COX-dependent mechanisms involved in the antinociceptive action of NSAIDs at central and peripheral sites

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Abstract

Despite the diverse chemical structure of aspirin-like drugs, the antinociceptive effect of NSAIDs is mainly due to their common property of inhibiting cyclooxygenases involved in the formation of prostaglandins. Prostaglandins are potent hyperalgesic mediators which modulate multiple sites along the nociceptive pathway and enhance both transduction (peripheral sensitizing effect) and transmission (central sensitizing effect) of nociceptive information. Inhibition of the formation of prostaglandins at peripheral and central sites by NSAIDs thus leads to the normalization of the increased pain threshold associated with inflammation. The contribution of peripheral and central mechanisms to the overall antinociceptive action of NSAIDs depends on several factors including the location of the targets of drug action, the site of drug delivery and the uptake and distribution to the site of action.

The present work reviews the data on the regulation and location of cyclooxygenases at central and peripheral sites of the nociceptive pathway and focuses on the role of COX in the generation and maintenance of pain hypersensitivity. Experimental and clinical evidences are used to evaluate the significance of the peripheral and central antihyperalgesic effects of NSAIDs.

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Keywords: NSAIDs; Hyperalgesia; Antinociceptive effects

Abbreviations: CFA, Complete Freund’s adjuvant; CNS, Central nervous system; COX, Cyclooxygenase; DRG, Dorsal root ganglion; NSAIDs, Non-steroidal anti-inflammatory drugs; PG, Prostaglandin; TTX-R, Tetrodotoxin-resistant sodium channels.

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed and widely used drugs in the management of pain, especially pain associated with inflammatory conditions. Despite the wide use of NSAIDs during the last century (the first NSAID, aspirin, was developed in the late 1800s), for a long period only little was known about the mode of action of these drugs. It was not until the 1970s that investigations into the mode of action of aspirin-like drugs were taken over by prostaglandin researchers, who showed an association between prostaglandin production and the action of aspirin-like drugs (Vane, 1964). In 1971, Vane discovered that NSAIDs could inhibit prostaglandin synthesis and proposed that this mechanism was the basis of their pharmacological action (Vane, 1971). This hypothesis was supported by other experimental data demonstrating the presence of prostaglandins at sites of inflammation (Willis, 1969; Di Rosa et al., 1971) and their ability to reproduce some of the cardinal signs of inflammation (Arora et al., 1970). The biomolecular target of NSAIDs was not identified until 1976 when a purified and enzymatically active cyclooxygenase (COX) was isolated from sheep vesicular glands (Hemler & Lands, 1976). It took several years more i.e. until the late 1980s before it was discovered that COX exists in at least two isoforms (Kujubu et al., 1991; Hla & Neilson, 1992), COX-1 and COX-2, and that “classical” NSAIDs are non-selective inhibitors of both isozymes (Xie et al., 1992).

Initially, the principle mode of the antinociceptive action of NSAIDs was considered to be related to their anti-inflammatory action and was thought to be due solely to the inhibition of prostaglandin production at the site of inflammation. This argument has its origin in the experimental observations of Horton (1963), Willis (1969), Juhlin and Michaelsson (1969), Crunkhorn and Willis (1971), Karim (1971) and, particularly, those of Ferreira (1972). By estimating pain in healthy volunteers following the intra-dermal administration of various inflammatory mediators (histamine, bradykinin and alprosadil (PGE1)), Ferreira could show that whilst PGE2 ‘per se’ produced no pain, its presence was essential for the induction of pain by histamine and bradykinin. These findings form the basis of the currently accepted view that PGs are not generally algogenic but act as sensitizing agents for enhancing the nociceptive properties of various inflammatory mediators. Additional evidence for the concept that NSAIDs exert their anti-nociceptive action peripherally comes from tissue distribution data obtained from whole-body autoradiography after administration of various NSAIDs in rats (Brune, 1974). In particular, it was shown that NSAIDs, because of the acidic moiety, can be extensively accumulated in inflamed tissues, where they exert their pharmacological action. At that time, the distribution of NSAIDs in other tissues, in particular in the CNS, was construed only as an explanation for the organ specific toxicity and was not thought to be related to their antinociceptive action (Brune, 1974).

The traditional belief that NSAIDs have exclusively a peripheral mode of action was not challenged until the beginning of the 1990s in the wake of the growing evidence that the anti-inflammatory and the antinociceptive effects of NSAIDs are unrelated (McCormack & Brune, 1991). So, an existence of some central antinociceptive mechanisms, an idea initially put forward by Hazlick as early as 1926 (Jurna, 1926), has been suggested (Ferreira et al., 1978; Carlsson et al., 1988). Although various mechanisms have been proposed to account for central effects of NSAIDs (Bjorkman, 1995), inhibition of prostaglandin synthesis (Abdel-Halim et al., 1978; Ferreira et al., 1978) in the CNS, and particularly in the spinal cord (Jurna et al., 1992; Malmberg & Yaksh, 1992), appears to be a property of all NSAIDs. Furthermore, the finding that both COX isozymes, i.e. COX-1 and COX-2, are expressed in the CNS (Kaufmann et al., 1997) and the observation that experimental induction of peripheral inflammation is associated with an increase in the expression of COX-2 in the spinal cord (Beiche et al., 1996) have been used as evidence supporting a central antinociceptive mechanism of action of NSAIDs (Vasquez et al., 2001; Vanegas, 2002).

This review of the central and peripheral antinociceptive mechanisms of action of NSAIDs mainly focuses on the inhibition of cyclooxygenase-mediated prostaglandin synthesis, as a class-like pharmacological property of NSAIDs. Cyclooxygenase-independent actions of NSAIDs, including cellular mechanisms mediated via interference with transcription factors (Tegeder et al., 2001b) and direct modulation of the activities of various ion channels (Lee et al.,
The mechanisms and clinical manifestations involved in inflammatory pain, a condition commonly treated with NSAIDs, are dealt with first and this is followed by a discussion on the location and regulation of the main target of NSAIDs, cyclooxygenases at the central and peripheral sites. Biochemical aspects of prostaglandin synthesis are presented and special attention is given to the mechanisms of the prostaglandin-mediated hyperalgesia. The final section deals with the antihyperalgesic action of NSAIDs where attention is given to the currently available experimental and clinical evidence supporting their peripheral and central mechanisms. The contribution of both mechanisms to the overall antinociceptive action of this class of analgesics is discussed.

2. Inflammatory pain

The nociceptive signalling in physiological pain is initiated by activation of the specialized pain receptors (nociceptors), which are polymodal sensory fibres of the primary sensory neurons located in trigeminal and dorsal root ganglia (DRG). Although the nociceptors are able to respond to a wide range of stimulus modalities, different noxious stimuli generally cause activation of a single receptor [e.g. heat activates TRPV1 receptors (Caterina et al., 1999) and mechanical force, P2X3 receptors (Nakamura & Strittmatter, 1996)]. The activation of nociceptors generates depolarizing currents (transduction), which are conducted to the spinal cord along unmyelinated, slow conducting C fibres and more rapidly conducting Aδ primary sensory fibres (conduction). This sensory inflow then activates secondary sensory neurones in the dorsal horn of the spinal cord through synaptic transfer (transmission), which project to the cortex via a relay in the thalamus.

Whilst physiological pain has a protective function in warning the body of potentially damaging stimuli, inflammatory pain associated with any kind of tissue damage has a pathological character. The specific hallmark of inflammatory pain is sensitization, which is a process involving a reduction in the threshold for activation, an increase in response to a given stimulus and the appearance of spontaneous activity in the nociceptors. It manifests itself clinically as hyperalgesia (enhanced response to noxious stimuli) or alldynia (sensation of pain in response to a previously non-noxious stimulus). Both phenomena are an expression of neural plasticity which is a response of the nervous system to the peripheral tissue injury and inflammation (Woolf & Salter, 2000). Sensitization can occur at both the peripheral and central level of nociceptive processing (Woolf, 1983), where prostanoids are potent sensitizing agents involved in the modulation of transduction and transmission of nociceptive information.

3. Cyclooxygenase-prostanoid cascade in nociceptive processing

3.1. Prostaglandin synthesis

Despite the diverse chemical structure of aspirin-like drugs, the antinociceptive effect of NSAIDs is mainly due to their common property of inhibiting cyclooxygenases involved in the formation of prostanoids. Prostanoids are formed by most cells and act as autocrine and paracrine lipid mediators. They are not stored but are synthesized de novo from membrane-released arachidonic acid mobilized by phospholipases (PLA2) when cells are activated by mechanical trauma, cytokines and growth factors, etc. Conversion of arachidonic acid to prostanoid endproducts is carried out by cyclooxygenases (COX), also known as prostaglandin H synthase (PGHS), at two different sites on the enzyme. Arachidonic acid is initially cyclized and oxidized to the endoperoxide PGG2 at the cyclooxygenase site of the COX and the product then reduced to a second endoperoxide PGH2 at the peroxidase site (Garavito & deWitt, 1999). Subsequent formation of prostaglandin end products from PGH2 depends on the presence of specific synthases that produce the functionally important prostanoids PGE2, PGF2, PGI2 (prostacyclin) and TXA2 (thromboxane).

These prostaglandins may undergo facilitated transport out of the cell by prostaglandin transporters (PGT) and other carriers and exert autocrine or paracrine actions on a family of prostaglandin receptors on the cell membrane that bind PGE2 (EP1, EP2, EP3, EP4 receptors), PGD2 (DP1, DP2 receptors), PGF2 (FP receptor), PGI2 (IP receptors) and TXA2 (TPo and TPβ receptors). Prostaglandin receptors, with the exception of DP2 which is a chemoattractant receptor, belong to three clusters within a distinct subfamily of a G-protein-coupled superfamily of receptors. The “relaxant” receptors IP, DP1, EP2 and EP4 in one cluster signal via Gs-mediated increases in intracellular cyclic adenosine monophosphate (cAMP). The “contractile” receptors EP1, FP and TP form a second group that signals via Gq-mediated increases in intracellular calcium. The EP3 receptor is regarded as an “inhibitory” receptor that couples to Gi and decreases cAMP formation. The differential expression of the synthases and prostaglandin receptors are determinants of the prostanoïd-production profile within various cells.

3.2. Biochemistry of cyclooxygenases (COX)

COX exists as two isoforms, COX-1 and COX-2. It has recently been shown that the COX-1 protein family consists of at least four different mRNA variants derived from the COX-1 gene. These include COX-1 itself, COX-3 and the two truncated partial pCOX-1 sequences, pCOX-1a and pCOX-1b (Chandrasekharan et al., 2002; Dinchuk et al., 2003). Apart from COX-1, only the COX-3 transcript, which contains the catalytic structure of COX-1 and retained
intronic 1, has been shown to possess cyclooxygenase activity in dogs. However, on the basis of nucleotide sequence data obtained in humans, the existence of COX-3 has been called to question by at least two independent research groups (Dinckhuk et al., 2003; Schwab et al., 2003).

COX-1 and COX-2 are membrane-associated enzymes with a molecular weight of 71 kDa and an amino-acid sequence similarity of 63% (Vane et al., 1998; Hawkey, 1999). The COX-2 gene is a small immediate early gene (8.3 kb), whereas COX-1 originates from a much larger (22 kb) gene (Garavito et al., 2002; Vane et al., 1998).

The identification of two isoforms of COX in the early 1990s offered the simple and attractive hypothesis. It was believed that COX-1, being found in almost all cells, is the constitutive “house-keeping” enzyme responsible for production of basal “beneficial” PGs, vital for protecting the stomach through production of mucus and the maintenance of renal blood flow. Furthermore, COX-2, which has low expression or is undetectable in most cells but increases dramatically in a variety of pathological conditions, was proposed to be an inducible enzyme responsible for the “pathological” production of PGs during inflammation and in cancerous states. However, experience gained from the introduction of selective COX-2 inhibitors showed that the mechanisms inherent in the above hypothesis were more complicated than initially thought since evidence was accruing that COX-1 and COX-2 both have physiological and pathological roles (Garavito et al., 2002). A notable exception thus concerns the COX isoforms in the CNS and the localization, regulation and involvement of these in nociception will be discussed in the subsequent section.

3.3. Cyclooxygenase (COX) and prostanoids at peripheral sites

COX-2 is the predominant isoform expressed in injured tissue and a main source of prostanoids during inflammation. This evidence comes from various experimental models, including the subcutaneous air pouch (Appleton et al., 1995) and carrageenan-induced pleurisy in the rat (Tomlinson et al., 1994). In these models, polymorphonuclear leucocytes, phagocytosing mononuclear cells and fibroblasts show an increased expression of COX-2 and PGE2 is the most abundant prostanoid found in the injured tissue. However, it is important to note that the quantity of prostanoid produced and the profile of prostanoid production during the inflammatory reaction can change. For example, in the carrageenan-induced pleurisy model, elevated PGE2 levels are only observed during the early stages of inflammation, whereas the production of PGD2 is most pronounced during the final stages of the response (Gilroy et al., 1999). Thus, the quantity and variety of prostanoids produced during inflammation and which can contribute to peripheral sensitization are determined by the nature and the activation state of the cells present in the inflammatory lesion.

Although the induction of COX-2 expression by inflammatory stimuli is mainly responsible for the high prostanoid levels at the site of inflammation, the role of COX-1 in modulating the inflammatory response should not be overlooked. The involvement of COX-1 in the inflammatory response is supported by experimental findings showing an increase in COX-1 in circulating monocytes on exposure to LPS (McAdam et al., 2000) and the early production of prostaglandins in stimulated mast cells (Reddy & Herschman, 1997). There are also results from studies in mice deficient in the expression of COX-1 or COX-2 which indicate that COX-1 has a unique role in the initiation of certain inflammatory responses, for example, in the arachidonic acid-induced inflammation of the ear and in the subdermal air pouch model (Langenbach et al., 1995, 1999).

Both COX isoforms are involved together in the inflammatory reaction and may contribute to peripheral sensitization where the earliest prostanoid response is dependent on COX-1 and COX-2 becomes a major source of prostanoid production as inflammation progresses.

3.4. Cyclooxygenase (COX) and prostanoids in CNS

In contrast to the situation in the periphery, both COX-1 mRNA and COX-2 mRNA as well as COX-1 and COX-2 proteins are expressed constitutively in neurons and non-neuronal elements of cervical and lumbar sections of the spinal cord (Beiche et al., 1996). COX-2 appears to be the predominant isoform and is present in neurons of all laminae, particularly the superficial layers, motoneurons and non-neuronal cells such as astrocytes (Goppelt-Streebe & Beiche, 1997; Willingale et al., 1997; Beiche et al., 1998). COX-1 expression at the spinal level is not extensive and can only be found in the cytoplasm of glial cells. Dorsal root ganglion (DRG) cells contain mainly COX-1 which is located in the cytoplasm, nuclear membrane and axonal processes of small- and medium-sized neuronal cell bodies (Willingale et al., 1997). The presence of COX-2 mRNA in DRGs, however, has also been reported (Inoue et al., 1999).

Although both isoforms are constitutively expressed in the spinal cord, there is a significant difference in the way in which they are regulated. Whereas COX-2 expression can be induced above the constitutive level by several experimental conditions, the same stimuli cause no significant increase in COX-1 mRNA. Thus, an increase in COX-2 mRNA is seen in DRG cell cultures stimulated with IL-1β (Inoue et al., 1999); COX-2 expression in the spinal cord of experimental animals is increased after intraspinal injection of exogenous IL-α (Tonai et al., 1999) and after induction of spinal cord injury associated with increased levels of endogenous IL-α and IL-1β (Resnick et al., 1998; Tonai et al., 1999).

The up-regulation of spinal COX-2 also takes place during peripheral inflammation. In experimental animals, the induction of neuronal and non-neuronal COX-2 in ipsi- and contralateral portions of the cervical and lumbar cord...
has been observed after hindpaw injection of several irritants such as carrageenan (Hay & de Belleroche, 1997; Ichitani et al., 1997; Ebersberger et al., 1999; Maihofner et al., 2000), zymosan (Maihofner et al., 2000; Tegeder et al., 2001a) and complete Freund’s adjuvant (CFA) (Beiche et al., 1996, 1998a; Hay & de Belleroche, 1998; Samad et al., 2001). The up-regulation is paralleled by a substantial elevation in basal and evoked PG, mostly PGE2, in the cerebrospinal fluid and hyperalgesive behaviour of the animals. In contrast to the events which take place during the inflammatory response in peripheral tissue where both phospholipase A2 (PLA2), another rate-limiting step in prostaglandin synthesis, and COX-2 contribute to the increased production of prostaglandins, in the spinal cord there is no increase in the activity of PLA2 (Saunders et al., 1999, 2001). Thus, COX-2 in the spinal cord appears to have a major role in the elevation of PGE2 during peripheral inflammation and is mainly responsible for the central hypersensitivity observed with inflammation. However, this does not exclude COX-1 in the spinal cord also being a source of spinal PGs in peripheral inflammation and, indeed, this has been demonstrated in COX-2-deficient knockout mice (Ballou et al., 2000). Recent findings have also shown that COX-1 plays an important role in spinal nociceptive processing and sensitization after surgery (Zhu et al., 2003) and that the expression of COX-1 in the spinal cord changes in a time- and laminar-dependent manner after nerve injury (Zhu & Eisenach, 2003). This suggests that the inhibition of spinal COX-1 may be useful in the treatment of post-operative and neuropathic pain.

A significant increase in COX-2 mRNA is also observed in supraspinal structures of the CNS including the pons, ventral midbrain, hypothalamus, thalamus and areas of cortex limited to somatosensory processing. These changes resemble the up-regulation of COX-2 in the spinal cord which occurs in response to peripheral inflammation (Samad et al., 2001) and are associated with an increase in PGD2 in cerebrospinal fluid, a major prostaglandin found in rodent brain homogenates (Abdel-Halim et al., 1978).

An important question concerns the nature of the linkage between peripheral inflammation and the up-regulation of COX-2 in the CNS where both neuronal and humoral mechanisms may be important. On the neuronal side, prolonged activity in small primary afferents generated by local inflammation results in afferent-evoked release of glutamate/aspartate and substance P in the spinal cord leading to activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NK-1 (neuromedin-1) receptors and this is followed by activation of NMDA (N-methyl-D-aspartate) receptors in dorsal horn neurones (Dickenson et al., 1997). Stimulation of these receptors may produce a synaptic activity-dependent increase in the transcription of a variety of enzymes, including spinal COX-2. On the humoral side, peripheral inflammatory reactions associated with tissue injury result in the release of pro-inflammatory cytokines such as TNF-α and IL-1β, which can enhance the transcription of COX-2. Samad et al. (2001) addressed this question in a study of the COX-2 expression in the spinal cord in animals with a complete sensory and motor blockade of sciatic nerve conduction carried out prior to inducing hind-paw inflammation with CFA. Neural blockade produced a slight but not complete attenuation of the COX-2 mRNA induction in the lumbar spinal cord and electrical stimulation at C-fibre-strength of the sciatic nerve increased the induction of spinal COX-2 by much smaller extent than that produced by inflammation. These findings and the knowledge that the transcription of COX-2 in the spinal cord is delayed (COX-2 up-regulation is at maximum 6 h after the induction of inflammation) lead Samad et al. to favour a non-neuronal mechanism of central COX-2 induction mediated by IL-1β. It has, indeed, been shown that the intrathecal injection of IL-1β causes the up-regulation of COX-2 and there is a significant reduction in COX-2 mRNA levels following the intrathecal administration of IL-1β receptor antagonists and interleukin-convert ing enzyme (ICE) inhibitor. The current view is that circulating IL-1β, which is released at peripheral sites after injury and cannot pass the blood–brain barrier, induces COX-2 and specific PGE2 synthases (mPGES) in the cell lining of the barrier. This is followed by the entry of de novo synthesized PGE2 into the brain and cerebrospinal fluid and prostanooid receptor activation in neurons and microglia.

3.5. Mechanisms of prostaglandin-mediated hyperalgesia

Prostaglandins are potent sensitizing agents, which are able to modulate multiple sites in the nociceptive pathway enhancing transduction (peripheral sensitizing effect) and transmission (central sensitizing effect) of nociceptive information. PGE2 is thought to be a principle mediator of the hypersensitivity (Daher & Tonussi, 2003) but several prostanooids show similar effects (Ferreira & Lorenzetti, 1981; Hamilton et al., 1981).

The hyperalgesic properties of prostaglandins in the periphery have been demonstrated in human and experimental studies. The subcutaneous injection of a small dose of PGE2 in human volunteers produces long-lasting hyperalgesia to mechanical and chemical stimuli although PGE2 per se does not produce spontaneous pain (Ferreira, 1972). Monoclonal antibodies against PGE2 inhibit hyperalgesia in carrageenan-induced rat paw edema and reduce the nociceptive dorsoflexion response to the intraperitoneal injection of phenylbenzoquinone in mice (Mnich et al., 1995). In vitro, PGE2 is able to significantly sensitize the canine testicular polymodal receptors of sensory C-fibre receptors to heat and bradykinin by acting on EP2 and EP3 receptors, respectively (Mizumura et al., 1987; Kumazawa et al., 1996).

The central hyperalgesic properties of prostanooids have been established mainly in experimental studies with intrathecal administration of PGE1, PGE2, PGF2α, PGI2 and TxB2 which evoke thermal and mechanical hyperalgesia.
(Uda et al., 1990; Minami et al., 1992, 1994) and mimic the central sensitization associated with peripheral inflammation (Vanegas & Schaible, 2001). These effects appear to be mediated by several subtypes of prostanoid receptors (Tilley et al., 2001) including EP1 (Stock et al., 2001), EP3 (Minami et al., 2001) and IP receptors (Murata et al., 1997). The observation that IP, EP1, and EP3 receptors are co-expressed in peripheral and central structures involved in the nociceptive pathway is consistent with this hypothesis (Oida et al., 1995).

3.5.1. Peripheral sensitization

The main mechanism involved in the hyperalgesic action of prostaglandins is traditionally considered to be due to a sensitizing effect on primary afferent nerves (Davies et al., 1984). The molecular targets associated with this mode of action, however, have only recently been identified where both direct and indirect mechanisms of the hyperalgesic action of PGs have been discussed. The direct effects are mediated by the action of prostaglandins on EP/IP receptors and modulation of ion channels in primary afferents. The indirect effects are directed towards enhancing the sensitivity of sensory neurons to noxious agents such as heat and bradykinin and also assumed to contribute significantly to the PG-mediated peripheral sensitization (Fig. 1).

When PGs act via prostaglandin receptors, they decrease the activation threshold of a specific subclass of voltage-gated sodium channels i.e. TTX-R Na⁺ (tetrodotoxin-resistant sodium channels) (Gold et al., 1996a) which are expressed in nociceptors and are involved in the transduction of nociceptive information. These channels are believed to contribute significantly to the firing-rate and duration of the action potential in small-diameter sensory neurons (Baker & Wood, 2001). PG-mediated modulation of the TTX-R Na⁺-current involves phosphorylation of the TTX-R channels following activation of the protein kinase A (PKA) pathway (England et al., 1996). Protein kinase C (PKC) is also thought to be involved but the exact role of the enzyme is not clear (Gold et al., 1998). Which of the two known TTX-R Na⁺-channel subtypes within DRG (Na⁺,1.8 or Na⁺,1.9) are targeted by prostaglandins and under what conditions this occurs has also yet to be determined.

Behavioural analysis of Na⁺,1.8-deficient mice revealed modest deficits in acute sensation to noxious stimuli and a delayed onset of inflammatory thermal hypersensitivity, although the maximal response was equivalent to that in wild-type animals (Akopian et al., 1996). Such observations support the involvement of Na⁺,1.8 in hypersensitivity resulting from tissue injury and indicate that this subtype of TTX-R Na⁺-channels is a target for prostanoids. However, redundancy of voltage-gated Na⁺ channel subtypes in nociceptor function has not been ruled out.

It is known that PGE₂ and PGI₂ can sensitize primary afferent neurons by inhibiting voltage-gated potassium currents and this mechanism could contribute to neuronal excitability (England et al., 1996; Nicol et al., 1997). This modulation, like the enhancement of the TTX-R sodium current described above, also results from the activation of protein kinase A (Evans, et al., 1999) and leads to an increase in membrane resistance, a decrease in the firing threshold and an increase in the number of action potentials per stimulus. PGE₂ may also inhibit a potassium current by increasing intracellular calcium in capsaicin-sensitive primary afferent neurons (Gold et al., 1996b).

In addition to the actions described above, prostaglandins can also enhance the sensitivity of sensory neurons to excitatory chemical agents such as bradykinin acting via B₂ receptors (Cui & Nicol, 1995) and capsaicin acting via TRPV₁ receptors (Lopshire & Nicol, 1998).

3.5.2. Central sensitization

PGE₂ is released within the spinal cord after peripheral nociceptive stimulation. Results from in vivo spinal microdialysis and sampling of cerebrospinal fluid show an increase in PGE₂ following i) acute activation of small afferents using intraplantar injection of formalin and application of heat (Malmberg & Yaksh, 1995; Scheuren et al., 1997); ii) chronic inflammation following the injection of carrageenan in a knee joint and intraplantar injection of FCA and zymosan (Ebersberger et al., 1999; Guhring et al., 2000; Samad et al., 2001); and iii) intrathecal administration of substance P, NMDA and kainate (Yang et al., 1996; Hua et al., 1999) and the systemic administration of cytokines (Samad et al., 2001). These increases in the release of PGE₂ have functional relevance since they are typically blocked.
by the intrathecal and systemic administration of COX inhibitors.

Although specific binding sites for PGE₂ (Kawamura et al., 1997) as well as proteins and mRNA of all four known subtypes of PGE₂ receptors (EP₁–EP₄) have been detected in the dorsal horn of the spinal cord, the exact molecular and cellular elements involved in PGE₂-mediated central hyperalgesia have not yet been fully elucidated. The effects of prostaglandins are thought to occur from an action on both presynaptic and post-synaptic membranes of the primary afferent synapse in substantia gelatinosa of the spinal cord (Fig. 2). An action of PGE₂ on prostanoid receptors at the presynaptic membrane may cause enhancement of nociception by facilitating the spinal release of the excitatory neurotransmitter glutamate (Nishihara et al., 1995) and neuropeptides (substance-P and/or calcitonin gene-related peptide) (Nicol et al., 1992; Hingtgen & Vasko, 1994) from primary afferent C-fibre terminals, as has been demonstrated in DRG cells and isolated spinal cord tissue. These effects are mediated by an increase in the inward calcium current.

At the post-synaptic level, PGE₂ can directly activate deep neurons in the dorsal horn via EP-2-like receptors, thus enhancing the transmission of nociceptive responses (Baba et al., 2001). Recent evidence indicates that PGE₂ may also facilitate the transmission of nociceptive input by blocking inhibitory glycnergic neurotransmission to dorsal horn neurones (Harvey et al., 2004) by activation of EP₂-like receptors, cholera-toxin-sensitive G-proteins and cAMP-dependent protein kinase in the inhibitory neurones (Ahmadi et al., 2002).

4. Central and peripheral antihyperalgesic effects of non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a disparate group of weakly acidic, highly protein-bound compounds having the common pharmacological property of inhibiting prostaglandin biosynthesis (Smith et al., 1994; Kirtikara et al., 2001). This inhibition results from a variety of effects on cyclooxygenases including the irreversible inactivation of COX (e.g. by aspirin) and reversible competitive inhibition of COX (e.g. with ibuprofen). NSAIDs usually normalise the increased pain threshold associated with inflammation rather than elevate a normal pain threshold and thus their antinociceptive action is more accurately described as antihyperalgesic than as analgesic.

The existence of a central component in the antinociceptive action of NSAIDs demonstrated by Ferreira et al. (1978) is supported by the finding of a significant dissociation between the anti-inflammatory and antinociceptive effects of aspirin-like drugs (Brune et al., 1991; McCormack & Brune, 1991). Quantification of this dissociation has been carried out using a dissociation index which is defined as the mean potency of the NSAID in an in vivo model of inflammation (i.e. ED₅₀ required to inhibit carrageenan-induced edema) divided by the mean potency of the agent in an in vivo model of pain (i.e. ED₅₀ required to reduce the number of writhings after intraperitoneal injection of phenylbenzoquinone) (McCormack & Urquhart, 1995). The magnitude of this dissociation with various NSAIDs can be visually assessed by plotting the index.
against a clinical measure of the antihyperalgesic efficacy of the NSAID determined in the post-dental extraction pain model (i.e. mean placebo-corrected 4-h sum of pain intensity differences) and this dissociation parameter may reflect the net effect of the interaction between COX-dependent peripheral and central sites of action (the possibility that additional mechanisms of action, other than an inhibition of PG-synthesis are involved, cannot be ruled out). Using these quantification methods, the NSAIDs ketoprofen, ketorolac and bromfenac had particularly large dissociation indices suggesting that the contribution of non-peripheral antinociceptive mechanisms in the action of these drugs may be of particular significance.

From the pharmacological point of view, the relative contribution of central and peripheral mechanisms to the overall antinociceptive action of an NSAID depends on:

- site of drug delivery (e.g. systemic, local–peripheral, epidural, spinal intracerebro-ventricular) and
- uptake and distribution from the site of drug delivery, as determined by factors such as physical and chemical properties of the NSAID, specific transport mechanisms, local and systemic blood flow and tissue barriers to drug permeation such as the blood–brain barrier.

The particular role of these factors is discussed in the subsequent sections.

4.1. Intrathecal delivery of non-steroidal anti-inflammatory drugs (NSAIDs) in behavioural studies in animals

An accepted approach for establishing that NSAIDs alleviate pain by acting on the CNS is to measure antinociceptive activity after direct application to spinal and supraspinal tissues and this approach has gained particular importance in behavioural studies in animals. The intrathecal application of NSAIDs has been tested in models of acute short-term and long-term inflammatory pain, including formalin-induced flinching (the so-called formalin test), carrageenan-induced thermal hyperalgesia, zymosan-induced thermal hyperalgesia and CFA (Table 1).

The formalin test is a classical model of acute inflammatory pain. Subcutaneous injection of formalin into the hind paw of the animal induces a stereotypical biphasic response, consisting of an early, short-lasting painful response occurring about 3 min after injection, followed by a prolonged period of tonic/persistent pain after 20–30 min. The first phase results from a direct activation of C-fibres due to the peripheral stimulus, whereas the second phase involves a period of sensitization associated with acute inflammation. The precise origin (i.e. central or peripheral) of the second phase is a subject of debate (Tjolsen et al., 1992; Yashpal et al., 1998), therefore, its inhibition with systemically administered NSAIDs (Hunskaar & Hole, 1987; Geisslinger et al., 1994; Yashpal & Coderre, 1998) may have both peripheral and central components. However, a significant reduction in nociceptive behaviour after intrathecal application of NSAIDs at doses that are inactive systemically is clear evidence for a central nociceptive mode of action. The rank order of potency and ID₅₀ on intrathecal delivery is: indomethacin ≥ flurbiprofen > ketorolac > zomepirac > S(+)-ibuprofen ≥ ibuprofen (racemic) > acetylsalicylic acid > acetaminophen (Malmberg & Yaksh, 1992). Intrathecal application of R(-)-flurbiprofen, which is only a very weak COX-inhibitor, also shows antinociceptive activity (Brune et al., 1991; Geisslinger et al., 1994; Malmberg & Yaksh, 1994) suggesting that the central mode of action of R-flurbiprofen is independent of COX-inhibition (Geisslinger et al., 1994).

The central antihyperalgesic effects of NSAIDs have been extensively studied in the modified tests of acute pain, where the nociceptive stimuli (thermal or mechanical) are applied to that part of the body (e.g. paw) which is inflamed following subcutaneous injection of an irritant such as carrageenan, zymosan and CFA. In experiments of this type

<table>
<thead>
<tr>
<th>Experimental pain model</th>
<th>Drug</th>
<th>Effect on nociceptive behaviour</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flinching after formalin injection (formalin test, phase 2)</td>
<td>Indomethacin</td>
<td>Inhibition</td>
<td>(Yamamoto &amp; Nozaki-Taguchi, 1996)</td>
</tr>
<tr>
<td></td>
<td>Ketorolac</td>
<td>Inhibition</td>
<td>(Malmberg &amp; Yaksh, 1993)</td>
</tr>
<tr>
<td></td>
<td>Indomethacin; flurbiprofen; ketorolac; zomepirac; S(+)-ibuprofen</td>
<td>Inhibition</td>
<td>(Malmberg &amp; Yaksh, 1992)</td>
</tr>
<tr>
<td></td>
<td>R-ibuprofen</td>
<td>No effect</td>
<td>(Dirig et al., 1997)</td>
</tr>
<tr>
<td></td>
<td>S-ibuprofen</td>
<td>Inhibition</td>
<td>(Yamamoto &amp; Nozaki-Taguchi, 1996)</td>
</tr>
<tr>
<td>Carrageenan-induced thermal hyperalgesia</td>
<td>Indomethacin</td>
<td>Inhibition</td>
<td>(Dirig et al., 1998)</td>
</tr>
<tr>
<td></td>
<td>S(+)-ibuprofen</td>
<td>Inhibition</td>
<td>(Gühring et al., 2000)</td>
</tr>
<tr>
<td>Zymosan-induced thermal hyperalgesia</td>
<td>Indomethacin</td>
<td>Inhibition</td>
<td></td>
</tr>
<tr>
<td>Injection of Freund's complete adjuvant (CFA)</td>
<td>S(+)-ibuprofen</td>
<td>Inhibition</td>
<td>(Seybold et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>R(-)-ibuprofen</td>
<td>No effect</td>
<td></td>
</tr>
</tbody>
</table>
it could be shown that the inflammation produced by the subcutaneous injection of carrageenan into the paw is associated with a significant decrease in the nociceptive threshold to heat (Hargreaves et al., 1988) and this decrease correlated with an increased expression of COX-2 in the spinal cord and other regions of the CNS (Ichitani et al., 1997). Intrathecal application of indomethacin (Yamamoto & Nozaki-Taguchi, 1996) and $S(+)$-ibuprofen (Dirig et al., 1998) could block the carrageenan-induced thermal hyperalgesia. Similar effects of intrathecally applied indomethacin have been observed in the zymosan model (Guhring et al., 2000) in which the drug attenuated the mechanical and thermal hyperalgesia induced by the intraplantar injection of zymosan (Meller & Gebhart, 1997). The intrathecal application of NSAIDs was also effective in the long-term inflammatory pain induced by intraplantar injections of CFA (Stein et al., 1988). In this model, $(S)$-ibuprofen, but not $(R)$-ibuprofen, attenuated the flexor reflex dose-dependently and did not exert this effect in untreated rats (Seybold et al., 2003).

The above observations show convincingly that intrathecally administered NSAIDs are effective in reducing behavioural hyperalgesia in animal models of inflammatory pain and these findings are additional support for the hypothesis that the CNS is an additional site of action for the antinociceptive effects of NSAIDs.

4.2. Central and peripheral antinociceptive mechanisms of non-steroidal anti-inflammatory drugs (NSAIDs) in human studies

Several approaches have been used to assess central and peripheral mechanisms of action of NSAIDs in humans. Human experimental pain models, in particular, have proved to be important tools in the assessment of the pharmacological effects of NSAIDs. There are only few human models available, which are sensitive to NSAIDs and nearly all of them relate to nociception in skin. Cutaneous injury leads to alterations in thermal and mechanical hyper-sensitivity of the damaged tissue (“primary hyperalgesia”) and to mechanical hypersensitivity in the skin surrounding the injury (“secondary hyperalgesia”) (Meyer et al., 1994). It is believed that primary hyperalgesia is mostly mediated by peripheral mechanisms and that secondary hyperalgesia is produced by central sensitization (Torebjork et al., 1992; Vanegas, 2004). Thus, experimental evaluation of these two forms of hyperalgesia following the administration of NSAIDs may provide a further insight into the sites of action of aspirin-like drugs. In practice, this approach is hardly possible. The main limiting factor in such studies is that not all experimental models permit a clear differentiation between primary and secondary hyperalgesia and the observed pain hypersensitivity may have both central and peripheral origins. For example, hyperalgesia in pinching models, where pain is induced by the repeated stimulation of the interdigital web between the middle and ring fingers, is supposed initially to be due to peripheral sensitization, however, with continuation of the pinching stimulus, central components are also involved (Growcott et al., 2000). In the “freeze lesion” model, where hyperalgesia is produced by a short-lasting freezing of skin, the observed hypersensitivity is dominated by peripheral mechanisms but it is suspected that there is an additional contribution due to spinal sensitization (Kilo et al., 1995). In fact, of all the human experimental pain models where sensitivity to NSAIDs has been established (only double-blind, randomized, placebo-controlled studies are included; Table 2) the assessment of drug effects on primary and secondary hyperalgesia has been only performed in the cutaneous burn injury model (Petersen et al., 1997). In this model, ibuprofen reduces pain induced by motor brush stimulation within the area of secondary hyperalgesia but has no effect on the responses to pinpricks and stroking in this area making it difficult to confirm the involvement of central mechanisms using this technique.

Recently, we have described a pharmacokinetic–pharmacodynamic approach for assessing the relative contribution of central and peripheral mechanisms in the antihyperalgesic

<table>
<thead>
<tr>
<th>Model</th>
<th>Stimulus type</th>
<th>Number of subjects</th>
<th>Medication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinch model</td>
<td>Mechanical</td>
<td>12</td>
<td>Aspirin 1000 mg; aspirin 1500 mg</td>
<td>(Forster et al., 1988)</td>
</tr>
<tr>
<td>Pinch model</td>
<td>Mechanical</td>
<td>22</td>
<td>Ibuprofen 800 mg; dipyrone 1000 mg; paracetamol 1000 mg</td>
<td>(Forster et al., 1992)</td>
</tr>
<tr>
<td>Pinch model</td>
<td>Mechanical</td>
<td>24</td>
<td>Ibuprofen 1200 mg; ibuprofen 2400 mg</td>
<td>(Kilo et al., 1995)</td>
</tr>
<tr>
<td>Freeze lesion</td>
<td>Mechanical; thermal</td>
<td>10</td>
<td>Ibuprofen 400 mg; ibuprofen 800 mg</td>
<td>(Nielsen et al., 1990)</td>
</tr>
<tr>
<td>Laser induced pain</td>
<td>Argon laser</td>
<td>12</td>
<td>Diclofenac 100 mg</td>
<td>(Burian et al., 2003)</td>
</tr>
<tr>
<td>Freeze lesion</td>
<td>Mechanical</td>
<td>21</td>
<td>Ibuprofen 600 mg</td>
<td>(Bickel et al., 1998)</td>
</tr>
<tr>
<td>UVB model</td>
<td>Mechanical; thermal</td>
<td>32</td>
<td>Ibuprofen 800 mg</td>
<td>(Sycha et al., 2003)</td>
</tr>
<tr>
<td>Pinch model</td>
<td>Mechanical</td>
<td>20</td>
<td>Ibuprofen 600 mg</td>
<td>(Petersen et al., 1997)</td>
</tr>
</tbody>
</table>

* Only double-blind, randomized, placebo-controlled studies are included.
effect of diclofenac in the experimental model of “freeze lesion”. We carried out algogenic measurements of the induced hyperalgesia, whilst monitoring the peripheral drug concentrations at the site of injury using intradermal microdialysis following the application of topical diclofenac (65 mg) versus oral diclofenac (93 mg) (Burian et al., 2003). The doses of the two formulations were selected so as to achieve similar diclofenac concentrations at the site of injury. We could show that oral diclofenac was markedly superior to diclofenac applied topically despite the fact that the tissue concentrations at the site of injury were almost equal. Since the systemic concentrations produced by topically applied diclofenac were negligible, we concluded that a non-peripheral, presumably central, component was also involved in the antinociceptive effect of orally administered diclofenac. The relative contribution of the central component accounted for approximately 40% of the total analgesic efficacy of oral diclofenac.

A further approach for confirming that NSAIDs possess central antihyperalgesic activity is the assessment of their action on nociceptive reflexes. This is conducting parallel measurements of the subjective pain threshold and the objective nociceptive flexion reflex threshold of the biceps femoris in response to the transectaneous electrical stimulation of the ipsilateral sural nerve and skin in the distal receptive field of the nerve (Willer & Bathien, 1977). A significant increase of the reflex threshold after intake of a drug versus placebo suggests involvement of the CNS. This method has been used to verify the presence of a central component in the action of indomethacin (Guieu et al., 1987), ketoprofen (Willer & Harrewyn, 1987) and ibuprofen (Sandrini et al., 1992). The central effects of ketoprofen, in particular, have been evaluated in healthy subjects and paraplegic patients with complete spinal section due to trauma (Willer et al., 1989). In contrast to normal subjects, where ketoprofen injection results in a rapid and significant increase in the threshold for the nociceptive reflex, there was no significant change in the nociceptive threshold in paraplegic patients, indicating that the observed central effects of ketoprofen depend, at least in part, on the involvement of supraspinal structures.

Nociceptive reflexes can be also induced in orbicularis oculi by electrical stimulation of the cornea and supra-orbital nerve. In this neurophysiological model, piroxicam significantly suppresses the corneal and blink reflexes and this action is not reversed by naloxone (Fabbri et al., 1992). Other observations on such centrally-mediated, non-opioid, actions of NSAIDs have been reported in the case of piroxicam and lysine acetylsalicylate (Ferracuti et al., 1994).

The central and peripheral analgesic effects of NSAIDs have also been examined in clinical models of pain. The assessment of the relative contribution of central and peripheral mechanisms with such models is difficult because diagnostic tools for identifying specific mechanisms of pain in patients are not available (Woolf & Max, 2001). For example, post-operative and joint pain may involve both peripheral and central mechanisms (Schaible, 2004; Schaible et al., 2002) which means that the individual contribution of the two components after systemic administration of an NSAID cannot be determined. On the other hand, measurement of the peripheral action of an NSAID in these models is possible after local application. Romsing et al. (2000) have conducted a systematic review of 16 randomized, controlled, double-blind studies in a total of 844 patients. The efficacy of locally applied NSAIDs (intra-articular injections, components of intravenous regional anaesthesia (IVRA) and intra-wound at the surgical site) was compared to that after systemic administration and placebo in post-operative patients (Romsing et al., 2000). The review provided evidence for a clinically relevant peripheral antinociceptive action in regard to the intra-articular NSAIDs, whereas the data for IVRA and wound infiltration of NSAIDs in post-operative pain were inconclusive and additional data from further large-scale placebo-controlled trails are needed.

A recently published meta-analysis has shown that topically applied NSAIDs in patients with osteoarthritis have a clinically relevant peripheral antinociceptive action (Lin et al., 2004). Topically applied NSAIDs have been superior to placebo in the first two weeks of treatment, when peripheral mechanisms producing pain may be of special importance in such patients.

The effects of aspirin-like drugs have been extensively studied in pain following dental extraction (wisdom tooth removal). Dental pain after extraction is a sensitive and reproducible model for studies on analgesic drugs suitable for use in relatively minor surgery (Schou et al., 1998). Gordon et al. (2002) determined analgesia in relation to the level of prostanoids at the site of injury following the systemic and local administration of NSAIDs in order to determine the relationship between prostanoid levels and analgesia (Gordon et al., 2002). The intramuscular administration of 30 mg ketorolac tromethamine produced parallel decreases in pain and the PGE2 and TxB2 levels at the surgical site. However, injection of smaller doses of the drug (a 1-mg intramuscular dose, or a 1-mg submucosal dose at the extraction site) produced analgesia without a detectable effect on peripheral PGE2 levels, suggesting that non-peripheral, presumably central, mechanisms are responsible for the observed analgesic effect. The authors concluded that central mechanisms involved in NSAIDs-mediated analgesia are much more sensitive to the effects of NSAIDs than peripheral mechanisms.

The ability of NSAIDs to alleviate pain by an action on CNS has been confirmed in patients with intractable pain due to various types of cancer. In these patients, the intrathecal administration of small doses of lysine–acetylsalicylate (equivalent to acetylsalicylic acid 500 µg/kg) brought rapid and prolonged pain relief. These results were confirmed in a more extended study with 60 cancer patients (Pellerin et al., 1987).
4.3. Influence of pharmacokinetic factors on central and peripheral mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs)

There is no close correlation between the plasma concentrations of NSAIDs and their clinical efficacy. The major pharmacokinetic determinant of the antinociceptive action is the extent of their distribution to central and peripheral sites (Day et al., 1988).

4.3.1. Peripheral site

The joints of the body are major peripheral sites of action of NSAIDs in rheumatic patients and the degree of uptake into synovial fluid is of considerable clinical interest. The trans-synovial transport is a relative slow diffusion process governed partly by the pharmacological characteristics of the individual NSAID and partly by the properties of the joint and joint space (Day et al., 1999). The simultaneous assessment of concentrations of NSAIDs in plasma and the synovial fluid compartment has been studied after single and chronic administrations of NSAIDs. The results reveal that NSAIDs can be divided into two groups according to their pharmacokinetic behaviour (Netter et al., 1989). The first type comprises those NSAIDs with short or intermediate plasma elimination half-life (e.g. salicylates, ibuprofen, indomethacin, diclofenac). Their concentration in synovial fluid may exceed those in plasma. The second group includes NSAIDs with a long plasma elimination half-life (e.g. phenylbutazone, piroxicam, meloxicam) (Bannwart et al., 2001). The concentrations of these drugs in synovial fluid are lower than in plasma; their free concentrations, however, do not appear to differ significantly from each other (Lapicque et al., 2000).

In spite of the extensive data on the concentrations of the various NSAIDs at peripheral sites, the extent to which they correlate with the peripheral antinociceptive response has not been assessed in detail. Such studies are difficult from a pharmacokinetic point of view because the data obtained cannot be interpreted adequately without information on the protein binding in peripheral tissues and this is especially true for drugs which are bound there to a lesser extent than in plasma. The disposition of the drug and the formation of active metabolites and enantiomers (not only the parent drug) must also be taken into account.

4.3.2. Central site

In order to exhibit a central antinociceptive action, NSAIDs must enter the CNS from the bloodstream. Optimum delivery of drug molecules into the CNS is hindered by the blood–brain barrier (BBB) which tightly controls the exchange of substances between the blood and the CNS. The penetration of NSAIDs into spinal and supraspinal structures, a process believed to occur mainly by passive diffusion, varies from drug to drug (Davison et al., 1961; Bannwarth et al., 1989) and is thought to be limited by the binding capacity of the drug to plasma proteins (Ochs et al., 1985). It is noteworthy, however, that the fraction of drug entering the brain through the BBB is not only the unbound fraction but may also include a part of the bound fraction dissociated from the protein in the perfusate (Tanaka & Mizojiri, 1999). This phenomenon has been demonstrated for isoxicam, tenoxicam and meloxicam by using the carotid injection technique in rats where both the bound and unbound fractions of the drugs were available for transfer into the brain. (Jolliet et al., 1997). Results of binding studies with a special polymeric formulation of ketoprofen have shown that the binding of ketoprofen to plasma proteins is not the major factor governing the exchange between blood and the CSF (Matoga et al., 2002).

An important factor affecting the disposition of NSAIDs is the degree of ionisation and therefore pH. NSAIDs with low ionisation will show higher lipid solubility and better penetration into the CNS (Matoga et al., 1999). However, the degree of lipophilicity alone does not correlate well with the ability to diffuse into CNS and other physicochemical properties of the drug such as molecular size are important. This has been particularly demonstrated for arylopropionic acid NSAIDs using quantitative structure–activity relationship (QSAR) analysis (Pehourcq et al., 2004).

In contrast to the pharmacokinetics of NSAIDs in peripheral sites (i.e. synovial fluid), the concentrations of NSAIDs in the human CNS have not been extensively studied and there are two main reasons for this: a) the CSF compartment cannot easily be sampled and b) NSAIDs are extensively protein-bound, so that accurate estimation of their concentration in CSF requires specific and very sensitive analytical methods (Bannwarth et al., 1989). Therefore, only few data on concentration of NSAIDs in CNS in humans are available. Bannwarth et al. (1990) have shown that indomethacin given intramuscularly rapidly crosses the blood–brain barrier and can be detected in CSF 0.5 h after administration (Bannwarth et al., 1990) where the level may exceed that in plasma. Similar findings have been reported following the intramuscular administration of ketoprofen (Netter et al., 1985) and piroprofen (Zecca et al., 1988) with levels in the CSF detectable as early as 15 min after injection. In the case of orally administered ibuprofen, CSF concentrations rise rapidly and can exceed the unbound plasma levels of the drug within 90 min (Bannwarth et al., 1995). All these NSAIDs are characterised by a rapid distribution within CNS due to their high lipid solubility (Bannwarth et al., 1989). The analgesia produced by these drugs may show a more marked central component than other NSAIDs. Attempts to correlate their CSF concentrations with central analgesic activity, however, have not yet been made.

5. Conclusion

NSAIDs are potent antinociceptive agents, whose efficacy in reducing pain is widely recognized in various
pain conditions, including post-surgical pain and chronic pain associated with arthritis and cancer. Although NSAIDs have long been used in clinical practice, opinion on the mechanism of their antihyperalgesic action remains controversial. According to published findings, it appears that the inhibition of prostaglandin synthesis by NSAIDs takes place at the site of peripheral inflammation and in the CNS indicating that both peripheral and central mechanisms are involved in the antinociceptive action of these drugs. The relative contribution of peripheral and central COX-dependent mechanisms to the overall antinociceptive action depends on the particular NSAID used, the site of drug delivery and the pharmacokinetic characteristics of the drug especially those determining its penetration to the sites of action (i.e. access to peripheral and spinal COX).

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