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CJ-023,423 (Grapiprant) a Potential Novel Active Compound with Antihyperalgetic Properties for Veterinary Patients

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Abstract: Companion animals are now living longer and so are more commonly manifesting age- and pain-related disease. Nonsteroidal anti-inflammatory drugs are the most used drug in osteoarthritis and inflammatory pain of various aetiologies. Despite their safety profiles have been amended from the COX-non selective to the COX-2 selective inhibitor class, some adverse effects are still of concern especially in long term treatments. One prostaglandin (PG) downstream from the cyclooxygenase enzyme, PGE2, has been recognized as a pivotal mediator of pain and inflammation. The actions of PGE2 are produced by its interaction with four G-protein coupled receptors (EP1, EP2, EP3 and EP4). The EP4 receptor mediates PGE2-elicited sensitization of sensory neurons and studies have demonstrated that EP4 is a major receptor in mediating pain associated with both rheumatoid and osteoarthritis and in inflammation. CJ-023,423 (grapiprant) is a competitive antagonist of human and rat prostanoid EP4 receptors, under development for the control of pain and inflammation associated with osteoarthritisfor use in humans and dogs. A recent study has shown the good safety profile of this active ingredient in dogs. Despite this molecule is still far to be marketed because it pharmacokinetic/pharmacodynamics profile is need to be fully elucidated yet, it might be an interesting active ingredient for the veterinary medicine.

Keywords: Anti-Inflammatory, NSAID, EP4 Receptor, Novel Active Compound, Veterinary Medicine

Introduction

Companion animals are now living longer and so are more commonly manifesting age-related diseases of medical importance such as cancer, arthritis and metabolic disorders. They also share other life style, similarities that make them more suitable animal models than many of the traditionally used laboratory animals that can have drug resistance profiles that are quite different to those in humans (Giorgi, 2012). Most if not all these diseases are pain and inflammation associated. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and selective Cyclooxygenase (COX)-2 inhibitors are mainstays of the pharmacopoeia for the treatment of signs and symptoms of osteoarthritis and inflammatory pain of various etiologies.

Their mechanism of action is to decrease prostaglandin (PG) synthesis by inhibiting COX activities. Two isoforms of COX, COX-1 and COX-2, have been identified. COX-1 is constitutively expressed throughout the body and it is thought to play an essential role in normal gastrointestinal and renal function, whereas COX-2 is induced in the presence of inflammation. NSAIDs inhibit both isoforms and inhibition of COX-1 is thought to cause the adverse gastrointestinal effects such as gastric erosion, ulceration and haemorrhage, whereas inhibition of COX-2 is associated with the therapeutic effects of NSAIDs. Thus, inhibition of PG synthesis by NSAIDs has demonstrated clear efficacy in the reduction of pain and inflammation and also has been shown to have putative effects beyond pain, including gastrointestinal and renal effects. These effects have been shown to be more severe in several animal species rather than in human beings (Khan and McLean, 2012). Selective COX-2 inhibitors were designed to prevent those adverse effects mediated by inhibition of COX-1 (Zhang *et al*., 1997; Hinz and Brune, 2002), but prolonged use of COX-2-selective inhibitors

may, as with NSAIDs, confer a risk of cardiovascular events, including hypertension, edema, heart attack and stroke (Graham *et al*., 2005; Lenzer, 2005; Solomon *et al*., 2005). The cause of the adverse cardiovascular effects remains unclear, but it may include an imbalance in prostacyclin and thromboxane levels in the endothelium (Bing and Lomnicka, 2002) and blockade of prostanoid actions on renal function (Nasrallah and Hebert, 2005). Despite the COX-2 selective inhibitors of second generation have displayed reduced cardiovascular effects and so far they have never been reported in animal species, they still remain a concern for long lasting therapies (Kim and Giorgi, 2013).

Identification of new therapeutic targets downstream of COX may provide an opportunity for the development of new analgesics that interfere with prostanoid proinflammatory and pronociceptive actions with less gastrointestinal, renal and cardiovascular risk.

One PG downstream from the cyclooxygenase enzyme, PGE2, has long been recognized as a pivotal mediator of pain and inflammation (Dannhardt and Kiefer, 2001). The pathological and homeostatic effects of PGE2 are mediated via a family of G protein-coupled receptor subtypes, designated EP1–4 (Fig. 1). These receptor subtypes are distinguished by their distinct pattern of tissue distribution, signaling pathways and physiological functions (Coleman *et al*., 1994). EP1 is coupled to intracellular Ca^{2+} mobilization, EP2 and EP4 are coupled to stimulation of adenylate cyclase via Gs protein and EP3 is coupled to inhibition of adenylate cyclase via Gi protein. Studies performed either in mutant mice lacking the individual PG receptors (Stock *et al*., 2001) or with synthetic EP receptor agonist/antagonist (Nakayama *et al*., 2002) have not yet provided a coherent picture of which EP receptors are responsible for inflammatory pain. Recently it has been reported that EP4 knockdown with intrathecally delivered short hairpin RNA attenuates inflammation-induced thermal and mechanical behavioral hypersensitivity (Lin *et al*., 2006), suggesting that EP4 is a potential target for the pharmacological treatment of inflammatory pain. However, developing subtype-selective EP receptor antagonists has been difficult because of the existence of multiple PG receptor subtypes and the lack of the selectivity of synthetic PG analogs. Thus, defining the contribution of EP receptor subtype to pain sensitization on the basis of available antagonists remains elusive. Nowadays, pets are treated as members of the family and pet owners demand the same level of care they expect for themselves. This change in attitude has resulted in a push for the development of more effective and innovative veterinary therapies (Giorgi, 2012; Giorgi and Owen, 2012a; 2012b; Giorgi and Yun, 2012; Lee *et al*., 2014).

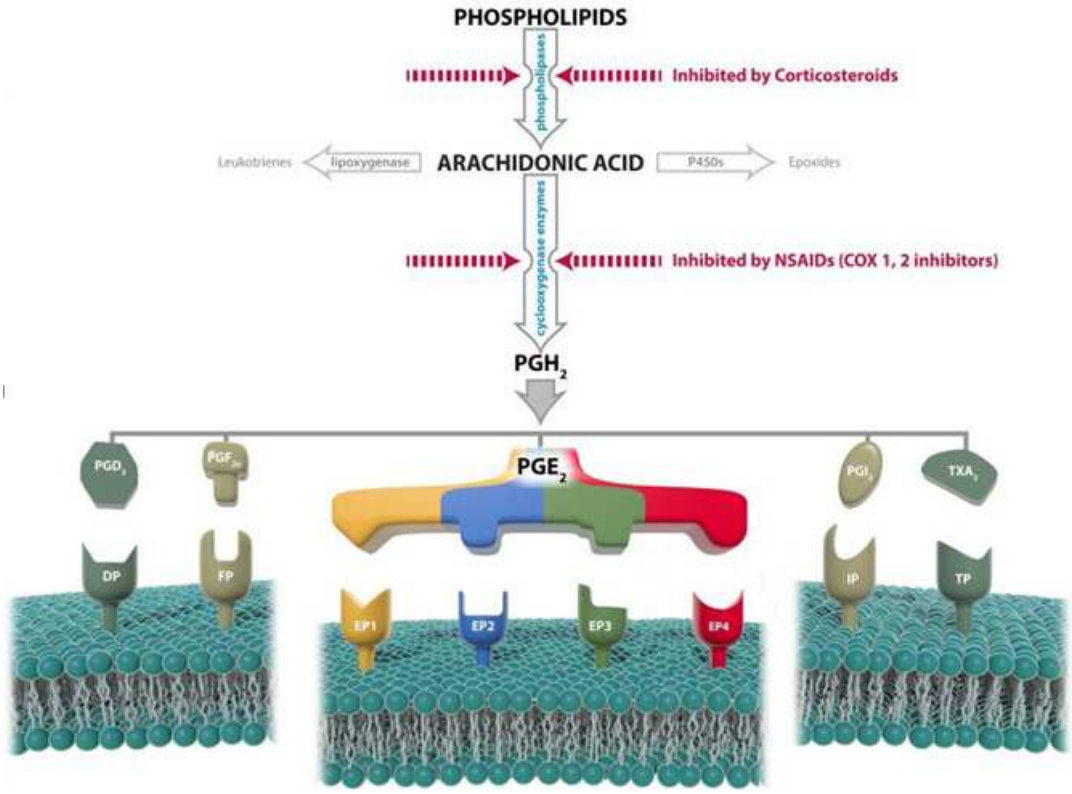

Fig. 1. Phospholipids cascade process involved in inflammation. Target points where diverse drugs can act are indicated

Is hence critical that the research in veterinary pharmacology is aimed to find out new active ingredients with good safety profile and efficacy.

One of the new promising molecules that has been testing with this purpose is the CJ-023,423 (N-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo [4, 5-c] pyridin-1-yl) phenyl] ethyl}amino) carbonyl]-4-methylbenzen esulfonamide), a novel, potent and selective EP4 antagonist (Nakao *et al*., 2007).

CJ-023,423 (also named grapiprant) is highly selective for the human EP4 receptor compared with other human prostanoid receptors (i.e., EP1, EP2, EP3, prostaglandin D, F and I receptors and tromboxan A receptor). Grapiprant was discovered in 2007 and it showed a competitive antagonist of human and rat prostanoid EP4 receptors with similar potency (pA2 = 8.3±0.03 and 8.2±0.2 nM, respectively). In addition it was at least 200 times more selective over other human prostanoid receptors. The *in vivo* pharmacological antagonism of EP4 receptor with grapiprant produces antihyperalgesic effects in rat models of inflammatory pain, suggesting that inflammatory pain can be treated by targeting a single PG receptor subtype EP4 (Nakao *et al*., 2007). Orally administrated CJ-023,423 reduced inflammatory pain such as carrageenan-induced mechanical hyperalgesia and CFA-induced weight-bearing deficit in rats. Grapiprant is now under development for use in humans and dogs for the control of pain and inflammation associated with osteoarthritis. Most of data are protected but recently a short abstract has shown the good safety profile of this active ingredient in dogs. Treatment with grapiprant was well-tolerated when given at doses up to 50 mg kg^{-1} for 9 months to Beagle dogs (Rausch-Derra and Rhodes, 2014). Treatment was associated with mild gastrointestinal signs and with mild and reversible decreases in serum total protein and albumin overtime, with incidence increasing as dose increased. Even with the high dose and long duration of this study, no treatment effects on liver or kidney function, or gross or his to pathological findings of the liver, kidney, or stomach, or on coagulation parameters were reported. The relative lack of toxic effects with grapiprant compared to those seen with non-steroidal anti-inflammatory drugs working via the inhibition of the cyclooxygenase enzymes was expected. Indeed grapiprant, which shows selective antagonism of the EP4 receptor, does not interfere with the production of prostanoids and therefore will not affect the other prostanoid receptor pathways, as occurs with cyclooxygenase inhibitor drugs.

Targets downstream of COX inhibition, such as selective EP4 antagonism, might therefore provide an opportunity for the development of more specific and better tolerated analgesics beyond COX inhibition. Further studies are now needed to investigate the pharmacokinetic and pharmacodynamics profile in the target species.

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