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Review

Toxicity of non-steroidal anti-inflammatory drugs: a review of melatonin and diclofenac sodium association

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Summary. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the purpose of anti-inflammation, antipyretic, and analgesia. For this aim, they are used for the alleviation of pain, fever, and inflammation associated with rheumatoid arthritis, sports injuries, and temporary pain. However, treatment with NSAIDs may be accompanied by adverse effects such as gastrointestinal damage and platelet dysfunction. As with the other NSAIDs, diclofenac sodium (sodium-(o-((2,6-dichlorophenyl)-amino)-phenyl)-acetate) (DS), an NSAID, has potent anti-inflammatory, analgesic, and antipyretic effects. However, treatment with DS may cause some adverse cerebral and cerebellar effects such as convulsions, disorientation, hallucination, and loss of consciousness. Melatonin (MLT) is a free-radical scavenger and possesses antioxidant properties. It has been reported to easily cross the blood-brain barrier, and is found in high concentrations in the brain after exogenous administration. It is also a neuroprotector in a wide range of conditions affecting the central nervous system CNS due to its free-radical scavenging activities and lipophilic-hydrophilic properties. Neuroprotective actions of MLT have been discovered in both in vitro and in vivo, and are a powerful scavenger of oxygen and nitrogen free radicals. Thus, MLT can protect the cell membrane, organelles, and core against free-radical damage. Therefore, it has been postulated that exogenous MLT acts as a neuroprotector contrary to DS neurotoxicity. In this review, we aimed to discuss the possible neuroprotective effects of MLT on DS toxicity.

Key words: Nonsteroidal anti-inflammatory drug, Diclofenac sodium, Melatonin, Neuroprotective effect

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Introduction

Recently it has been shown that some of the nonsteroidal anti-inflammatory drugs (NSAIDs), i.e. sulindac, sulindac sulfide, sulindac sulfone, indomethacin, acemetacin, tolmetin, etodolac, ketorolac, and oxaprozin, exhibit scavenging activity for H_2O_2 (Costa et al., 2005). The pyrazole derivatives dipyrone and aminopyrine are well known potent scavengers of singlet oxygen (Costa et al., 2008). Fernandes et al. (2004) has demonstrated that indomethacin, acemetacin, tolmetin, and etodolac exhibit effective scavenging activity against ROS and RNS. Studies have also reported that some NSAIDs are able to afford neuroprotection by means of several mechanisms in addition to the prostaglandin-dependent pathway (Sairam et al., 2003), while other NSAIDs (the nonselective COX inhibitor diclofenac and the selective COX-2 inhibitor celecoxib) are not able to afford neuroprotection (Sairam et al., 2003; Ragbetli et al., 2007). Therefore, like some other NSAIDs, diclofenac sodium (DS) not only has neuroprotective but also neurotoxic effects on the central nervous system (CNS) (Ragbetli et al., 2007). It has been suggested that melatonin (MLT) acts as a neuroprotector contrary to DS neurotoxicity since MLT is a free-radical scavenger and possesses antioxidant properties (Reiter et al., 1997; Odaci and Kaplan, 2009). For these reasons, in this review, we aimed to discuss the possible neuroprotective effects of MLT on DS toxicity.

Oxidative stress (OS) and reactive oxygen species (ROS)

Oxidative stress (OS) is an imbalance between reactive oxygen species (ROS) production and antioxidant defenses in the body (Akbulut et al., 1999;

Finkel and Holbrook, 2000; Bokov et al., 2004). The degree of oxidative stress is determined by this balance, and if that balance is deteriorated in favor of ROS, OS will appear. When the OS is severe, survival is dependent on the adaptation or resistance ability of the cell to OS and the repair-replace capacity of the cell for the damaged molecules (Finkel and Holbrook, 2000). In this respect, OS can potentially modify all organs, tissues, cells, and proteins. Moreover, certain tissues and specific protein targets may be especially sensitive (Finkel and Holbrook, 2000; Stadtman and Levine, 2003). Therefore, it has been suggested that OS may participate in the pathogenesis of many human diseases (Makker and Agarwal, 2009). These diseases include mainly atherosclerosis, cancer, diabetes, liver damage, rheumatoid arthritis, cataracts, AIDS, inflammatory bowel disease, CNS disorders, Parkinson's disease (PD), motor neuron disease, and conditions associated with premature birth (Agarwal and Prabakaran, 2005; Makker et al., 2009). OS also affects most of the vital organs during aging and lifespan (Akbulut et al., 1999; Finkel and Holbrook, 2000; Bokov et al., 2004).

Since the loss of balance between oxidants and antioxidants caused by the oxidants leads to oxidative stress (Sies, 1997), the antioxidative defense system is required to perform detection and detoxification of ROS (Finkel and Holbrook, 2000). This system is composed of several enzymes and small-molecular-weight molecules with antioxidant capabilities (Gitto et al., 2009). Therefore, physiological homeostasis is maintained by means of an improved enzymatic and non-enzymatic antioxidant defense system including glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx). They counteract and regulate overall ROS levels (Finkel and Holbrook, 2000). The effect mechanism of reactive oxygen species is schematized in Figure 1.

Oxidative damage in different regions of the central nervous system

It has been reported that variable metabolic rates lead to the region-specific accumulation of oxidative damage in different regions of the CNS, causing specific regions of the brain to become more vulnerable to senescence related disorders (Bokov et al., 2004). As part of the metabolic process in the brain, a significant amount of free radicals is also produced (Halliwell, 1992); additionally, some regions of the brain, such as the cortex, striatum, and hippocampus, are highly productive of free oxygen radicals (Hill and Switzer, 1984). Free radicals and their metabolites, containing oxygen or nitrogen atoms, are commonly referred to as ROS and RNS, respectively (Siu et al., 2006). The best known radicals generated from O_2 include the superoxide anion radical, the hydroxyl radical, and nitric oxide (NO) (Reiter et al., 1997). Therefore, free-radical inducing oxidative stress has been found as central to the mechanisms leading to neurodegenerative disorders in elderly people (Butterfield et al., 1997).

Free radicals are molecules or portions thereof which possess one or more unpaired electrons in their outer orbital, a state which greatly increases their reactivity (Reiter et al., 1997). Cellular generation of reactive oxygen species and the antioxidant defense system is summarized in Figure 2.

In the process of adenosine triphosphate (ATP) production and oxidative phosphorylation in the mitochondria, oxygen is reduced to water; during the transfer of electrons through the respiratory complexes of the electron transport chain, some electrons escape to form O_2, H_2O_2, and hydroxyl radical (Nohl et al., 2005). Uncontrolled generation of radicals and related reactants can cause oxidation of molecules in the cell membrane, decrease lipid fluidity, reduce transmembrane potential, augment calcium ion permeability, and increase peroxide end-products in the cells. Thus, radicals can cause cellular dysfunction and sometimes cell death (Reiter et al., 1997). It has been reported that radicals function mainly as a neuronal messenger molecule under normal and pathological conditions. For example, NO may act as both a neuroprotective and a neurodestructive agent when produced in excess in hypoxic and ischemic injuries (Kiliç et al., 2000; Muramatsu et al., 2000).

NO, ROS, and RNS induce mitochondrial damage, which further suppresses ATP production (Siu et al., 2006). This condition results in the mitochondrial permeability transition opening, which allows cytochrome c to be released (Siu et al., 2006). A released

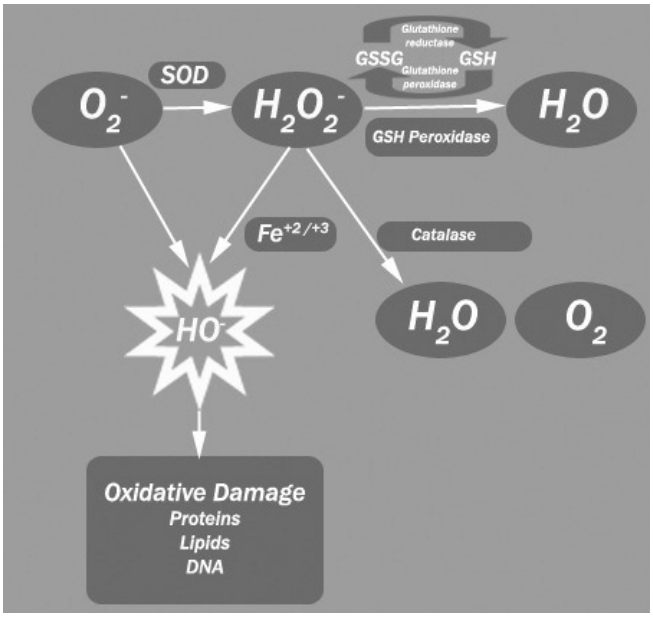

Fig. 1. In cells, imbalance between the production of antioxidants and rooxidants may cause increased production of free radicals (activated oxygen and reactive oxygen species). These free radicals may lead to damage of DNA and cellular proteins (Redrawn from Wakamatsu et al., 2008).

cytochrome c causes apoptosis with the activation of caspases (Brown, 1999; Acuña-Castroviejo et al., 2001; Fosslien, 2001; Toninello et al., 2004). Finally, mitochondrial damage by free radicals leads to neuronal damage if it occurs in neuronal tissue (Reiter et al., 2001a; Siu et al., 2006). Thus, oxidative stress causes cell membrane and synaptic disorganization as well as neural cell signaling dysfunction by damaging lipids, proteins, nucleic acids, and mitochondria, followed by apoptosis and/or necrotic events (Cui et al., 2004). It also leads to the dysfunction of many metabolic cell pathways (Fig. 3).

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are commonly used for anti-inflammation, antipyretic, and analgesia (Siu et al., 2000; Kudo et al., 2003; Chang et al., 2005a). They are widely used for the alleviation of pain, fever, and inflammation associated with rheumatic-degenerative joint diseases, sports injuries, and temporary pain (Siu et al., 2000; Ericson and Källén, 2001).

Treatment with NSAIDs may be accompanied by adverse effects such as gastrointestinal damage, platelet dysfunction, and convulsions when co-administered with quinolone-derivative antibacterial drugs (Davey, 1988; Segev et al., 1988; Yakushiji et al., 1992). Their therapeutic and adverse effects result mostly from the inhibition of COX, which produces prostaglandins (PGs) from arachidonic acid. However, other mechanisms, secondary to PG synthesis inhibition, have been proposed as being involved in the antinociceptive activity of NSAIDs (Lee et al., 2003). Many traumatic agents cause cell damage by activating the arachidonic acid cascade. In such situations, NSAID intake can stimulate the prostaglandin pathway and lead to damage of the endothelium and CNS (Fig. 4).

Neurotoxicity of nonsteroidal anti-inflammatory drugs

Prostaglandins are involved in both the normal and abnormal function of every organ and system in the human body (Siu et al., 2000). PGs in turn have been shown to stimulate astrocytic glutamate release into the synaptic cleft (Bezzi et al., 1998; Sanzgiri et al., 1999). These characteristics of PGs suggest that they have both useful and damaging actions.

Cyclooxygenase is an enzyme that catalyzes the rate-limiting step in the formation of PGs from arachidonic acid (Siu et al., 2000). Although isoform COX-1 is constitutively expressed in many cell types, COX-2 is selectively expressed in neurons of the cerebral cortex, hippocampus, and amygdala and only occasionally in reactive glial cells in the brain (Siu et al., 2000; Andreasson et al., 2001) and results in a dual inhibitory effect on both the cyclooxygenase and lipoxygenase pathways (Scholer et al., 1986; Hirst et al., 1999; Hoozemans et al., 2001).

On the other hand, COX-2 can be expressed in other CNS cell types such as endothelial. COX-2 upregulation in response to lipopolysaccharide mediates fever induction and contributes to changes in the blood-brain barrier (Cao et al., 1997; Chan et al., 1997; Li et al., 1999), and is believed to contribute to CNS

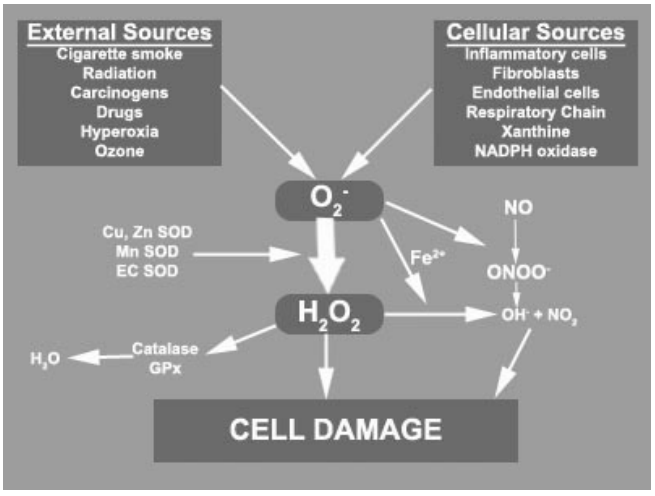

Fig. 2. Cellular generation of reactive oxygen species (Redrawn from Rahman et al., 2006).

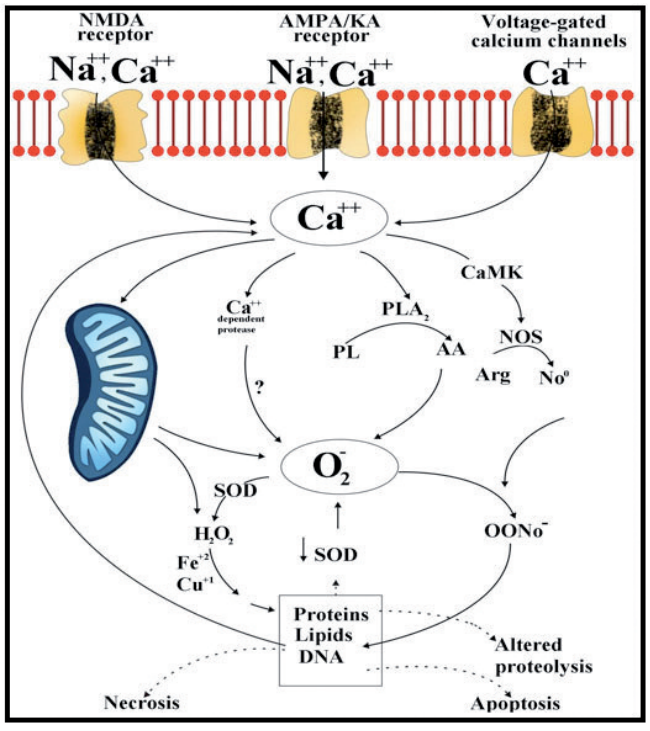

Fig. 3. Oxidative stress causes disorganization and dysfunction of metabolic pathways of cells (Redrawn from Kulkarni and Naidu, 2003).

inflammatory processes (Hirst et al., 1999; Yermakova et al., 2001). Yermakova et al. (2001) has shown that COX-1 expression in CA3 hippocampal neurons does not change in Alzheimer's disease (AD); however, more microglial cells expressed COX-1 in AD than in control tissue. It has been reported that increased neuronal COX-2 expression may be detrimental to neurons by means of increasing oxidative stress (Yermakova and O'Banion, 2001). It has also been reported that COX-2 was up-regulated in the midbrain of experimental Parkinsonian models and in patients with PD (Teismann et al., 2003; de Meira Santos Lima et al., 2006). In one study, it was suggested that selective COX-2 inhibition prevented microglial activation and cell loss of dopaminergic neurons in the substantia nigra in an experimental Parkinsonism by dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) (Esposito et al., 2007). Therefore, it has been suggested that some COX-2 inhibitors have therapeutic efficacy against neurodegeneration related to inflammatory reaction. COX inhibitors such as resveratrol utilize calcium-activated potassium channels and voltage-gated potassium channels for the antinociceptive mechanism (Subbaramaiah et al., 1998; Granados-Soto et al., 2002). In Figure 5, the COX action mechanism is summarized.

Moreover, NSAIDs have heterogeneous pharmacological properties based not only on their COX-inhibitory action but also on other properties, including their inhibitory effects on the synthesis of NO radical and some effects on inflammation-related transcription factors and inflammatory cytokine associated changes (Asanuma and Miyasaki, 2007). Many NSAIDs modulate activities of various ion channels by COX inhibition (Shaw et al., 1995; Kirkup et al., 1996; Lee and Wang, 1999; Voilley et al., 2001). NSAIDs generally inhibit COX activity and therefore may prevent neuroinflammation, and some NSAIDs have recently been shown to target γ-secretase, an enzyme required for the generation of Aß peptides, and then decrease the production of $Aß_{42}$, which is more toxic and fibrillogenic. Several COX-2-specific NSAIDs can increase $Aß_{42}$ production by inhibiting γ-secretase activity. Aside from these effects, neuroinflammation and disease progression may also be affected by NSAIDs acting on peripheral cells or immune cells; thus, alteration occurs in the production of growth factors and cytokines, which can pass easily from the blood-brain barrier (BBB) (Fig. 6).

In some cases, the pharmacological effects of NSAIDs are independent of the inhibition of COX activity. Sairam et al. (2003) have suggested that the neuroprotective ability of sodium salicylate (SA) is independent of PG mediation. It deactivates the hydroxyl radical and thus protects dopamine (DA) depletion in the striatum caused by 1-methyl-4-phenylpyridinium (MPP^+) (Sairam et al., 2003). Ton et al. (2006) have shown that there is no significant association between the use of nonaspirin NSAIDs and incidence of PD (2006). It is reported that aspirin and salicylate inhibit nuclear factor-B (Kopp and Ghosh, 1994) and the activity of inhibitory B kinase (Yin et al., 1998).

It has been shown that NSAIDs can enhance the heat shock response as a reaction to hyperthermia and other toxic conditions by the induction of heat shock proteins (Hsps) (Batulan et al., 2005). The heat shock cognate proteins and Hsps proteins (e.g. Hsp70, the major inducible member of the Hsp family) function as chaperones during protein synthesis, intracellular transport, and degradation of abnormally folded proteins (Morimoto, 1998; Jolly and Morimoto, 2000) and inhibit apoptosis (Ravagnan et al., 2001; Mosser and Morimoto,

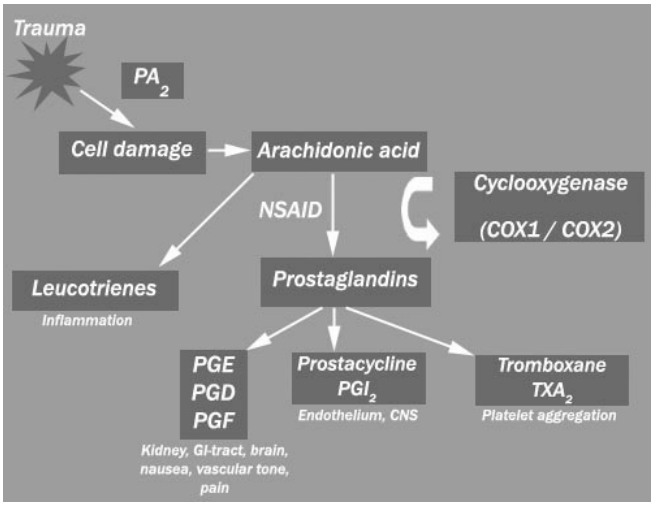

Fig. 4. Trauma triggers the arachidonic acid cascade. By the action of cyclooxygenase, various tissue specific prostaglandins (PG) are made (Redrawn from Naesh, 2006).

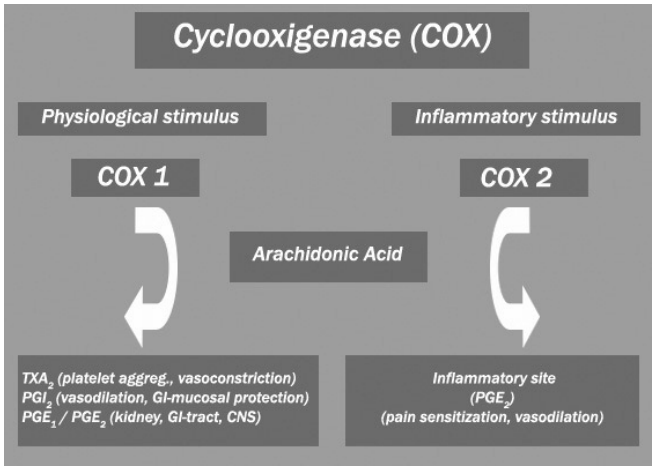

Fig. 5. Scheme of COX action mechanism (Redrawn from Naesh, 2006).

2004). It has been suggested that Hsp70 protects against hyperthermia, oxidative stress, glutamate excitotoxicity, and ischemia in the nervous system (Kelly et al., 2001; Lee et al., 2001; Yenari, 2002).

On the other hand, NSAIDs can enhance the cellular heat shock response by inducing Hsp70. In one study, sodium salicylate and niflumic acid were tested in the spinal motor neurons of dissociated spinal cord cultures subjected to hyperthermia and to the subsequent stresses associated with amyotrophic lateral sclerosis; both NSAIDs lowered the temperature threshold for Hsp70 expression in glia but not in motor neurons (Batulan et al., 2005). That study has demonstrated that treatment with these two NSAIDs failed to overcome the high threshold for the activation of heat shock response in motor neurons (Batulan et al., 2005). Therefore, it may be said that the COX-inhibitory actions of all nonaspirin NSAIDs do not have the same neuroprotective effects. This shows that the protective effects of each NSAID should be evaluated individually. The relation between stress and NSAIDs is illustrated in Figure 7.

Several studies have reported the inconsistent effects of NSAIDs on the neurotoxicity of MPTP or MPP^+ in vivo (Teismann and Ferger, 2001; Esposito et al., 2007). It has been demonstrated that while some NSAIDs such as aspirin provide neuroprotection from MPTP at the striatal and nigral levels (Teismann and Ferger, 2001), other NSAIDs, including diclofenac sodium, have no protective effect on MPTP toxicity. Even celecoxib, which is a specific COX-2 inhibitor, aggravated MPP^+-induced striatal DA depletion in rats (Sairam et al., 2003). Moreover, ibuprofen inhibits microglial proliferation by cell cycle arrest (Elsisi et al., 2005). It is well known that NSAIDs that significantly arrest the cell cycle at the G0/G1 phase induce cytotoxicity and cell death (Chang et al., 2005b).

It has also been observed that diclofenac sodium was ineffective in the Parkinsonian model induced by other neurotoxins MPP^+ or 6-OHDA (Sairam et al., 2003; Asanuma and Miyasaki, 2007). One study has found that indomethacin, ibuprofen, ketoprofen, and diclofenac significantly potentiate MPP^+-induced cell death in PC12 cells (Morioka et al., 2004). Furthermore, it has been reported that NSAIDs induce apoptosis in a variety of cells (Lu et al., 1995; Han et al., 2001; Yamazaki et al., 2002). Additionally, Dairam et al. (2006) have suggested that the non-steroidal anti-inflammatory agents tolmetin and sulindac inhibit liver tryptophan 2,3-dioxygenase activity and alter brain neurotransmitter levels (Dairam et al., 2006).

Therefore, it may be said that NSAIDs may cause cell death by mechanisms other than COX inhibition. The mechanisms of some NSAID-induced cell death are not clear; however, these mechanisms may be multifactorial, including diminishing the effects of antioxidants such as MLT, apoptosis, ROS, activity of the caspase-dependent cascade, activation of the peroxisome proliferator-activated receptor (PPAR), arrested cell cycle, and increasing the intracellular accumulation of toxic agents by inhibiting the activities of multidrug resistance proteins (MRPs) (Kusuhara et al., 1998; Klampfer et al., 1999; Pique et al., 2000). Kusuhara et al. (1999) have demonstrated that ROS contributes to apoptotic cell death induced by NSAIDs in cultured gastric cells. It has been demonstrated that several NSAIDs cause apoptosis through caspase-dependent cascade (Kusuhara et al., 1998; Klampfer et al., 1999; Pique et al., 2000).

It has been reported in the literature that the direct activation of PPAR by some NSAIDs results in apoptosis in several types of cells (Kusunoki et al., 2002; Yamazaki et al., 2002). Morioka et al. (2004) have demonstrated the possibility that, in experimental PD induced by the neurotoxin MPP^+, the regulation of the

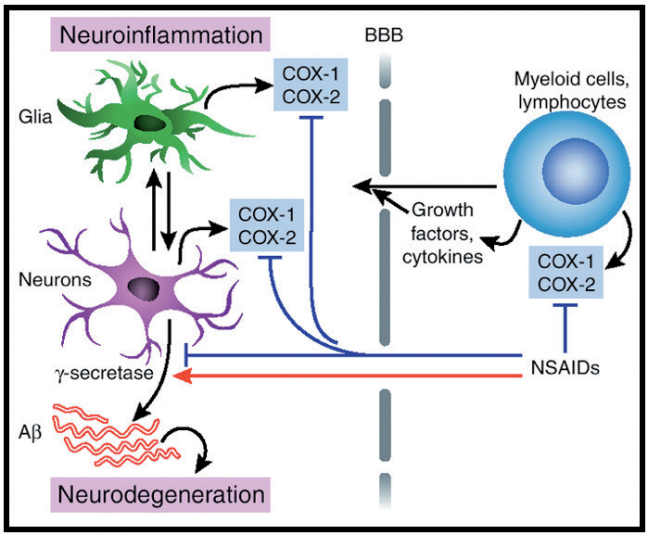

Fig. 6. NSAID activity in the inhibition of cyclooxygenase (COX) and its effect on peripheral cells or immune cells (Redrawn from Sahagan et al., 2005).

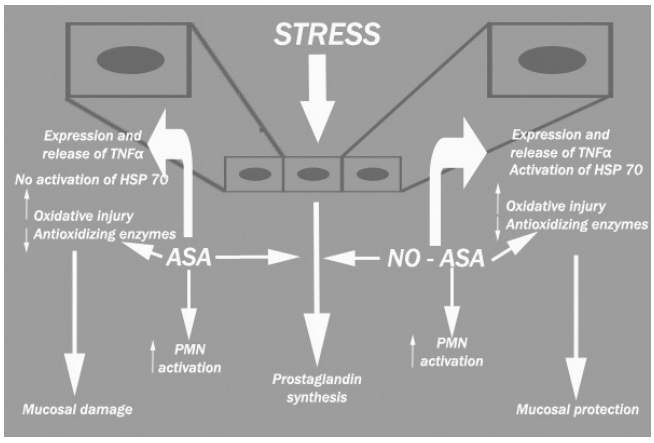

Fig. 7. Relation between stress and NSAIDs (Redrawn from Brzozowski, 2003).

membrane-transport systems of MPP^+ might be associated with the potentiating actions of NSAIDs. This study has demonstrated that incubation of PC12 cells with some NSAIDs significantly increases the intracellular accumulation of $[^3H]MPP^+$, and several NSAIDs potentiate MPP^+-induced cell death through a blockade of MRPs belonging to a superfamily of ATP-binding cassette transporters rather than the inhibition of COXs activities in PC12 cells (Morioka et al., 2004). It has also been suggested that some NSAIDs, including diclofenac, inhibit the activities of MRPs, including MRP4 in PC12 cells, leading to an increase in the intracellular concentration of MPP^+ and aggravation of cell toxicity (Morioka et al., 2004).

As a result, pro-apoptotic proteins such as NF-kB are released by these two different pathways (Figure 8). In addition to all the undesirable effects of NSAIDs on nervous the system mentioned above; some researchers have suggested that NSAIDs have a positive effect on neuroprotection. These studies have suggested that some other mechanisms may also be involved at the neurotransmitter level (Mohanakumar et al., 2000; Acuña-Castroviejo et al., 2001; Sairam et al., 2003). For example, both tolmetin and sulindac reduce DA levels in the striatum, suggesting that these NSAIDs may have the potential to exacerbate or induce DA-deficient neurological disorders (Dairam et al., 2006).

Diclofenac sodium

Diclofenac sodium (sodium-(o-((2,6-dichloro-phenyl)-amino)-phenyl)-acetate), an NSAID, is characterized by a relatively low molecular weight and has potent anti-inflammatory, analgesic, and antipyretic effects (Scholer et al., 1986; Siu et al., 2000; Kudo et al., 2003; Chang et al., 2005a). It inhibits COX, decreases release of arachidonic acid, and increases uptake of arachidonic acid (Cardinali et al., 1982). In clinical practice, DS is widely used for the alleviation of pain, fever, and inflammation associated with arthritis, rheumatoid arthritis, osteoarthritis, acute gout, dysmenorrhoea, and is sometimes used postoperatively (Siu et al., 2000; Beck et al., 2003; Savaser et al., 2005). It is known that DS essentially acts by inhibiting the enzyme COX, reducing the arachidonic acid release, and enhancing its uptake (Siu et al., 2000). On the other hand, the antinociceptive effect of diclofenac may result from the activation of some potassium channels (Ortiz et al., 2002). Diclofenac opens ATP-sensitive potassium channels, and these results in the activation of the nitric oxide-cyclic GMP pathway (Lee et al., 2003).

It has been found that treatment with DS may be accompanied by adverse effects such as serious upper gastrointestinal bleeding, platelet dysfunction, and cardiovascular hazard (Russell, 2001; Liu et al., 2005; Andersohn et al., 2006; Capone et al., 2007; Ragbetli et al., 2007). Treatment with DS may cause some adverse cerebral (i.e. convulsions) and cerebellar effects (Bright and McNulty, 1991; Klc et al., 2004; Liu et al., 2005; Capone et al., 2007). Bright and McNulty (1991) have reported a case in which a subject became disoriented, hallucinated, lost consciousness, and suffered respiratory arrest after ingesting five diclofenac tablets (375 mg total), two ibuprofen tablets (400 mg total), and one indomethacin capsule (75 mg).

The effects of NSAIDs on the gastrointestinal system are illustrated in Figure 9. However, the side effects of DS on the human CNS are unclear (Kudo et al., 2003). For this reason, experimental studies have been conducted to assess DS toxicity on CNS in both the prenatal and postnatal period. For example, DS-induced teratogenicities have been reported during organogenesis

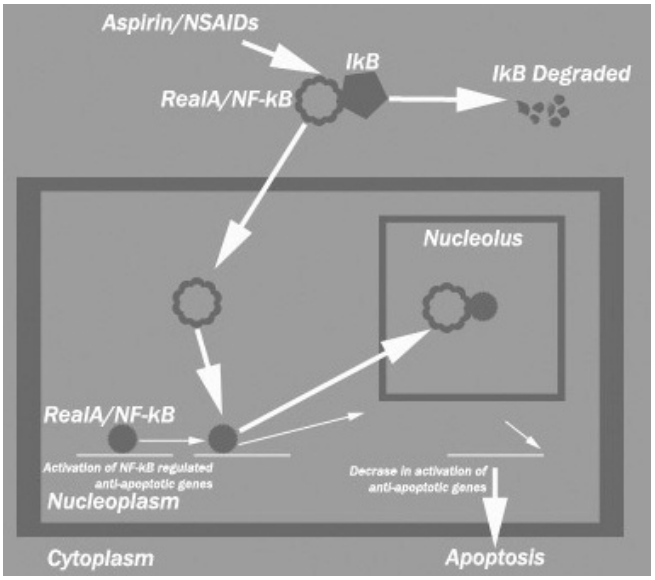

Fig. 8. Model for the pro-apoptotic effects of NSAIDs and the regulation of NF-kappaB (Redrawn from Stark and Dunlop, 2005).

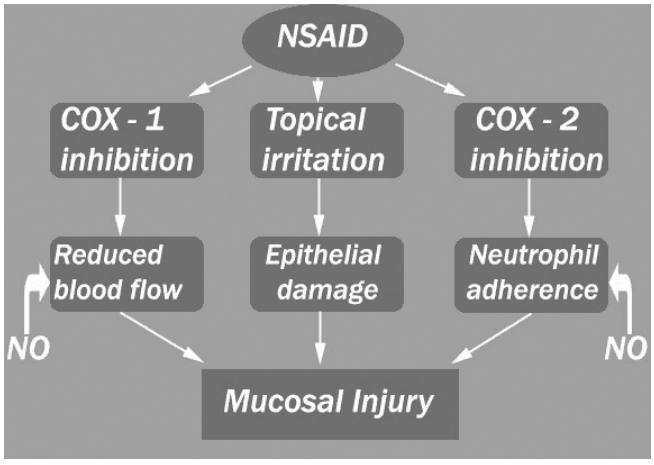

Fig. 9. Effect mechanism of NSAIDs on gastrointestinal system (Redrawn from Wallace, 2007).

(Chan et al., 2001; Kudo et al., 2003; Siu and Lee, 2004; Ragbetli et al., 2007). It has recently been asserted that if an embryo is exposed to DS during the critical period of development (i.e. between E11 and E15), the generation, proliferation, and migration of Purkinje cells may be affected; therefore, DS may cause abnormal development of the cerebellum (Kudo et al., 2003). Ragbetli et al. (2007) have reported that the Purkinje cells of a developing cerebellum may be affected by administration of DS during the prenatal period. They reported that significant cell loss occurred in the total number of Purkinje cells in 4W-old and 20W-old DS-treated groups in comparison to their controls (Fig. 10).

Studies have also reported that quantitative changes in the hippocampal region after exposure to DS may occur (Klc et al., 2004). They have shown a significant increase of glial cell reaction after repeated epidural DS injection. Regarding this subject, Gokcimen et al. (2007) found a significant decrease of the granule cell number in a 4W-old DS-treated group in comparison to their control group (Fig. 11).

In another study, it was demonstrated that DS leads to an increase in the intracellular concentration of MPP^+ by inhibiting the activities of MRPs in PC12 cells and that DS therefore causes aggravation of cell toxicity (Morioka et al., 2004). Thus, like some other NSAIDs, DS has not only neuroprotective effects but also neurotoxicity resulting from active metabolites of the drug, oxidative stress, and apoptosis (Hickey et al., 2001; Inoue et al., 2004). DS may also affect peripheral nerve morphology (Kusuhara et al., 1998). Canan et al. (2008) have researched the effects of DS on the development of sciatic nerve fiber in rats. According to the results of this study, axons were degenerated and the axon number was significantly decreased in groups that received diclofenac sodium (Fig. 12).

Surprisingly, another study found that diclofenac sodium did not cause a significant decrease in axon number in the rat median nerve. In addition, the study found that degenerated axons were very common in the diclofenac sodium treated group in comparison to the control group (Fig. 13) (Ayranci et al., 2010).

Melatonin

Melatonin is an important signal molecule that is widely distributed in nature. It is found in vertebrate animals and humans, but is also a component of

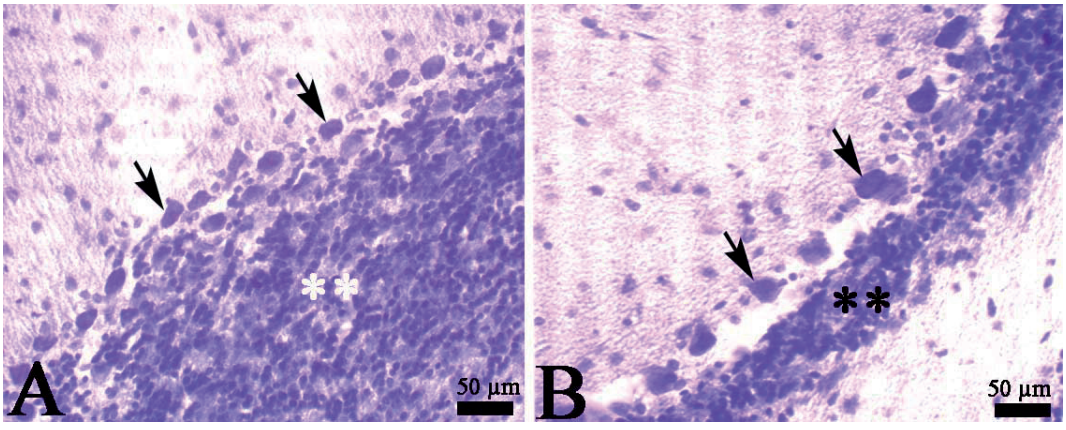

Fig. 10. Light microscopical sections of cerebellar cortex of control **(A)** and diclofenac treated rats **(B)**. Arrows and asterisks indicate Purkinje cells and granular cell layer, respectively.

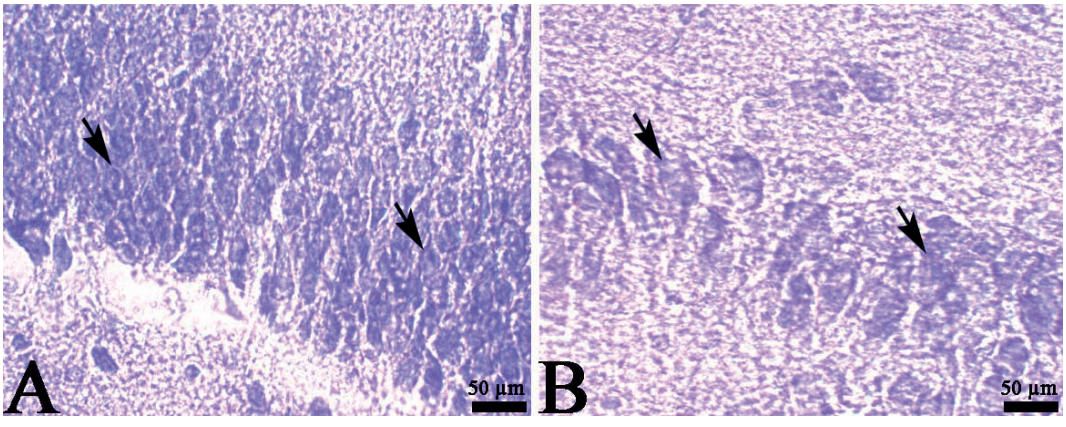

Fig. 11. Light microscopical sections of denate gyrus of control **(A)** and diclofenac treated rats **(B)**. Arrows indicate granular neurons in both groups.

unicellular organisms, plants, and fungi (Reiter et al., 2007a; Bob and Fedor-Freybergh, 2008; Odaci and Kaplan, 2009). It is produced mainly by the pineal gland, which is the major site of its synthesis in vertebrates. Its name is based on its effect on lightening the melanin pigmentation in frog skin (Touitou, 2001; Odaci and Kaplan, 2009). It is also produced in small amounts in extra-pineal sites the retina, gastrointestinal system, Harderian gland, ovary, skin, immune system, and some cerebral structures, and also by leukocytes (Itoh et al., 1997; Djeridane et al., 1998; Slominski et al., 2002; Carrillo-Vico et al., 2004; Siu et al., 2006; Jimenez-Jorge et al., 2007; Reiter et al., 2007a,b).

Chemically, melatonin is an indolamine, a tryptophan derivative (N-acetyl-5-methoxytryptamine), and is synthesized from serotonin in a two-step biochemical sequence via N-acetylation reactions catalyzed by arylalkylamine N-acetyltransferase and via O-methylation catalyzed by hydroxyindole-O-methyltransferase (Reiter et al., 2007a,b; Odaci and Kaplan, 2009) .

The most potent environmental factor regulating the metabolism of the mammalian pineal gland is the light-dark cycle. The endogenous levels of serum and cerebrospinal fluid of MLT show dramatic diurnal variability (Pääkkönen et al., 2006). MLT is secreted primarily at night, when it reaches levels 10 times higher than those present in the daytime (Touitou, 2001). Its secretion begins in the evening and lasts until morning. While darkness promotes MLT secretion, light exposure inhibits it. The retinal ganglion cells stimulated by light send information to the suprachiasmatic nuclei of the hypothalamus and through the sympathetic pathway to the pineal gland. Furthermore, the retina and the suprachiasmatic nuclei also receive numerous inputs from other brain areas. Thus, blood MLT exhibits a circadian rhythm and influences the sleep-wake cycle (Touitou, 2001; Cardinali et al., 2006). The synthesis mechanism of MLT is summarized in Figure 14.

It has been reported that MLT is a neuroprotector (Reiter et al., 1995; Reiter, 2003; Leon et al., 2005). Its neuroprotective actions have been discovered both in vitro (Giusti et al., 1995) and in vivo (Uz et al., 1996). The actions of MLT are essentially associated with the fact that both itself and its metabolites are powerful scavengers of oxygen and nitrogen free radicals (Leon et al., 2005; Hardeland et al., 2007; Manda et al., 2007; Tan et al., 2007). Moreover, it has been reported that MLT has an antioxidant activity and maintains a toxicity-free tissue environment (Maldonado et al., 2007). MLT

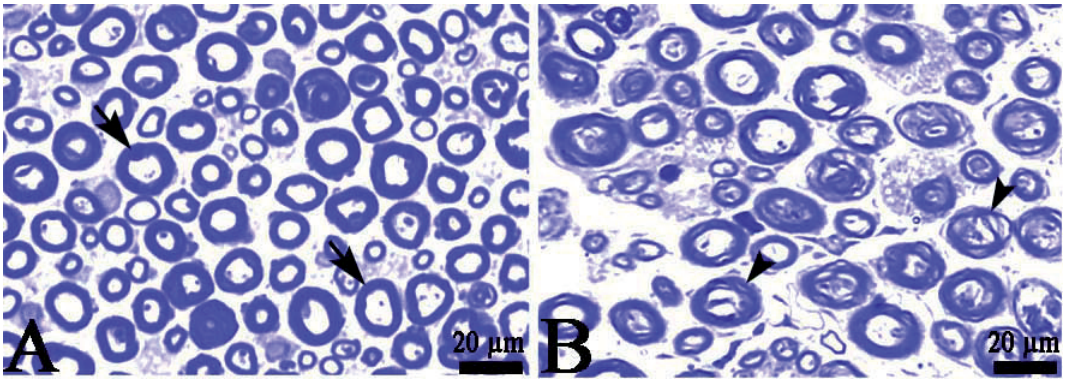

Fig. 12. Light microscopical sections of sciatic nerve of control **(A)** and diclofenac treated rats **(B)**. Arrows and arrow heads indicate healthy and degenerated axons, respectively.

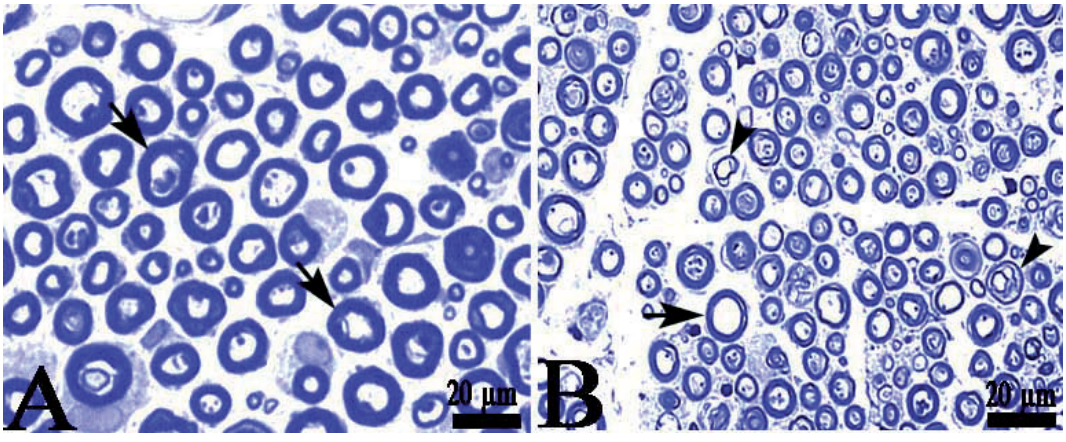

Fig. 13. Light microscopical sections of median nerve of control **(A)** and diclofenac treated rats **(B)**. Arrows and arrow heads indicate healthy and degenerated axons, respectively (Ayranci et al., 2010).

protects cells from the damaging effects of a variety of oxidants, including hydroxyl radicals, which initiate lipid peroxidation (Leon et al., 2005), peroxyl radicals, which are lipid peroxidation products and propagate lipid peroxidation (Pieri et al., 1994), and the peroxynitrite anion (Tan et al., 1993, 2007; Catalá, 2007). MLT also scavenges the peroxynitrite anion, which is a reaction product of superoxide and nitric oxide and may induce mitochondrial oxidative damage (Cuzzocrea et al., 1997; Gilad et al., 1997). In addition, MLT inhibits the nitric oxide synthase (Pozo et al., 1997) and scavenges nitric oxide directly (Mahal et al., 1999; Noda et al., 1999). MLT has also reduced electron leakage at the mitochondrial level, avoiding radical generation (Leon et al., 2004). This antioxidant function of MLT has been shown in whole brain tissue extracts (Reiter, 1998; Lin and Ho, 2000). Additionally, MLT has embargoed the expression of the apoptotic mediator tumor necrosis factor alpha (Mazzon et al., 2006). The effect mechanism of melatonin is shown in Figure 15.

In addition, it has been suggested that exogenous MLT plays a role in inhibiting acute inflammatory reactions by modulating inflammatory cytokines (Rodriguez et al., 2007). Thus, MLT directly detoxifies by scavenging reactive species such as hydroxyl radicals, hydrogen peroxide, singlet oxygen, nitric oxide, peroxynitrite anion, and peroxynitrous acid, or indirectly by inducing a number of antioxidative enzymes, e.g. superoxide dismutase, GPx, GR, and CAT, in addition to inhibiting a proxidative enzyme, 5- and 12-lipo-oxygenases, and nitric oxide synthase (Lin and Ho, 2000; Reiter et al., 2002; Pandi-Perumal et al., 2006; Siu et al., 2006). Finally, due to its free-radical scavenging activities and both lipophilic and hydrophilic properties, MLT has been reported as a potential neuroprotective agent (Reiter et al., 1997; Reiter, 1998). The effects of melatonin on inflammatory cells and cytokines are shown in Figure 16.

Melatonin as an antioxidant

MLT is known as an endogenous antioxidant. Endogenous antioxidants are the first line of defense and act by scavenging potentially damaging free-radical moieties (Sies, 1997; Finkel and Holbrook, 2000; Reiter et al., 2000; El-Sokkary et al., 2003; Rodriguez et al., 2004). In addition to the antioxidant defense system within the organism, several exogenous antioxidants such as vitamins, drugs, and food have also been reported (Ames et al., 1993). For example, nonsteroidal anti-inflammatory drugs (NSAIDs) are used for the treatment of inflammatory processes. Their inhibitory activity against cycloxygenase (COX) enzymes catalyses the formation of prostaglandin (PG) precursors from arachidonic acid (Fernandes et al., 2004). In addition to their anti-inflammatory effect, NSAIDs have a putative scavenging activity.

Melatonin and its metabolites are isolated firstly from bovine pineal glands (Reiter and Maestroni, 1999). It has been reported that melatonin is a potent free-radical scavenger (Tan et al., 1993; Catalá, 2007) and a wide antioxidant (Tan et al., 1993; Jimenez-Jorge et al., 2007). Melatonin has an immunomodulatory and antioxidant effect in the organism (Reiter et al., 2001b), and has been reported as having antioxidant activity in whole brain tissue extracts (Reiter, 1998; Lin and Ho,

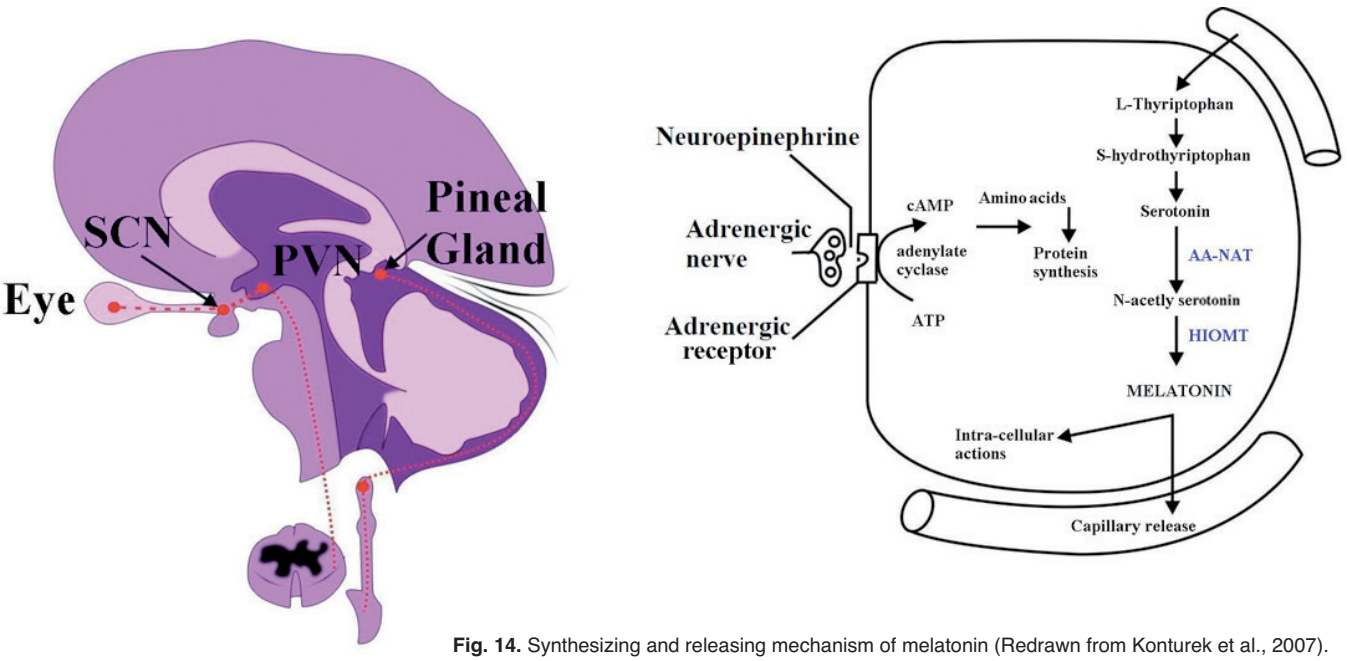

Fig. 14. Synthesizing and releasing mechanism of melatonin (Redrawn from Konturek et al., 2007).

2000). It is well known that MLT and its metabolites are significant scavengers of free radicals and peroxynitrite (Hardeland and Pandi-Perumal, 2005). In addition to the protective effects of enzymatic antioxidant defenses, MLT has been reported to be a free-radical scavenger and to possess antioxidant properties (Reiter et al., 1997; Odaci and Kaplan, 2009). Therefore, it is known as an endogenous antioxidant, which neutralizes free radicals, ROS, and reactive nitrogen species (RNS) (Reiter et al., 1997; Odaci and Kaplan, 2009). It also stimulates several antioxidative enzymes, which increase its efficiency as an antioxidant.

In terms of direct free-radical scavenging, MLT interacts with the highly toxic hydroxyl radical with a constant rate equivalent to that of other highly efficient hydroxyl radical scavengers and also neutralizes hydrogen peroxide (H_2O_2), singlet oxygen, peroxynitrite anion, nitric oxide, and hypochlorous acid. It is reported that MLT's effects are mediated through increased GSH levels, and SOD, GPx, and glutathione reductase (GR) are also stimulated by MLT (Reiter et al., 2000; Cuzzocrea and Reiter, 2001). Therefore, it protects cells, tissues, and organs against oxidative damage induced by a variety of free-radical generating agents and processes (Reiter et al., 1997; Odaci and Kaplan, 2009).

MLT indirectly scavenges by stimulating a number of antioxidative enzymes including c-glutamylcysteine synthase, glucose 6-phosphate dehydrogenase (Hardeland, 2005; Eskiocak et al., 2007), SOD, GPx, GR, and hemoperoxidase / CAT in addition to inhibiting a proxidative enzyme, 5- and 12-lipo-oxygenases, and nitric oxide synthase (Reiter et al., 2002; Pandi-Perumal et al., 2006). Thus, as a result of stimulation of these enzymes, MLT indirectly scavenges a variety of reactive species including the hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide, peroxynitrite anion, and peroxynitrous acid. MLT also inhibits the peroxidative enzyme iNOS (Reiter et al., 2001b; Hardeland and Pandi-Perumal, 2005).

It has been indicated that MLT could prevent advanced oxidative protein products (Dubocovich et al., 2003). Furthermore, it has been reported that MLT reduces electron leakage from the mitochondrial electron transport chain, thereby limiting free-radical damage and reducing oxidative stress (Leon et al., 2005). MLT acts on the G protein-coupled MLT receptors MT_1 and MT_2 (formerly known as MLT 1a and MLT 1b), which are typically linked to the inhibition of cAMP mediated signaling (Dubocovich, 1988; Witt-Enderby et al., 2006). These receptors are expressed in various types of mammalian neurons, including in the human brain (Savaskan et al., 2002; Thomas et al., 2002; Uz et al., 2005; Brunner et al., 2006; Jimenez-Jorge et al., 2007; Wu et al., 2007).

It has been suggested that MLT reduces NO production via inhibiting NOS activity (Pozo et al., 1997; Hardeland and Pandi-Perumal, 2005). Moreover, MLT stimulates the activity of endogenous antioxidant enzymes, including GPx and GR (Reiter et al., 2000; Cuzzocrea and Reiter, 2001). MLT also restores the cytochrome oxidase activity in the hypoxic nodose ganglion, improves mitochondrial ATP production, reduces electron leakage from respiratory complexes, and scavenges radicals that are generated at the mitochondrial level (Acuña-Castroviejo et al., 2003; Chang et al., 2005b; Leon et al., 2005). The effects of MLT on mitochondria, which are the main source of free radicals related to electron transfer to molecular oxygen at the matrix site, are a result of increases in mitochondrial respiration and ATP synthesis in conjunction with the rise in complex I and IV activities (Martin et al., 2000, 2002; Acuña-Castroviejo et al., 2003; Leon et al., 2005). The effects on the respiratory chain may represent new opportunities for the prevention of radical formation, in addition to eliminating radicals already formed. Thus, MLT directly scavenges a variety of free radicals and reactive species

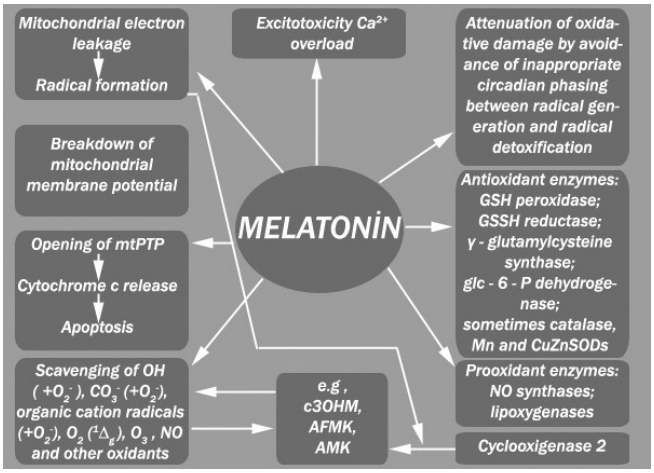

Fig. 15. Mechanism of melatonin on different pathways (Redrawn from Hardeland and Pandi-Perumal, 2005).

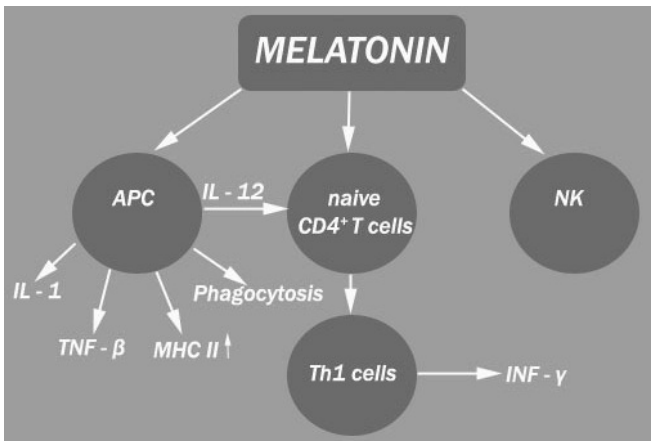

Fig. 16. Effect of melatonin on inflammatory cells and cytokines (Redrawn from Szczepanik, 2007).

including the hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide, peroxynitrite anion, and peroxynitrous acid (Hardeland and Pandi-Perumal, 2005). The effects of melatonin on the respiratory chain of mitochondria are shown in Fig. 17.

The neuroprotective effects of melatonin

MLT readily crosses BBD and is found in high concentrations in the brain after exogenous administration (Dubocovich et al., 2003). It is a potential neuroprotective agent in a wide range of conditions affecting the CNS (Antolin et al., 2002; Baydas et al., 2005a,b; Srinivasan et al., 2006) owing to its free-radical scavenging activities and lipophilic-hydrophilic properties (Reiter et al., 1997; Reiter, 1998). Thus, MLT is able to protect the cell membrane, organelles, and core against free-radical damage (Turgut et al., 2007). For example, it can protect against injury through its radical-scavenging action (Tan et al., 1993; Reiter et al., 2000). MLT also has a strong antiapoptotic signaling function (Pandi-Perumal et al., 2006).

One widely accepted hypothesis for explaining the pathogenesis of senescence-related disorders is oxidative stress (Kokoszka et al., 2001). Feng et al. (2006) have reported that MLT administration decreased the amount of thiobarbituric acid-reactive substances, increased glutathione levels and superoxide dismutase activity, and counteracted the up-regulation of Bax, caspase-3, and prostate apoptosis response-4 expression, thereby significantly reducing oxidative stress and neuronal apoptosis. It has been reported that MLT significantly attenuated mitochondrial DNA damage in the substantia nigra induced due to MPTP and its active metabolite MPP^+ by reducing the free-radical generation and collapse of the mitochondrial membrane potential (Pandi-Perumal et al., 2006).

The protective effects of melatonin on protein against oxidative damage

Modifications of protein due to free radicals may result in changes in protein function, chemical fragmentation, or increased susceptibility to proteolytic attack (Droge, 2002). The oxidative damage to proteins is reflected by a decrease in the levels of protein thiols, as a result of oxidation of protein thiol groups by free radicals and an increase in levels of advanced oxidation protein products, which are terminal products of protein exposure to free radicals (Cakatay et al., 2003). Oxidation of proteins can also lead to the cleavage of the polypeptide chain and to the formation of cross-linked protein aggregates (Stadtman and Levine, 2003; Davies, 2005; Eskiocak et al., 2007).

It has been reported that MLT can protect against protein degradation caused by free radicals. Abe et al. (1994) have suggested that GSH-depleted newborn rats treated with MLT did not develop cataracts. In this case, MLT's protective effect may be related to its antioxidative potential. In another study, MLT treatment partly prevented the increases in protein oxidation after hypoxia in the brain tissue (Eskiocak et al., 2007). It concluded that exogenous MLT could be beneficial in the treatment of newborn rats with hypoxia, and suggested the useful effect of MLT on protein oxidation and nitric oxide during hypoxia (Eskiocak et al., 2007).

The protective effects of melatonin on DNA against oxidative damage

Oxidation of molecules in the nucleus leads to DNA fragmentation and mRNA mutagenic changes (Siu et al., 2006). In the oxygen free radical-induced damage to DNA, free radicals have been shown to cause strand breakage, formation of DNA-protein crosslinks, and alteration of the purine and pyrimidine bases (Nagai et

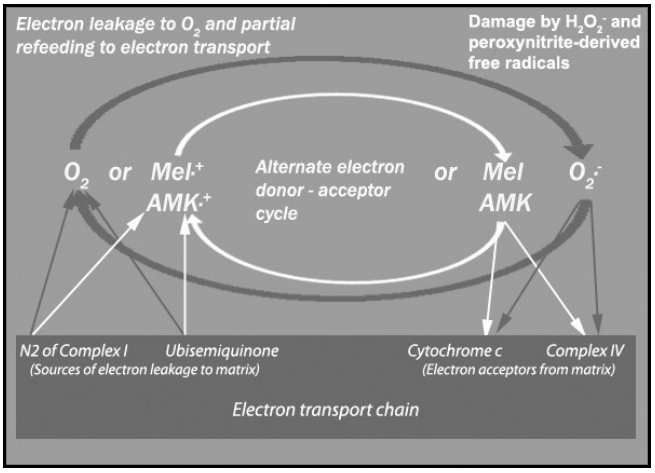

Fig. 17. Effects of melatonin on the respiratory chain of mitochondria (Redrawn from Hardeland and Perumal, 2005).

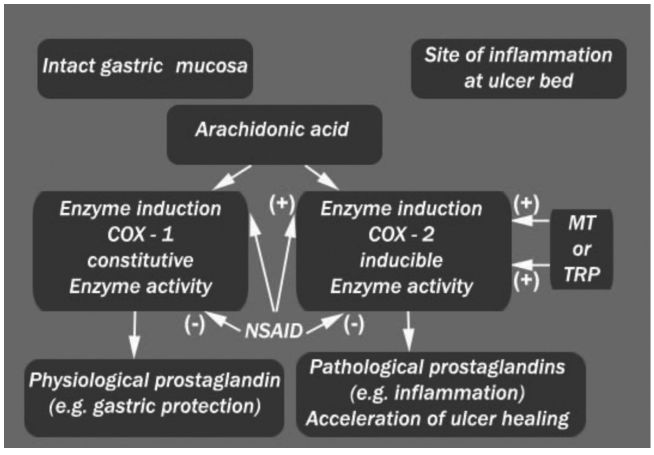

Fig. 18. Mechanism of melatonin (MT) on pathological conditions (Redrawn from Konturek et al., 2007).

al., 2008). One of the main DNA modifications produced by oxygen free radicals is generation of 8-OHdG, which is one of the most sensitive biomarkers for oxidative stress (Doetsch and Cunningham, 1990). It has been reported that Ref-1 (also known as HAP1, Ape1, and APEX1), which are class II hydrolytic apurinic/apyrimidinic DNA repair endonucleases (Demple et al., 1991; Robson and Hickson, 1991; Robson et al., 1991), function in base excision repair of basic DNA lesions generated by spontaneous hydrolysis or by exposure to reactive oxygen radicals (Doetsch and Cunningham, 1990). Furthermore, it has been suggested that MLT stimulates a number of antioxidative enzymes (Eskiocak et al., 2007). It has been reported that MLT can run through membranes and barriers and accumulate in cell nuclei because of its high lipophilicity, and protects DNA against oxidative stress (el-Aziz et al., 2005; Hussein et al., 2005).

The protective effects of melatonin on lipids against oxidative damage

Free radicals may cause their own destruction as a result of generation of lipid peroxidation reacting with the PUFA in the membranes (Reiter et al., 1997). Leaden and Catalá (2005) have reported that MLT has a protective effect on ascorbate-Fe^{2+} lipid peroxidation of PUFA in rat brain microsomes. It has been shown that MLT prevents lipid peroxidation during hypoxia-ischemia (Cuzzocrea et al., 2000a,b; Tütüncüler et al., 2005). Akbulut et al. (2008) have demonstrated that the levels of GSH, which is the most important endogenous antioxidant in the brain tissue, were lower in the cerebral cortex and the cerebellum of aged rats when compared to younger controls.

The protective effects of melatonin on tissue against oxidative damage

It has been found that MLT protects tissues against free radical-induced oxidant damage (Sener et al., 2006). In many studies, it has been shown that MLT is a free-radical scavenger and has antioxidant effects (Cuzzocrea et al., 2000a,b; Cabeza et al., 2001; Pei et al., 2002). MLT therefore protects DNA, lipids, and proteins against oxidative damage (Tan et al., 1993; Reiter, 2000). It also has a high lipophilic ability to cross all biological membranes, and this feature aids its protective effects against oxidative stress (Sener et al., 2006). Jimenez-Jorge et al. (2007) have shown that, when the pineal gland is not yet producing MLT, it is synthesized by the brain and could be used for protection of the brain from free-radical damage (Jimenez-Jorge et al., 2007).

Brain tissue is highly sensitive to free-radical damage because of its high utilization of oxygen; for this reason, brain MLT production is very important in the fetal stages of development (Halliwell and Gutteridge, 1985). Antioxidative protection by MLT occurs as a result of its effect on both receptor mechanisms and gene expression, which do not require receptors, such as direct scavenging of free radicals and electron exchange reactions with the mitochondrial respiratory chain. Cellular mechanisms of MLT involved in neuroprotection continue to be explored. Studies have shown that MLT is a direct radical scavenger and an indirect antioxidant (Reiter, 1998; Tan et al., 1998; Baydas et al., 2001). Melatonin reduces lipid peroxidation and scavenges the hydroxyl radical, which initiates lipid peroxidation, and the peroxyl radical, which propagates the process of lipid peroxidation (Pieri et al., 1994; Poeggeler et al., 1994). Moreover, it has been demonstrated that hypochlorous acid, hydrogen peroxide, singlet oxygen, and peroxynitrite anion are scavenged directly by MLT (Gilad et al., 1997; Allegra et al., 2003).

In addition, MLT stimulates mRNA levels and the activities of endogenous antioxidant enzymes, including SOD, GPx, and GR (Reiter et al., 2000; El-Sokkary et al., 2003; Rodriguez et al., 2004). Baydas et al. (2003) and Osuna et al. (2002) have shown that MLT protects neural tissues against neurotoxicity due to homocysteine-induced lipid peroxidation. It has been suggested that MLT directly blocks steps in the apoptotic pathway due to the absence of release of cytochrome c,

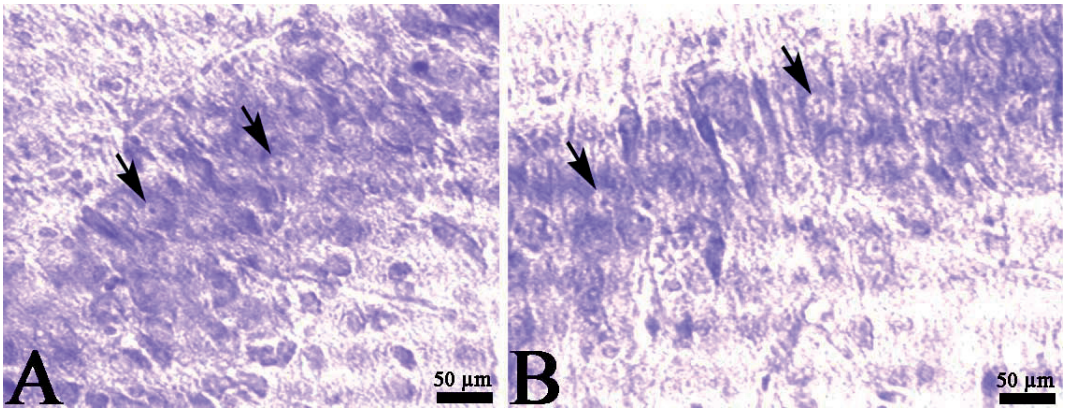

Fig. 19. Light microscopical sections of hippocampal pyramidal cells of control **(A)** and DS-treated rats **(B)**. Arrows indicate pyramidal neurons in both groups, and the asterisk indicates a necrotic cell in the DS group.

down-regulation of the pro-apoptotic protein Bax, up-regulation of the anti-apoptotic protein Bcl-2, and reduced DNA fragmentation in MLT-treated hyperhomocysteinemic rats (Baydas et al., 2005a,b). Letechipía-Vallejo et al. (2007), in an experimental study, have shown the neuroprotective effect of MLT against the pathophysiological mechanisms of brain damage occurring early after ischemia and reperfusion (Letechipía-Vallejo et al., 2007). They have demonstrated that treatment by MLT of global cerebral ischemia results in a significant long-term preservation of the neuronal population in the Ammon's horn (Letechipía-Vallejo et al., 2007). Turgut et al. (2007) have shown the neuroprotective effects of MLT on hydrocephalus-induced choroid plexus changes in infantile rats. Guven et al. (2007) have suggested that MLT partially protects against epirubicin-induced cardiotoxicity. Suresh et al. (2006) have demonstrated the neuroprotective effect of MLT during Pb-induced neuronal apoptosis (Suresh et al., 2006). The authors have suggested that this neuroprotection is associated with the possible metal-chelating effect of MLT reducing the cell damage and increasing the production of intracellular GSH levels.

Some experimental studies have also documented a bone-protecting action of MLT which operates by decreasing bone resorption in ovariectomized rats provided with estradiol (Ladizesky et al., 2003) and methylprednisolone (Ladizesky et al., 2006). Mogulkoc et al. (2006) have shown that hyperthyroidism increased oxidative damage in cerebral, hepatic, and cardiac tissues of rats and that MLT supplementation suppressed oxidative damage. Sharma et al. (2006) have shown a physiological neuroprotection action of MLT against Parkinsonian neurodegeneration in the nigrostriatal system in a 6-hydroxydopamine model of Parkinson's disease. Studies have reported a marked increase in mRNA and protein expression in rat C6 glioma cells after treatment with MLT (Armstrong and Niles, 2002; Sharma et al., 2006) The glial-cell-line-derived neurotrophic factor, which is a potent survival factor for dopaminergic neurons in the CNS (Kirik et al., 2004; Smith et al., 2005), may be involved in some of the neuroprotective effects of MLT (Sharma et al., 2006).

It has been noted that MLT receptors are present in regions of the human brain such as the hippocampus (Savaskan et al., 2001, 2005). MLT's antioxidative and neuroprotective properties demonstrated in the hippocampus include synaptic plasticity in pyramidal neurons (El-Sherif et al., 2003), regulation of the expression of cell adhesion molecules (Baydas et al., 2002), and serotonin release (Monnet, 2002). The MT_1, MT_2, and MT_3 membrane receptors of MLT are responsible for effects such as the circadian rhythm and protection against oxidative stress (Dubocovich and Markowska, 2005; Pandi-Perumal et al., 2006). The antioxidant effect of the MT_3 receptor, characterized as the enzyme quinone reductase 2, occurs by its prevention of electron transfer reactions of quinines (Foster et al., 2000). Other antioxidant effects of MLT occur by its direct inhibition of the mitochondrial permeability transition pore (Andrabi et al., 2004). MLT also scavenges some organic radicals such as protoporphyrinyl cation radicals, 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) cation radicals, substituted anthranylyl radicals, and peroxyl radicals (Hardeland and Pandi-Perumal, 2005; Hardeland, 2005; Pandi-Perumal et al., 2006).

The neuroprotective effects of melatonin against neurotoxicity of diclofenac sodium

NSAIDs may change neurotransmitter levels (Mohanakumar et al., 2000; Sairam et al., 2003). Dairam et al. (2006) have shown that tolmetin and sulindac inhibit tryptophan 2,3-dioxygenase with a concomitant increase in 5-HT levels in the hippocampus and reduced DA levels in the striatum (Dairam et al., 2006). Sharma et al. (2006) have demonstrated a physiological neuroprotection action of MLT against Parkinsonian neurodegeneration in the nigrostriatal system in a 6-hydroxydopamine model of Parkinson disease (Sharma et al., 2006). It has been reported that MLT affects serotonin release (Monnet, 2002). Although the effects of DS on neurotransmitters in the CNS are not yet known, it has been suggested that NSAIDS may change neurotransmitter levels. Therefore, it may be said that MLT protects against the abnormal effects of NSAIDs, and probably of DS, on neurotransmitters. In addition, it is known that PGs markedly enhance MLT synthesis at night (Cardinali et al., 1982; Voisin et al., 1993). Nevertheless, NSAIDs that inhibit PG synthesis (Vane, 1971) have the ability to reduce MLT synthesis. For example, it has been shown that some NSAIDs such as aspirin and ibuprofen (Murphy et al., 1986; Surrall et al., 1987) reduce MLT synthesis in humans. However, in one study, it has been reported that tolmetin, not sulindac, increases the amount of MLT produced by the rat pineal gland, possibly by the effect of this drug on the MLT synthesis pathway in the pineal gland (Dairam et al., 2006). Thus, NSAIDs, including DS, may cause neurotoxicity by decreasing the synthesis of MLT. Several studies have suggested that active metabolites of DS cause drug toxicity by oxidative stress and apoptosis (Hickey et al., 2001; Inoue et al., 2004). Furthermore, it is well known that MLT and its metabolites are potent free-radical scavengers and antioxidants, which protect cells from damage induced by a variety of oxidants (Tan et al., 1993, 2007; Catalá, 2007). MLT also has a strong antiapoptotic signaling function (Pandi-Perumal et al., 2006). The mechanism of melatonin on pathological conditions is shown in Figure 18.

It has also been suggested that DS suppresses the differentiation of neuronal stem cells into neurons and inhibits their proliferation via the induction of apoptosis, in contrast to other NSAIDs (Andreasson et al., 2001; Kudo et al., 2003). Kudo et al. (2003) have shown that DS inhibits the differentiation of neural stem cells into neurons. Chang et al. (2005a) have suggested that NSAIDs cause cell cycle arrest and apoptosis of

osteoblasts. Some studies have reported that antioxidant components such as vitamin E and superoxide dismutase decreased the oxidative toxicity of DS (Cantoni et al., 2003; Gomez-Lechon et al., 2003; Inoue et al., 2004). Gokcimen et al. (2007) have shown a significant cell loss in the pyramidal cell layer of the cornu ammonis of 20W-old DS-treated rats in comparison to their controls, but no significant difference between 4W-old groups was found (Fig. 19) (Gokcimen et al., 2007). COX inhibition of some NSAIDs also modulates activities of various ion channels (Shaw et al., 1995; Asomoza-Espinosa et al., 2001; Voilley et al., 2001). It has been reported that DS activates the nitric oxide-cyclic GMP pathway and subsequently opens the ATP-sensitive potassium channels (Asomoza-Espinosa et al., 2001).

MLT can have relevant downstream effects on Ca^{2+}-activated K^+ channels (Dubocovich and Markowska, 2005; Pandi-Perumal et al., 2006). Both DS and MLT may be competing for potassium or other ion channels. Additionally, therefore, MLT may protect against the neurotoxicity of DS by modulating the ion channels. Morioka et al. (2004) have demonstrated that some NSAIDs, including DS, lead to an increase in the intracellular concentration of MPP^+ and aggravation of cell toxicity in PC12 cells (Morioka et al., 2004). Another study has suggested that MLT significantly attenuates mitochondrial DNA damage in the substantia nigra induced by MPTP and its active metabolite MPP^+: free-radical generation was reduced, and the collapse of the mitochondrial membrane potential and cell death were antagonized (Chen et al., 2005). In summary, MLT, as a powerful antioxidant, can protect against DS induced oxidative stress.

Conclusion

Melatonin has a wide antioxidant action, which can protect lipids and proteins, as well as both nuclear and mitochondrial DNA, by means of its ubiquitous actions as a direct free-radical scavenger and an indirect antioxidant. The neurotoxic mechanisms of DS are not clear. However, like some other NSAIDs, it may cause apoptosis through a caspase-dependent cascade, diminishing the effects of antioxidants such as MLT, ROS, the activation of PPAR, cell cycle arrest, and an increase in the intracellular accumulation of toxic agents by inhibiting the activities of MRPs. To our knowledge, no study has focused on the neuroprotective effects of MLT against the neurotoxicity of DS. Therefore, we reviewed the literature on the antioxidant and antiapoptotic actions of MLT and the neurotoxic actions of DS, and discussed the probable neuroprotective effects of MLT against the neurotoxicity of DS. Finally, we concluded that exogenous MLT may protect against some neurotoxic actions of DS.

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