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Novel Actions of Nonsteroidal Anti-Inflammatory Drugs on Vascular Ion Channels: Accounting for Cardiovascular Side Effects and Identifying New Therapeutic Applications

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used medications for the treatment of both acute and chronic pain. Selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib (Celebrex®), rofecoxib (Vioxx®), and diclofenac, have been among the most widely prescribed NSAIDs because they prevent the generation of prostaglandins involved in inflammation and pain, but avoid some of the gastrointestinal complications associated with less selective COX-1/COX-2 inhibitors. In 2004, rofecoxib (Vioxx®) was voluntarily withdrawn from the market because of adverse cardiovascular side effects. This led to an explosion of research into the cardiovascular effects of the 'coxibs', which revealed differential cardiovascular risk profiles among the members of this drug class. The differential risk profiles may relate to the tendency of some of the drugs to elevate blood pressure (BP). An important component of BP regulation is dependent on the contractile state of vascular smooth muscle cells (VSMCs), which is controlled to a large extent by the activities of KCNQ (Kv7 family) potassium channels and L-type calcium channels. Our recently published data indicate that celecoxib, but not rofecoxib or diclofenac, at therapeutically relevant concentrations, acts as a Kv7 potassium channel activator and a calcium channel blocker, causing relaxation of VSMCs and decreasing vascular tone. These vasorelaxant ion channel effects may account for the differential cardiovascular risk profiles among the different COX-2 inhibitors. We further speculate that these properties may be exploited for therapeutic benefit in the treatment of cardiovascular diseases or other medical conditions.

Keywords

Nonsteroidal Anti-inflammatory Drugs; Cyclooxygenase-2 inhibitors; Cardiovascular effects; Vascular Ion Channels; Blood pressure

Nearly 1 in 4 Americans suffers from chronic pain and many of those seek relief from pain by taking non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs block the cyclooxygenase enzymes (COX-1, COX-2) that often mediate inflammation-related pain. Every day, approximately 3 million Americans take NSAIDs; more than 100 million NSAID prescriptions are written annually in the United States (1,2). Selective COX-2 inhibitors Celebrex® (celecoxib) and Vioxx® (rofecoxib) were introduced to the market in 1999 and

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Conflicts of Interest
No potential conflicts of interest to disclose.

were among the most frequently prescribed new drugs in the United States until 2004, when Vioxx® was voluntarily withdrawn from the market because of a reported increased risk of myocardial infarction and stroke in patients taking the drug for prolonged periods of time. A systematic review of randomized clinical trials of COX inhibitors revealed that rofecoxib, a highly COX-2-selective agent, and diclofenac, an NSAID with COX-2/COX-1 selectivity similar to celecoxib, both significantly increased the risk of cardiovascular (CV) events (3). In contrast, a number of clinical studies failed to demonstrate an increased CV risk with celecoxib relative to placebo (3,4). The reason for the differences between celecoxib and other COX-2 inhibitors have been widely debated.

Differential effects on blood pressure might account for the differences in CV risk profiles. Meta-analysis of results from 19 clinical trials involving COX-2 inhibitors revealed a significantly lower risk for developing hypertension among patients treated with celecoxib compared with rofecoxib (5). Similarly, a retrospective analysis of medical records for patients treated with celecoxib or rofecoxib over a 90-day period revealed that, whereas systolic blood pressure was significantly elevated after 90 days of rofecoxib treatment, systolic blood pressures decreased slightly among the celecoxib-treated patients (6). A reduction in blood pressure might lead to fewer CV complications with celecoxib compared with other COX-2 inhibitors.

The regulation of vascular tone, and hence blood pressure, is under the control of a variety of ion channels in vascular smooth muscle cells (VSMCs). More specifically, two types of ion channels are perhaps most important in determining the contractile state of VSMCs: potassium (K^+) channels, which are primary determinants of the resting membrane voltage, and voltage-gated L-type calcium (Ca^{2+}) channels, activation of which allows Ca^{2+} influx and vasoconstriction. Drugs that target both types of channels (K^+ channel activators and L-type Ca^{2+} channel blockers) are used clinically as antihypertensive medications.

A number of different K^+ channel subtypes are expressed in VSMCs, including several members of the KCNQ (Kv7) family of voltage-gated K^+ channels. Kv7.1 – Kv7.5 channels are encoded by five genes (KCNQ1-5). In excitable cells like neurons, KCNQ K^+ currents, mediated predominantly by Kv7.2/7.3 channels, are crucial for regulating membrane excitability and K^+ transport, and their dysfunction causes corresponding diseases in those tissues (7,8). Consequently, novel drugs that target Kv7 channels are being tested, or are under development, to alleviate chronic pain, epilepsy, and stroke (9). Although Kv7 channels were long thought to be expressed predominantly in the brain, a pivotal role for Kv7 channels was recently identified in VSMCs, in which KCNQ1, KCNQ4 and KCNQ5 are now known to be expressed (10,11). Pharmacological alteration of the activity of these channels has dramatic effects on VSMC excitability, contraction and vascular tone (10-14). Our laboratory also recently discovered that the activity of vascular Kv7.5 channels is suppressed by the pituitary hormone arginine vasopressin (AVP) to mediate its physiological vasoconstrictor effects (11,15). We further demonstrated that Kv7 channel modulators, used clinically to treat a number of neuronal disorders, have pronounced effects on vascular Kv7 channels; these effects are associated with corresponding changes in vascular tone in isolated pressurized rat mesenteric arteries and changes in systemic blood pressure and mesenteric vascular resistance in live rats (11). By screening drugs with structures similar to the known Kv7 channel modulators used for other clinical applications, we have recently identified the COX-2 inhibitor celecoxib (Celebrex®) as a potent and effective activator of vascular Kv7 channels (16).

Our findings from electrophysiological analyses of the effects of celecoxib, rofecoxib, and diclofenac on vascular smooth muscle ion channels revealed that both Kv7 K^+ channels and L-type Ca^{2+} channels are affected by celecoxib: celecoxib is a potent activator of Kv7.5

channels and an inhibitor of L-type Ca^{2+} channels in VSMCs (16). Most importantly, neither rofecoxib nor diclofenac mimicked celecoxib in its effects on either Kv7 channels or L-type Ca^{2+} channels. The effects of celecoxib on vascular ion channels were apparently independent of its COX-2 inhibitory actions because an analog of celecoxib, 2,5-dimethyl-celecoxib (DMC), which does not inhibit COX-2 (17), was as effective as celecoxib in enhancing Kv7.5 currents and suppressing L-type Ca^{2+} currents (16).

The previously unknown effects of celecoxib on vascular ion channels may account for its reduced risk of CV side effects compared with rofecoxib or diclofenac. Our recent studies demonstrated that the Kv7 channel activator flupirtine reduced both systemic blood pressure and mesenteric vascular resistance in live rats (11). We also found that both flupirtine and celecoxib (but not rofecoxib or diclofenac) were very effective in dilating arteries preconstricted with vasopressin (11,16). It is therefore likely that the combined Kv7 channel activating and Ca^{2+} channel blocking actions of celecoxib exert an antihypertensive effect. We hypothesize that pro-hypertensive actions associated with COX-2 inhibition may predominate with agents like rofecoxib and diclofenac, whereas these actions are offset by the aforementioned protective antihypertensive actions of celecoxib, and celecoxib therefore produces fewer adverse CV effects.

A corrollary of this hypothesis is that celecoxib or its analogs might be useful as novel therapeutic agents to treat CV diseases such as hypertension. As noted above, many clinically used antihypertensive agents exert their effects via activation of K^+ channels or inhibition of Ca^{2+} channels. The vasodilatory actions of celecoxib, mediated via Kv7 channel activation and Ca^{2+} channel inhibition, are therefore consistent with a predicted antihypertensive effect. In support of this possibility, a previous examination of renal injury in salt-sensitive hypertension revealed that celecoxib treatment (but not rofecoxib or diclofenac) significantly lowered systolic blood pressures in hypertensive animals after 8 weeks of treatment and protected against renal injury (18). The celecoxib analog, DMC, might be expected to have a greater antihypertensive efficacy than celecoxib because DMC lacks COX-2 inhibitory activity and hence should avoid whatever pro-hypertensive effects may be associated with that activity.

Another potential therapeutic use for celecoxib or its analogs is cerebral vasospasm. Cerebral vasospasm is a devastating consequence of subarachnoid hemorrhage (SAH), which most commonly results from rupture of a cerebral aneurysm. In SAH, sustained spasm of the cerebral vasculature (including basilar and cerebral arteries) is associated with inflammation of the subarachnoid space and blood vessel walls (19). Both cerebral vasospasm and inflammation can result in tissue damage and impaired neurological function, i.e. stroke. According to recent American Heart Association statistics, stroke is the leading cause of adult disability in the United States and Europe and the number two cause of death worldwide. SAH is a common form of stroke and is estimated to account for 4.4% of stroke mortality and 27.3% of all stroke-related years of potential life lost before age 65, a measure of premature mortality (20).

Nimodipine, a calcium channel blocker (CCB) is a current staple of therapy to reduce vasospasm in patients with SAH (21). The rationale for nimodipine use is that it can prevent or reduce cerebral vasospasm by blocking calcium influx into vascular smooth muscle cells, thereby reducing smooth muscle contraction and dilating the cerebral vasculature. However, its efficacy in reducing or preventing SAH-induced cerebral vasospasm is highly variable and its tendency to lower blood pressure may oppose its beneficial effects (21,22). The combination of calcium channel blockade with potassium channel activation observed with celecoxib might be expected to more effectively dilate arteries than would an L-type calcium channel blocker alone. Furthermore, the anti-inflammatory effects of celecoxib might

provide an additional benefit in patients with SAH. Celecoxib has been extensively used as an anti-inflammatory agent in the clinical setting, including a recent small scale clinical trial in patients with intracerebral hemorrhage, in which celecoxib treatment was found to have beneficial anti-inflammatory effects (reduction of hematoma and edema volumes) without increasing the incidence of adverse events (23). Because of its demonstrated safety, its lower propensity to induce hypotension, and because its spectrum of effects would be expected to provide a greater benefit than the currently used CCB therapy, we propose that celecoxib may have greater efficacy than nimodipine in the prevention or reduction of SAH-induced cerebral vasospasm.

The ion channel effects of celecoxib may also have therapeutic relevance that extends beyond the cardiovascular system. In recent years there has been an explosion of interest in the use of COX-2 inhibitors as anti-cancer drugs (24). In the year 2000, celecoxib was approved by the FDA for use as adjunct therapy in the treatment of familial adenomatous polyposis, a condition characterized by abundant COX-2-expressing precancerous (adenomatous) polyps in the colon and rectum. More recently, several dozen analogs of celecoxib were generated with small alterations in their chemical structures (25). Some of these analogs retained COX-2 inhibitory activity, whereas many others did not. Their anti-tumor potency did not correlate with COX-2 inhibitory activity, suggesting that inhibition of COX-2 was not essential for the anti-cancer effects (25,26). One of these compounds, DMC, actually turned out to display stronger anti-cancer activity than celecoxib itself, despite having no detectable COX-2 inhibitory activity (17). We found that DMC was at least as effective as celecoxib in its activation of vascular Kv7.5 channels and inhibition of L-type Ca^{2+} channels (16).

The mechanisms underlying the anti-cancer effects of celecoxib and its analogs are still widely debated, but our findings raise the possibility that these effects relate to previously unrecognized actions on Kv7.5 channels. Potassium channels have received a great deal of attention as cancer targets (27-29). K^+ exiting through K^+ channels decreases intracellular K^+ concentration, which in turn favors apoptotic cell death (27,29). KCNQ5 (Kv7.5) may be a particularly interesting potential target. The anti-cancer effects of celecoxib have been determined to be cell cycle-dependent (G1 phase cell cycle arrest (30)) and KCNQ5 expression has been found to be upregulated in the G1 phase of the cell cycle in rat skeletal muscle myoblasts (31). KCNQ5 is expressed in a wide range of tissues (32-34), including colon, where the anti-cancer efficacy of celecoxib has shown the most promise, and KCNQ5 was identified among 189 genes (out of 13,023 genes analyzed) that had a high frequency of mutation in colorectal cancer (35). Additional studies will be required to determine whether the anti-tumor actions of celecoxib relate to its effects on Kv7.5 channels.

In summary, our recent discovery that celecoxib and its analog DMC are KCNQ (Kv7) potassium channel activators and L-type calcium channel blockers may have important ramifications in terms of predicting the cardiovascular side effects of NSAID therapy and identifying novel therapeutic targets for these agents.

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