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Review

Celecoxib and ion channels: A story of unexpected discoveries

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ABSTRACT

Celecoxib (Celebrex), a highly popular selective inhibitor of cyclooxygenase-2, can modulate ion channels and alter functioning of neurons and myocytes at clinically relevant concentrations independently of cyclooxygenase inhibition. In experimental systems varying from *Drosophila* to primary mammalian and human cell lines, celecoxib inhibits many voltage-activated Na^+, Ca^{2+}, and K^+ channels, including $Na_V1.5$, L- and T-type Ca^{2+} channels, $K_V1.5$, $K_V2.1$, $K_V4.3$, $K_V7.1$, $K_V11.1$ (hERG), while stimulating other K^+ channels—$K_V7.2$–5 and, possibly, $K_V11.1$ (hERG) channels under certain conditions. In this review, we summarize the information currently available on the effects of celecoxib on ion channels, examine mechanistic aspects of drug action and the concomitant changes at the cellular and organ levels, and discuss these findings in the therapeutic context.

Contents

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1. Introduction

The importance of selective inhibitors of cyclooxygenase-2 (COX-2) stems from their use as non-steroidal anti-inflammatory drugs (NSAIDs) with relatively fewer gastric side-effects. Non-selective NSAIDs inhibit both isoforms of cyclooxygenase, a house-keeping COX-1 and an inducible COX-2 (Kalgutkar et al., 1998). Gastrointestinal side effects of NSAIDs are associated with inhibition of gastric COX-1 that mediates the synthesis of a gastric protection factor prostaglandin E_2 (Singh and Triadafilopoulos, 1999) and so the main concept underlying the development of selective COX-2 inhibitors, or coxibs, was to create a "safer aspirin" (Burnier, 2005). After introduction to the market, coxibs (rofecoxib, valdecoxib, and celecoxib) quickly became the NSAIDs of choice. However, after substantial cardiovascular (CV) risks have been found in association with administration of rofecoxib (Vioxx), the drug has been withdrawn from the market in 2004. Removal of valdecoxib (Bextra) has followed quickly in 2005. Celecoxib (Celebrex) remains the only approved coxib for use in the USA. Two other members of this family, etoricoxib (Arcoxia) and lumiracoxib (Prexige), are still sold worldwide but not in the USA, although lumiracoxib has been already withdrawn in Australia and several other countries.

Clinical studies demonstrate that celecoxib may cause increased risk of serious and potentially fatal adverse CV thrombotic events, myocardial infarction, and stroke. The hazard ratio for the composite endpoint of CV complications is 3.1 for 400 mg celecoxib twice daily and 1.8 for 200 mg celecoxib twice daily (Solomon et al., 2008). However, the mechanism(s) implicated in these side effects are not known and a debate surrounding this issue largely revolves around the question whether or not the adverse CV effects of celecoxib result from inhibition of its proper target, COX-2, or arise from the off-target interaction of celecoxib with some other molecules (Shapiro, 2009). It is now established that celecoxib can interact with numerous molecular receptors other than cyclooxygenases. It directly modulates expression of numerous genes involved in many cellular processes, including metabolism (Cervello et al., 2011; Schonthal, 2010), cellular growth, proliferation and death (Dogne et al., 2007; Grosch et al., 2006; Hasinoff et al., 2007). For example, celecoxib inhibits carbonic anhydrases with nanomolar affinity (Weber et al., 2004), displays anti-bacterial activity against *Francisella tularensis* (Chiu et al., 2009), shows cytotoxicity towards rat cardiac myocytes (Hasinoff et al., 2007), and inhibits insulin-like signaling in *Caenorhabditis elegans* with a significant extension of the animal's lifespan (Ching et al., 2011). Recently, however, several reports on celecoxib's ability to directly modulate voltage-activated ion channels have emerged, adding to complexity and non-specificity of the drug action and opening a new dimension to the discussion around its adverse effects. These findings suggest a possibility of a rather straightforward mechanistic explanation for at least some of these effects because ion channel dysfunctions often accompany the primary causes of heart failure and can account for death due to arrhythmias (Amin et al., 2010; Martin et al., 2013). Moreover, as voltage-activated channels are involved in numerous cellular processes apart from providing for excitability, such as cell proliferation, cell volume control, apoptosis and immune responses (Franco et al., 2008; Jehle et al., 2011), these new data may be instrumental for explaining the corresponding changes in cellular functioning in the presence of celecoxib.

It has been shown that celecoxib can alter voltage-activated sodium, calcium and potassium currents, inhibiting or augmenting them with strikingly similar values of IC_{50} in the low micromolar range (Brueggemann et al., 2009; Du et al., 2011; Frolov et al., 2008a, 2011; Macias et al., 2010; Park et al., 2007; Zhang et al., 2007). Instances of myocyte dysfunction as a result of ion channel modulation have been reported in animal models. They include arrhythmic heartbeat in *Drosophila* and cultured rat ventricular cardiomyocytes (Frolov et al., 2008a), vasodilatation of rat mesenteric arteries (Brueggemann et al., 2009), prolongation of action potential duration in mouse cardiac myocytes and action potential shortening in guinea pig cardiac myocytes (Macias et al., 2010). Noteworthy, although research is mainly focused on the CV side effects of celecoxib, modulation of ion channels in other tissues and organs and the corresponding functional changes could be also important. In this article we review the up-to-date information on the effects of celecoxib on ion channels and the corresponding functional changes, discuss the mechanisms of celecoxib action and possible clinical implications.

2. Summary of the effects of celecoxib on ion channels

2.1. Inhibition of voltage-activated Na^+ channels

Several studies, which deal with effects of celecoxib on Na^+ channels, provide highly consistent results. Park and coauthors show that celecoxib can inhibit tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) Na^+ currents in rat dorsal root ganglion (DRG) neurons (Park et al., 2007). In the DRG neurons, the TTX-S current (can be completely blocked by 100 nM TTX) consists of currents through $Na_v1.1$, $Na_v1.6$, and $Na_v1.7$ channels, while the TTX-R current is based upon the currents through $Na_v1.8$ and $Na_v1.9$ channels. Celecoxib inhibits TTX-S and TTX-R currents

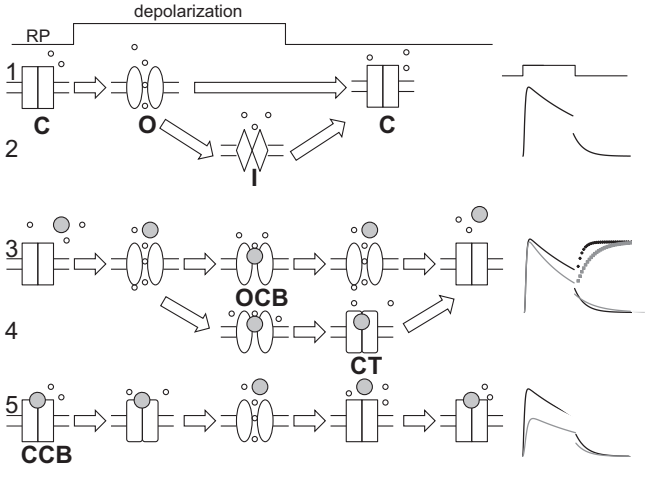

Fig. 1. Schematic depiction of channel gating in the presence of channel blockers. The upper trace shows changes in voltage; RP, resting potential, C, closed channels; O, open channels; I, inactivated channels; OCB, open channels blocked; CT, closed channels with blocker molecule trapped; CCB, closed channels blocked; small open circles, ions; closed gray circles, open-channel blocker molecules; black traces to the right correspond to currents in control, gray traces—to partially blocked currents; dotted traces represent time courses of recovery from inactivation in case of significant involvement of the line 4 gating pathway. See Section 3.2 for detailed explanations.