

REVIEW

Alzheimer's disease and related neurodegenerative disorders: implication and counteracting of melatonin

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Summary

Age related neurodegenerative disorders are becoming a serious public health problem. Alzheimer's disease (AD) is a progressive disease pathologically recognizable by deposition of neurofibrillary tangles and amyloid plaques. Oxidative stress probably plays a pivotal role in AD, but despite expectations, antioxidants such as vitamin E, vitamin C, β carotene, and flavonoids have failed as effective prophylaxis and/or treatment. Melatonin, a hormone controlling circadian rhythm, is a potent terminal antioxidant. *In vitro* tests and animal models have established that the application of melatonin could be beneficial for the amelioration of AD progression. Unfortunately, melatonin effects in human beings are not well understood and a lot of work has still to be done. The review summarizes the basic facts about melatonin and its prospects as a treatment for AD using its hormonal and antioxidant properties.

Key words: Alzheimer's disease; amyloid plaques; neurofibrillary tangles; tau; amyloid beta; oxidative stress; melatonin; antioxidant

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder with a not well understood aetiology. AD has become not only an ethical problem in public health care but it also an increasing item in care costs (Jonsson and Wimo 2009). Schumock (1998), for example, estimated the costs of AD treatment at the end of the 1990s, and calculated that the total cost per

patient in the United States was 195,000 USD, including nursing, drugs and family out-of-pocket expenses.

The aetiology of AD has not yet been established. It is recognized that amyloid beta and hyperphosphorylated tau protein (HPT) accumulates before the development of manifest AD (Leinonen et al. 2010), but the precise diagnosis of AD is not simple. The Mini-Mental State Examination (MMSE) cognitive test, lasting approximately 45 minutes, is a simple option for fast diagnosis of dementias including AD (Wilson et al. 2002), because AD, as well as other dementias, can be accompanied by cognitive dysfunction, by apathy, aggression, irritability, and aberrant motor behavior; although anxiety and apathy seem to be more typical of AD than of the other dementias (Wetzels et al. 2010).

As will be discussed later, AD is closely associated with the impairment of the electron

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transport chain in mitochondria and the consequent oxidative stress (Pickrell et al. 2009). The application of an antioxidant is hypothesized as a promising treatment for AD (Flaherty et al. 2010). Melatonin is a potent antioxidant and endogenous hormone, and, when administered exogenously, it can act as a potent protective drug against oxidative stress related disorder and intoxications (Pohanka et al. 2011a). The present review considers the implication of oxidative stress in AD, the potency of antioxidant treatment, gives a summary of the known facts and an estimation of promising ways to use melatonin as a drug for ameliorating AD pathogenesis.

ALZHEIMER'S DISEASE MOLECULAR PATHOGENESIS

Two major molecular mechanisms are related to AD pathology: amyloid beta deposition in the form of amyloid plaques and the creation of HPT forming neurofibrillary tangles. Amyloid beta is cleaved from the amyloid precursor protein (APP), but neither the physiological role of APP nor the mechanism of cleavage of the 42 amino acids long amyloid beta fragment (1-42) is fully understood. APP splitting is carried out by three secretases: α , β , and γ . Fragments provided by α -secretase are non-toxic and are not further modified by β - and γ -secretases into potentially dangerous forms (Cole and Vassar 2007). Neurotoxic amyloid beta is created in two steps. In the first step, APP is cleaved by β -secretase (known also as an aspartic protease BACE 1 or memapsin 2). In the second step, γ -secretase containing the transmembrane protein presenilin finalizes the production of amyloid fragments (Coen and Annaert 2010). Amyloid beta peptides of different lengths can appear; typically 39–43 amino acids long (Kadlick et al. 2004). The most neurotoxic is the amyloid beta consisting of 42 amino acids (Jan et al. 2011a), which dominates the shorter amyloid peptides in AD patients (Kuperstein et al. 2010). Moreover, it is the most hydrophobic and fibrillogenic form of the cleaved fragments and it can simply form amyloid plaques in neurons (Murphy and LeVine 2010).

HPT is the second hallmark of damaged neurons in AD patients, and this pathogenesis is based on the deposit of neurofibrillar tangles inside the neurons. The origin of the tau is in the cytoskeleton where it stabilizes microtubules (Kao et al. 2010), becomes hyperphosphorylated due to not well understand mechanisms and can cause dementia diseases called tauopathy. Beside tauopathy in AD patients, tau is also implicated in the pathogenesis of Parkinson's

disease (Lei et al. 2010). HPT contains phosphates bound via GSK-3 β kinase into Ser199, Ser202, Ser 396, and Ser 404 (Cai et al. 2011).

Two major molecular changes relate to AD. The link between neurofibrillary tangles and amyloid plaques is not well recognized, but the deposition of amyloid plaques probably starts before the formation of neurofibrillary tangles (Zheng et al. 2002). The whole pathogenesis is also tightly connected to the immune system and neuroinflammation probably plays a crucial role in the development of AD (Casoli et al. 2010). Although AD is not specific to a particular region, the cerebral cortex and hippocampus are the most damaged regions (Raji et al. 2009).

ALZHEIMER'S DISEASE AND OXIDATIVE STRESS

There are several theories of senescence. Unfortunately, a definite answer to the question of why and how ageing appears has not been established. Two theories relating to AD, seem to be the most plausible: firstly, ageing is the result of the chronic impact of reactive oxygen species, and secondly, resistance to oxidative stress is decreased due to some endogenous and/or exogenous effectors (Gilca et al. 2007). Oxidative insult probably triggers or augments AD pathology. On the other hand, the aetiology of many diseases and tissue damage may relate to oxidative stress and some authors suggest that reactive oxygen species are only a consequence and not a primary cause in these situations (Juránek and Bezek 2005).

Amyloid beta (1-42) toxic impact is not based only on the deposition of amyloid plaques but also on the adverse effects of redox reactions. Met 35 is responsible for the toxic properties of amyloid beta as it is associated with the generation of oxidative stress and the oxidative modification of macromolecules (Butterfield and Kanski 2002). Replacement or oxidation of Met 35 leads to the abolition or reduction of amyloid beta (1-42) toxicity (Clementi et al. 2006). The molecular mechanism of the pro-oxidant activities of amyloid beta (1-42) is not clear. It can reduce Cu^{II+} to Cu^{I+} and thus trigger a Fenton reaction (Boyd-Kimball et al. 2004), and it can also initiate cytochrome c release from the mitochondria and activation of apoptotic cascades. Substitution of Met 35 by norleucine abrogates the apoptotic cascade as proven on PC12 cell lines (Clementi and Misiti 2005). Cell lines affected by amyloid beta (1-42) and its fragments suffer from oxidative insult via the

excessive production of nitric oxide, superoxide, and hydrogen peroxide as well as their reaction products such as peroxynitrite (Ill-Raga et al. 2010). Trans-4-hydroxy-2-hexenal is proven reactive product of the degradation of lipid membranes in the presence of amyloid beta (1-42) in neuronal cell lines or the brains (Butterfield and Lauderback 2002). The implication of amyloid beta (1-42) in oxidative stress is also confirmed by the fact that antioxidants such as vitamin E prevent amyloid beta (1-42) induced oxidative stress in model animals (Butterfield 2002).

The link between tau respective HPT and oxidative stress on the one hand and amyloid beta (1-42) and the formation of free radicals on the other is not clear. Though there is a need for further data about its role in the body the physiological role of tau is well researched and it has been proved that it is a compound able to fight wild oxidative and heat stress and to take part in the maintenance of homeostasis (Sultan et al. 2011). Brain tissue damage can cause hypoxia and thus generate oxidative stress (Guzy et al. 2005).

CURRENT OPTIONS FOR ALZHEIMER'S DISEASE TREATMENT

The pharmacotherapy of AD is based on the moderation of its manifestation, and calming of depressions, aggression etc. is a common process for the treatment of AD as well as the other dementias. Causative treatment of AD is not currently available. The common AD therapies mainly use inhibition of enzyme acetylcholinesterase (AChE), an enzyme participating in the termination of cholinergic neurotransmission. As the lack of the neurotransmitter acetylcholine is a negative process in the brain of AD patients, the AChE inhibitors can resolve acetylcholine deprivation. There are many known AChE inhibitors, but the prospects for AD treatment are conditioned by good penetration through the blood brain barrier. Inhibitors so far tested, such as the tetrahydroacridinium derivative tacrine and organophosphate metrifonate (trichlorfon) have adverse effects and clinical application has been terminated (Lopez-Arrieta and Schneider 2006, Alfirevic et al. 2007). The derivatives of tacrine have also been extensively investigated; however, they are not approved for therapeutic purposes (Pohanka et al. 2008, 2009, Korabecny et al. 2010). The AChE inhibitors currently available for AD treatment are donepezil, rivastigmine, and galantamine (Bonner and Peskind 2002). Another drug, huperzine, is being considered for clinical application; its variant

huperzine A is especially preferred and acts not only as a non-competitive AChE inhibitor, but also as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist (Zhang and Hu 2001). Some countries, such as China, provide huperzine as a regular drug (Desilets et al. 2009).

Memantine is the only available AD drug that acts in a way other than on the cholinergic system. It is a non-competitive antagonist of the NMDA receptor binding in the open channel form of the receptor (Potter 2010), which is a non selective ion channel playing an excitatory role. It is speculated that the receptor is involved in Alzheimer's disease aetiology as it enhances the deposition of amyloid oligomers (Decker et al. 2010). Memantine is implicated in the reduction of amyloid beta (1-42) toxicity and is probably able to attenuate tau phosphorylation (Song et al. 2008). It can also protect neurons from calcium induced excitotoxicity (Lipton 2005). However, despite being well suited for the amelioration of some negative processes, it is not able either to resolve or to significantly slow down the progression of AD (Bassil et al. 2010). Past and current drugs for AD treatment are summarized in Table 1.

It has been proposed that other pathways can be affected in AD treatment. Inhibitors of γ and β secretases are promising compounds for clinical trials and growing interest can be expected in the development of novel compounds influencing secretases activity (He et al. 2010). As AD might be a consequence of oxidative insult and/or activation of the glial cells, the next effort will probably be aimed at resolving inflammatory processes and oxidative stress in the early stages of AD. From this point of view, melatonin can be a prospective compound in several pathways.

ACTION OF ANTIOXIDANTS IN PATHOGENESIS OF ALZHEIMER'S DISEASE

As the pathogenesis of AD is strongly related to the generation of oxygen and nitrogen reactive species, the application of low molecular weight antioxidants can be hypothesized as suitable for its counteraction. There is for example a proven protective effect of vitamin E on neural cell culture exposed to 42 amino acids long amyloid beta (Yatin et al. 2000) and similar results have been noted in animal brains (Butterfield 2002). However, plausible confirmation of vitamin E or any other low molecular weight antioxidant protective or therapeutic effect is missing, despite extensive investigation. Devore et al. (2010)

Table 1. Past and current drugs for Alzheimer's disease treatment.

| Drug | Systematic name | Mechanism of action | Fate |
|--------------|---|--|--|
| Donepezil | (<i>RS</i>)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one | non-competitive (reversible) AChE inhibitor | Marketed under trade name Aricept |
| Rivastigmine | (<i>S</i>)- <i>N</i> -Ethyl- <i>N</i> -methyl-3-[1-(dimethylamino)ethyl]phenyl carbamate | pseudoirreversible inhibition of AChE and BChE | Available under trade name Exelon |
| Galantamine | (4 <i>aS</i> ,6 <i>R</i> ,8 <i>aS</i>)-5,6,9,10,11,12-hexahydro-3-methoxy-11-methyl-4 <i>aH</i> -[1]benzofuro[3 <i>a</i> ,3,2- <i>ef</i>] [2] benzazepin-6-ol | competitive (reversible) inhibition of AChE | Marketed under different trade names such as Nivalin, Razadyne, Reminyl... |
| Huperzine A | (1 <i>R</i> ,9 <i>S</i> ,13 <i>E</i>)-1-Amino-13-ethylidene-11-methyl-6-azatricyclo[7.3.1.0 _{2,7}] trideca-2(7),3,10-trien-5-one | non-competitive (reversible) inhibitor of AChE and non-competitive antagonist of NMDA receptor | Available in China; clinical trials are not concluded |
| Metrifonate | (<i>RS</i>)-2,2,2-trichloro-1-dimethoxyphosphoryl-ethanol | irreversible inhibitor of AChE and BChE | Withdrawn in AD treatment due to adverse effects; available as antihelminthic |
| Tacrine | 1,2,3,4-tetrahydroacridin-9-amine | non-competitive (reversible) inhibitor of AChE and BChE | Originally marketed as Cognex; withdrawn due to adverse effects, especially hepatotoxicity |
| Memantine | 3,5-dimethyladamantan-1-amine | non-competitive antagonist of NMDA receptor binding in the open channel form of receptor | Marketed under trade names Abixa, Axura, Ebixa, Memox, Namenda... |

AChE – acetylcholinesterase; BChE – butyrylcholinesterase; NMDA – N-methyl-D-aspartic acid

disclaimed any plausible beneficial effect of vitamin C, β carotene, and flavonoids on the onset of AD pathogenesis. On the other hand, they found slight improvement in AD as an effect of vitamin E when administered in high doses. Most of the experimental work unfortunately, has failed to follow the composition of the vitamin E supplement. As seen from the work of Mangialasche et al. (2010), for example, the forms of vitamin E have unequal efficacy. In vitamin E preparation, β tocopherol had better efficacy than α tocopherol, α tocotrienol, and β tocotrienol. Clinical trials proved a slight improvement in AD progression due to tocopherols, but the effect is not protective enough (Sano et al. 1997). Moreover, the low effect of the treatment process can be overbalanced by the adverse effects of antioxidants (Soni et al. 2010). It should also be emphasized that the previously noted improvements

are only slight and the effects are hard to recognize. Co-application of vitamin E with AD drugs is, nevertheless, recommended in AD therapy (Doraiswamy 2002).

MELATONIN BIOLOGICAL EFFECTS

Melatonin (N-acetyl-5-methoxytryptamine) is a pineal gland hormone regulating time cyclicality in both animals and humans (Prendergast 2010). In the lower life forms, melatonin can act as an antioxidant protecting against the harmful impact of reactive oxygen and nitrogen species (Bustos-Obregon et al. 2005). In mammals, two G-coupled melatonin receptors are known: melatonin receptors MT₁ and MT₂. The receptors are responsible for circadian and

seasonal responses, but the physiological implications are not fully recognized (Sugden et al. 2004). It has also become plausible that circadian regulation and hypnotic action are completely separate processes in the action of melatonin (Jan et al. 2011b). Beside the melatonin receptor, melatonin can act as an agonizing ligand of the retinoic acid receptor-related orphan receptor (ROR) $\alpha 1$ with the potential to control cell cycle and apoptosis-associated genes (Wiesenberg et al. 1995, Hill et al. 2009). The proven molecular impacts of melatonin are summarized in Fig. 1.

The role of melatonin as an endogenous antioxidant in humans and vertebrates is not clearly understood. Moreover, the lack of melatonin could be the reason for the higher incidence of Parkinson's disease and cancer in night workers and some other specific occupations (Schernhammer et al. 2006). In recent years, melatonin has been considered as a drug suitable for the suppression of the toxic impact of many compounds and ameliorating the pathogenesis of some diseases because of its fast suppression of oxidative stress (Korkmaz et al. 2009). Another impact – based on its expression of the IL-2 receptor – is not clearly understood. In animal models, it has been proved [by, for example, Mollace et al. (2005)] that melatonin mediates the inhibition of inducible nitric oxide synthase (iNOS), and cyclooxygenase 2 (COX2), and elevated levels of superoxide dismutase, glutathione reductase and glutathione peroxidase (as noted by, for example, Winiarska et al. 2006, Venkataraman et al. 2010). Melatonin could act as a very strong antioxidant. In comparison with the typical endogenous antioxidants, melatonin is an irreversible (also called 'suicidal') low molecular weight antioxidant. This means that the oxidized form of melatonin does not act as a pro-oxidative agent deteriorating redox status in other tissues, as is typical for the other antioxidants, and that it is not recovered into its initial molecule by the simple redox system. Moreover, the melatonin consumption products 6-hydroxymelatonin and N-acetyl-N-formyl-5-methoxykynurenamine, also act as antioxidants (Maharaj et al. 2007). The structures of melatonin and its degradation products are summarized in Fig. 2. The antioxidative effect of melatonin was recognized as suitable for its performance as a non-specific antioxidant after exposure to, for example, sulfur mustard (Pohanka et al. 2011a) or methamphetamine (Nopparat et al. 2010). On the other hand, there is some controversy in work on the impact of melatonin as the pro-oxidant activities of melatonin have also been recognized in human erythrocytal proteins (Dikmernoglu et al. 2008).

MELATONIN POTENTIAL FOR ALZHEIMER'S DISEASE TREATMENT

The prospects for melatonin as a treatment for AD are based on two independent pathways: a) scavenging of reactive oxygen and nitrogen species, and b) acting as a hormone or resolving sleep disturbance. Regarding the antioxidant action, oxidized melatonin does not act as a pro-oxidative agent, unlike the other endogenous low molecular weight antioxidants such as vitamin C, vitamin E, and glutathione (Tan et al. 2000). For this reason, melatonin could be found suitable in AD treatment in situations where the other antioxidants fail. On the other hand, rats with a melatonin enriched diet have been found to have significantly decreased levels of the antioxidant homocysteine (Murawska-Cialowicz et al. 2008). This points to a quite complex role for melatonin in organisms that could be negative as well as positive unless the application is supported by plausible experimentation. The prospects for melatonin in neuropathological processes in AD patients are underlined by the fact that the levels of melatonin can be low, as proved by Zhou et al. (2003) in an experiment on 121 subjects investigated postmortem. They recognized that individuals with a higher physiological level of melatonin had a reduced level of amyloid plaques and neurofibrillary tangles.

The role of melatonin as a potent molecule for the suppression of oxidative stress has been investigated by many teams. Experiments have shown that melatonin can ameliorate the overproduction of reactive oxygen species generated by complex I of the mitochondrial respiration chain by way of cardiolipin, an important part of the mitochondrial inner membrane protection (Petrosillo et al. 2008). Melatonin can keep the mitochondrial membrane fluidity as it protects from lipid peroxidation and it is speculated that mitochondrial membrane protection can slow down age related degeneration (García et al. 1997, 2010). However, this hypothesis needs to be confirmed and applied particularly to AD development in the early phases of pathogenesis. Recently, it was proved that the processes of senescence are altered in melatonin treated animals. Melatonin significantly modified not only oxidative stress related impairments, but also apoptotic processes and macroautophagic activities in senescence accelerated and slowed mice (Caballero et al. 2009). Alterations in NF κ B, iNOS, TNF α and IL1 levels in a mice model are also involved in the biological effect of melatonin (Cuesta et al. 2010). Considering that AD, Parkinson's disease and some other neurodegenerative disorders are thought to be related to chronic inflammation (Gemma 2010),

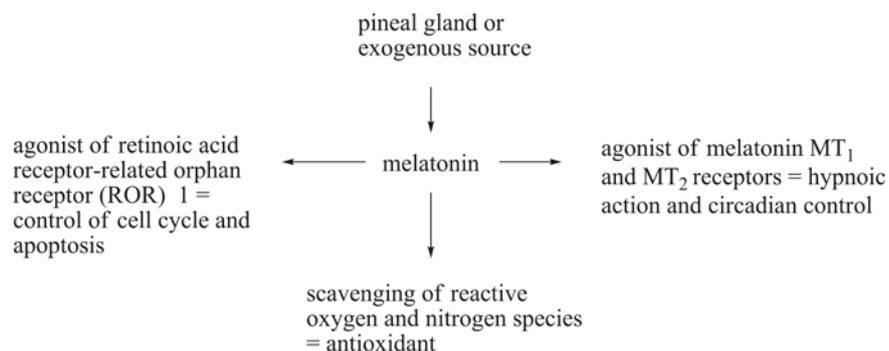


Fig. 1. Summarization of melatonin impact in mammal organism.

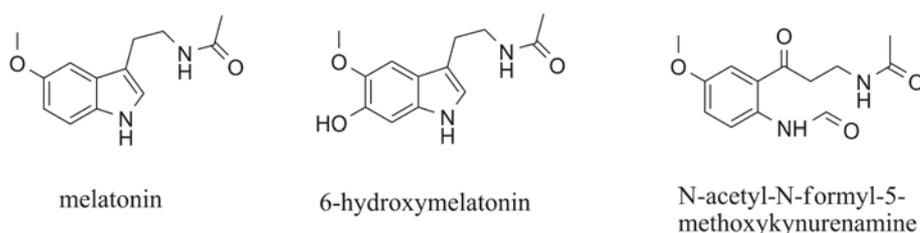


Fig. 2. Structures of melatonin and the most significant products of its oxidative degradation.

melatonin could be regarded as a compound for inflammation control (Wang and Wang 2006). On the other hand, if neurodegeneration is caused by neuroinflammation alone, the application of a standard steroidal or non-steroidal anti-inflammatory drug would be preferable. The role of the immune system in the nervous system is a complex one, and it can be detrimental when the autoimmune response for chronic inflammation is launched. Besides, the immune system function is necessary for protection against an invasion of pathogens (Gendelman 2002). It can be questioned whether the application of melatonin increases sensitivity to pathogens and enables pathogen invasion when the above mentioned suppression of innate immunity is considered. Unfortunately, this question has not yet been fully solved.

The link between circadian timing and the immune system has been hypothesized by many scientists (Berger 2008). The implication of melatonin in the modulation of apoptosis is similar to the effect of another antioxidant, epigallocatechin gallate. This green tea antioxidant was found to be able to influence extensively apoptosis in healthy mice exposed to sulfur mustard (Pohanka et al. 2011b).

The application of 10 mg/kg melatonin was found to be suitable for the suppression of some detrimental processes in the nervous system. It also triggered the up-regulation of the ROR $\alpha 1$ level. On the other hand, the application was without any implication in MT₁ receptor presence in SAMP8 senescence accelerated mice and senescence slowed mice SAMR1 (Caballero et al. 2008). In this mouse model, the effects are corroborated for a long term application (five or ten months) that represents half and more of the life term given normal life expectancy. As reported by Gutierrez-Cuesta et al. (2007), the chronic administration of melatonin 10 mg/kg also had another significant effect in SAMP8 mice: reduced cell loss and oxidative damage of macromolecules. They found not only decreased hyperphosphorylation of tau, but also down-regulated activation of cdk5/p35 and its cleavage to cdk5/p25; these point to a link between melatonin and reduced neurodegeneration on the level of its molecular control. On the other hand, it should be emphasized that the effect described followed quite a high dose of melatonin. Were the dose to be recalculated to the average human weight, it would be approximately two hundred times higher than the dose 3 mg *pro toto* used for improvement of sleep quality (Nunes et al. 2008).

Melatonin action as a hormone can be suitable for the treatment of sleep disturbances. AD patients have fragmented sleep, disturbing the normal sleep-wake circadian rhythm (Song et al. 2010); melatonin can correct this and improve physical as well as mental shape (David et al. 2010). It should also be noted that melatonin production decreases with age and that it is produced on a limited scale in AD patients so that the administration could substitute for the suppressed function of the pineal gland. This reduced production is considered a possible cause of the beneficial effect of melatonin pharmacological performance (Karasek and Reiter 2002, Karasek 2004). Although melatonin can influence the body in several ways and is a compound of considerable scientific interest, most of the results discussed were found in animal models or cell lines. Any clinically confirmed melatonin beneficial effects should be further investigated in a wide study as some of the preliminary results are encouraging: in particular its efficacy in the improvement of sleep in patients should be critically assessed. In considering any clinically proved efficacy of melatonin to treat insomnia in the elderly (Wade et al. 2010), it should again be noted that beneficial physical effects in humans are strongly influenced by sleep improvement alone. Also, Furio et al. (2007) have ascribed the effect of melatonin in a AD related study to circadian regulation rather than an antioxidant action. Similar conclusions were reached by Dowling et al. (2008). However, their study was carried out on a total of fifty subjects treated for ten weeks. The groups of 16, 17 and 17 specimens are quite small and smaller changes were not probably recognized. A systematic review carried out in 2005 provided similar results: there is insufficient evidence to support the effectiveness of melatonin in the treatment of the cognitive and non-cognitive sequences of dementia (Jansen et al. 2006). More responsible data can be observed when melatonin is administered to people 55 years and over together with the investigation of the occurrence of new AD cases and the further progression of AD. Unfortunately, such clinical trials have not yet taken place.

CONCLUSIONS AND EXPECTATIONS FOR THE FUTURE

Despite the significant effect of melatonin on neuro-degeneration in experimental models, its potency in protecting neurons from aggravation is neither fully understood nor plausibly recognized in clinical studies. For the next decades, experiments

and trials on human beings can be expected. The pertinent experiments based on application of melatonin to human beings suffering from neurodegenerative disorders are now simplified by the fact that melatonin has been approved as a food supplement and drug for insomnia by the (U.S.) Food and Drug Administration agency and there are only minimal or no adverse effects (Taylor and Weiss 2009). The favourability of melatonin for treatment is emphasized by two facts: melatonin is quite cheap and simple to synthesis as a derivative of tryptophan with an intact indol core (Esteveao et al. 2010) and melatonin is maintained in the body for a long time. Some authors [e.g. Mistraretti et al. (2010)] have referred to the keeping of the pharmacological level in serum for 10 hours following enteral administration when the pharmacological level is reached after approximately 5 minutes with serum peak after 16 minutes.

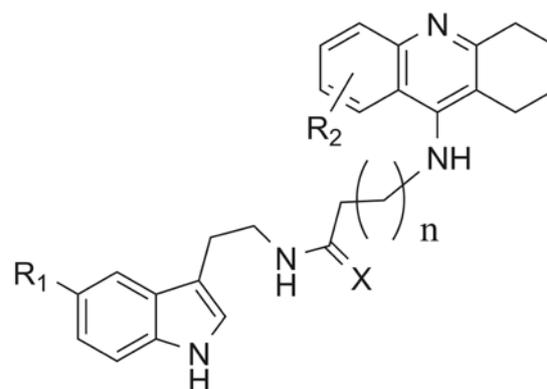


Fig. 3. **Derivatives composed from tacrine and melatonin prepared** by Fernandez-Bachiller et al. (2009). $R_1 = -H, -OCH_3$; $R_2 = -H, -Cl$, bis Cl (6,8 position); $X = O$ or S ; $n = 4, 5, 6$, or 7 .

Recent investigations have proposed that the deposition of amyloid plaque may be accelerated or even triggered by the interaction of amyloid beta (1-42) with the anionic subsite of AChE (Castro and Martinez 2006). Considering the stress insult necessary for amyloid beta deposition and amyloid plaque, the conjugates of the AChE inhibitor with antioxidant are promising drugs of the next generation. Tacrine-melatonin heterodimers have been extensively investigated in addition to the other compounds (Tumiatti et al. 2010). We can speculate how prepared compounds can be effective not only for the amelioration of AD symptomatic

manifestation but also because of their ability to slow down the pathogenesis progression. For example Fernandez-Bachiller et al. (2009) prepared derivatives of tacrine linked to melatonin via amine of tacrine and N-acetyl of melatonin. The prepared derivatives (see common structure in Fig. 3) kept good inhibitory potency to AChE as well as antioxidant ability *in vitro*. Especially the chloro and bischloro derivatives of tacrine linked to melatonin by six carbon long chains, had significantly higher selectivity to AChE compared to butyrylcholinesterase (BChE) retaining antioxidant ability and strong inhibitory potency to human AChE. We can expect next an effort to prepare new melatonin derivatives and confirmation of their effects on animal models in the short or medium term range. Unfortunately, the pertinent performance of these novel derivatives is limited, as the biological effect of melatonin complex on neurodegeneration is not fully understood.

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