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Review

Peripheral nerve and diclofenac sodium: Molecular and clinical approaches

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medications worldwide. Diclofenac sodium (DS), one of these NSAIDs, has a high specificity for arachidonic acid-degrading cyclooxygenase (COX)-2 enzymes. This drug can be used to relieve neuropathic pain. In this review, we examine the relevant researches, including in vivo, animal, and clinical human studies, with the aim of understanding the effect of DS on the peripheral nerves. In injured nerves, COX-2 is potently upregulated around the injury site. When a nerve is damaged, both COX-1 and COX-2 expression is increased in macrophages and Schwann cells. In addition, COX inhibitors can promote axonal outgrowth in cultured neurons. Neuropathic pain occurs after injury and leads to dysfunction of the peripheral nervous system. NSAIDs can modulate the nociceptive and inflammatory pain pathways and control neuropathic pain. DS may accelerate nerve regeneration and its effects on healing, as well as causing deleterious effects in the developing nerves. DS teratogenicity disrupts myelin sheath thickness and axon structure. Understanding the possible benefits and limitations of DS and specific conditions such as prenatal use will be of benefit in clinical practice.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications worldwide. The efficiency of these drugs has been documented in a number of clinical disorders and surgical procedures. They are commonly used for anti-inflammatory, antipyretic, and analgesic purposes (Siu et al., 2000). Their efficacy in reducing pain and inflammation are particular reasons for their use, and the analgesic effects of diclofenac sodium (DS) have also been demonstrated by its reduction of postoperative pain (Acosta et al., 2007; Ong et al., 2007). The analgesic efficacy, adverse effects, gastrointestinal and cardiovascular risks, and drug interactions of NSAIDs have been intensively studied to ensure that NSAIDs are clinically safe (Ong et al., 2007). NSAIDs have also been analyzed among themselves to identify which are more effective and have fewer side-effects.

The therapeutic effects of NSAIDs on pain and inflammation have been analyzed for many years. Not only their therapeutic effects, but also their biological activities are important. NSAIDs reduce pain and inflammation through inhibition of the pro-inflammatory enzyme cyclooxygenase (COX) (Ong et al., 2007). Non-selective NSAIDs inhibit both COX-1 and COX-2 (Ong et al., 2007; Simon, 1997).

This review addresses the history, current use, side-effects and beneficial effects of DS on peripheral nerves and its use in clinical practice. Additionally, the results of clinical and experimental research indicate that functional, cellular and molecular changes occur in the peripheral nervous system. We also highlight the use of DS in injured nerves in the genesis of neuropathic pain. This knowledge can assist with the design of innovative treatment strategies, since development and regeneration processes are critically important for nervous tissue.

2. Nonsteroidal anti-inflammatory drugs and diclofenac sodium

DS (sodium-(o-((2,6-dichlorophenyl)-amino)- phenyl)-acetate) is an NSAID which has generally been used due to its high specificity for the arachidonic acid-degrading enzyme COX-2, rather than its isoform COX-1, since the 1980s (Canan et al., 2008; Keskin et al., 2015). Prostaglandins (PG), important chemical mediators in the human body, excite and sensitize nociceptors (Acosta et al., 2007; Canan et al., 2008; Gokcimen et al., 2007). NSAIDs are prescribed in the treatment of postoperative pain. The anti-inflammatory effects of NSAIDs are due to an inhibition of the COX-1 and 2. Therefore, they lead to decrease in the PG production. In this context, DS inhibits COX-1 and COX-2, and arachidonic acid is converted into biologically active PGs (Acosta et al., 2007).

The effects of NSAIDs have been studied in various nervous tissues, including the cerebral cortex, hippocampus, and amygdala, dentate

Abbreviations: NSAIDs, nonsteroidal anti inflammatory drugs; DS, diclofenac sodium; CNS, central nervous system; COX-2/PGE2, COX-2-dependent PGE2; COX, cyclooxygenase; MCP-1, monocyte chemo attractant protein 1; NO, nitric oxide; PG, prostaglandin; ROS, reactive oxygen species; MCP-1, monocyte chemo attractant protein 1; MAGL, monoacylglycerol lipase

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gyrus, and peripheral nerves. Expression of the inducible isoform of COX has been demonstrated in the neurons of the cerebral cortex, hippocampus, and amygdala (Andreasson et al., 2001). Exposure to DS has also been shown to cause side-effects in the neurons of the dentate gyrus, in the form of significant neuron losses. Adverse effects of DS exposure have also been shown in both granular and pyramidal cells of the hippocampus (Gokcimen et al., 2007). Another study of the effects of prenatal exposure to DS on the peripheral nerves reported a significant decrease in the number of axons and mean axonal cross-sectional area in DS exposed rats (Keskin et al., 2015). DS also exhibits some different effects to those of other NSAIDs. It suppresses the differentiation of neuronal stem cells into neurons and also inhibits proliferation via the induction of apoptosis. It is important for the possible effects of DS to be analyzed because of its frequent and chronic use. The toxic effects are the main subjects of investigation, in addition to reducing the toxic effects of DS (Simon, 1997).

3. A brief histology and development of the peripheral nerve

The peripheral nervous system (PNS) connects the central nervous system (CNS) to the organs and is involved in the regulation of motor, sensory and autonomic functions (Bekar et al., 2014; Birch, 2013; Gardner and Bunge, 2005). There are several protective layers surrounding the peripheral nerves. These layers consist of different types of connective tissues and constitute approximately 21–81% of the peripheral nerves (Kline and Hudson, 1995). This tissue consists of the epineurium, perineurium and endoneurium (Hunt, 2002), (Fig. 1).

The outermost connective tissue layer encircling all the fascicles is known as the epineurium (Landers and Altenburger, 2003). This consists of longitudinally placed collagen type 1 and 3, elastic fibers, fibroblasts and varying proportions of fat tissue along the nerve (Burnstock and Milner, 1995). Its function is to protect the fascicles against the trauma that occurs during extremity movements. It therefore has a thicker structure, especially at the joint areas (Kaplan et al., 2009; Lundborg, 1987, 1988).

Each fascicle, consisting of a collection of nerve fibers, is enveloped by the mechanically stable and dense perineurium (Lundborg, 1987). This layer is more organized than the endoneurium, since it contains multilayered and lamellar cells in its inner layer and circular, longitudinal and oblique dense collagen fibers in its outer layer (Burnstock and Milner, 1995; Lawrence, 2000). The perineurium keeps the fascicles under low pressure, and the elasticity and integrity of the nerve can be maintained so long as this structure is intact (Lawrence, 2000). Due to the tight and impermeable connections between the cells of the perineurium, this layer functions as the blood-nerve barrier. This barrier plays an important role in maintaining the internal balance of the nerve fiber (Kaplan et al., 2009; Lawrence, 2000). A connective tissue layer known as the endoneurium, which derives from the mesoderm, envelops each nerve fiber. This structure encloses the Schwann cells and the axons. The endoneurium is connective tissue composed of collagen and reticular fibers; fibroblasts, macrophages, mast cells and a capillary system inside mucopolysaccharide ground matter, and serves to maintain the appropriate environment required for nerve functions (Geuna et al., 2009; Hunter et al., 2007; Kaplan et al., 2009; Mills, 2007).

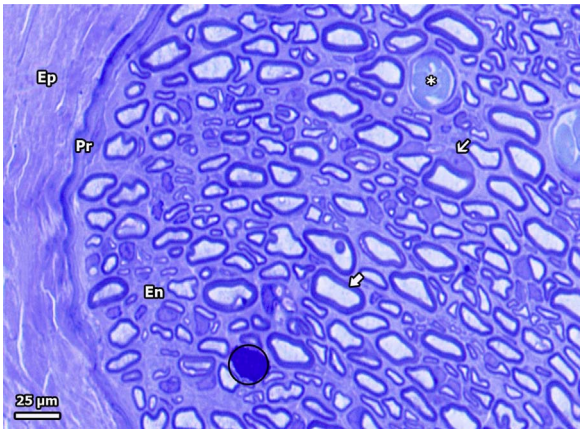

Fig. 1. Light microscopy image showing the histological structure of a peripheral nerve stained with toluidine blue. (Ep), epineurium; (Pr), perineurium; (En), endoneurium; (*), vessel surrounded by the connective tissue; (thin arrow), nucleus of the Schwann cell; (thick arrow), myelinated axon; (circular area), a mast cell.

The PNS consists of cranial, spinal and visceral nerves and cranial, spinal and autonomic ganglia. It derives from the central and peripheral nervous system outline formed by the thickening of the surface ectoderm in the middle part of the embryological plaque to constitute the neural plaque in the 3rd week of embryological development. The structures that develop from the edges of neural plaque are known as the plica neuralis. While the sulcus that is formed from plica neuralis forms the neural tube by being closed off, while the parts that do not participate in the formation of the neural tube constitute the crista neuralis. Crista neuralis derivatives give rise to several cell types of the nervous system and to non-neuronal cells (Moore et al., 2008; Morriss-Kay et al., 1993). The Schwann cells perform the peripheral nerve myelination. The cells that are derived from the neural crest migrate peripherally, envelop the axons and form the neurolemma sheath. At the beginning of the 4th month of fetal life, most nerve fibers assume a white appearance with the accumulation of myelin as it coils several times around the axon. Although the myelination of nerve fibers in the spinal cord starts on the 4th month of life, the myelination of some motor fibers descending from high brain centers to the spinal cord ends in the postnatal 1st year (Baumann and Pham-Dinh, 2001; Foran and Peterson, 1992; Matthews and Duncan, 1971; Song et al., 1999).

4. The role of diclofenac sodium in nerve regeneration and cell development

The inflammatory response plays a crucial role in the regulation processes of degeneration and regeneration that take place after peripheral nerve injury. COX is an enzyme responsible for catalyzing the conversion of arachidonic acid to prostaglandins. Two forms of rate-limiting enzymes in PGE_2 synthesis are COX-1 and COX-2. Inflammatory cells produce abundant amounts of COX-2-dependent PGE_2 (COX-2/PGE_2), and this increases in various disorders (Ma and Quirion, 2008).

COX-2 is potently upregulated around the injury site in damaged nerves. Once a nerve is damaged, both COX-1 and COX-2 expression is dramatically increased in injured nerve macrophages and Schwann cells (Ma and Quirion, 2008). Also, in injured nerves, the monocyte chemo attractant protein 1 (MCP-1), a product of the Schwann cells, becomes activated, and blood-borne monocytes thus migrate and differentiate into tissue macrophages. This indicates that MCP-1 stimulates COX-2 expression (Muja and DeVries, 2004; Tanaka et al., 2006) and PGE2 secretion (Masuko-Hongo et al., 2005) in invading macrophages and other cells. Macrophages play crucial roles, such as degenerating axonal residues and producing and releasing cytokines, growth factors, nitric oxide (NO) and eicosanoids as pro- or anti-inflammatory mediators in the injured nerve (Barton et al., 2017; Wagner and Myers, 1996). The fact that local COX-2-mediated PG production is dramatically increased after nerve injury, and that PGs are capable of modulating the expression of pro- and anti-inflammatory cytokines, suggests that there may be an important role for COX-2 and PGs in the evolution of nerve degeneration and regeneration (Ma and Eisenach, 2003). Both COX-1 and COX-2 expression are increased in macrophages and Schwann cells in animal models of inflammatory demyelinating diseases (Shin et al., 2003) (Fig. 2).

COX inhibitors have been reported to be capable of obstructing myelin debris signals that adversely affect regeneration, thereby