ in their ability to interact with a particular G-protein. Thus, agonists can “select” particular receptor/G-protein combinations that differ in their ability to stimulate particular effectors. It follows that a spectrum of ligands may be found, some that are pathway specific and some that target all effector pathways of a given receptor equally. The results presented by Tutor et al. [9] are very important findings as they provide a glimpse into agonist- or stimulus-directed trafficking in a physiological context. This notion is brought into even sharper relief by the observations that co-stimulation with agonist and anti-β₁AR antibodies revealed a synergism between them when lower doses were used. In addition, β₁-blockers such as atenolol or bisoprolol, which were capable of preventing isoproterenol-mediated activation of ERK signalling, had no effect on stimulation by anti-β₁AR antibodies. Thus, the anti-β₁AR antibodies may be acting as an allosteric agonist [15]. The authors suggest that the antibodies may induce conformations of the receptor that are distinct from those induced by agonists. It would have been interesting again to study the antagonist effects on dual stimulation.

One important consideration that this study raises is in the treatment of heart failure in patients with DCM. Specific blockers of β₁AR are often used to reduce the effects of increased sympathetic tone, which leads to this hypertrophy and eventually decompensated heart failure [16,17]. β₁AR stimulation leads directly to a Gs-mediated apoptosis, and it is perhaps not surprising that these receptors are downregulated during the compensatory phase of the development of heart failure (reviewed in [18]). The authors’ data indicate that the anti-β₁AR antibodies alter signalling downstream of the receptor in a manner distinct from the natural ligand, and this calls into question the systematic use of β₁-blockers to treat heart failure. Future therapies may also involve combinations of selected β₂-blockers with immuno-adsorption of anti-β₁AR antibodies in cases where these antibodies are present.

4. Questions remaining

This work opens several lines of inquiry that will need to be pursued in the coming years. First, it would be interesting to have some of these studies pursued in adult cardiomyocytes, certainly the most relevant cell type of patients suffering from DCM and other forms of heart failure where this phenomenon might be important. Next, it will be critical to identify the distinct populations of ERK targets activated by agonist, anti-β₁AR antibodies, or both together during the progression of DCM. How do agonist and antibody stimulation of ERK differ in the involvement of G-protein-coupled receptor kinases and β-arrestin? Do the antibodies recognize and interact with heterodimers of β₁AR and β₂AR, and are the functional effects distinct [19,20]? Do the antibodies affect receptor trafficking from the cell surface, and do they play a role in the downregulation of β₁AR seen during the development and progression of heart failure? It will also be interesting to determine the effects of the antibodies on additional receptor signalling pathways and on the interactions with other signalling partners normally recruited in response to agonist. Finally, the use of antibodies or antibody mimics may allow the development of new types of receptor ligands useful for both therapeutic purposes and for generating a better understanding of receptor function at the molecular level.

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References