Ageing and Neurodegeneration – The Role of Neurotransmitters' Activity

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Abstract: *Disease and ageing are linked in many ways and especially by the mechanisms they share. For many diseases, the process of ageing is the main culprit leading to the pathology. Hence, it is crucial to understand the process of ageing, and its molecular and cellular mechanisms to have a better understanding and perspective on these age-related diseases. Neurodegenerative diseases are probably the most common types of age-related diseases. Their pathology is complex, however, changes in neurotransmitter levels are almost always present. These types of changes occur during ageing as well, therefore, exploring the link between those processes can give a clue for possible treatments. Monoamine oxidases (MAOs) are enzymes that break down monoamine neurotransmitters and their dysregulation has long been recorded in age-related neurodegenerative diseases such as Alzheimer's and Parkinson's disease. There is strong evidence that modulating the MAOs' expression and activity can be beneficial for patients suffering from these illnesses. Herein we critically analyze the literature and make associations among ageing, MAOs' activity and neurotransmitters' levels, thus highlighting their role in neurodegenerative diseases.*

Keywords: *Ageing, Age-related disease, Neurodegenerative disease, Monoamine oxidase (MAO), MAO-A, MAO-B, MAOIs (monoamine oxidase inhibitors).*

Introduction

Ageing is a multifactorial process, distinguished by numerous events at the molecular, cellular and organismal levels. An overall functional decline is usually observed during ageing, which is associated with increased susceptibility to diseases that would probably result in the eventual death of the ageing organism [24]. Due to the development of new techniques in recent years scientists have focused their attention on the processes of ageing and its hallmarks. Extensive efforts have been invested in exploring its mechanisms as well as in the search for various strategies, which may prevent the ageing of the organism. Importantly, the pursuit of delaying the overall ageing but also the prevention and treatment of age-related diseases present the cornerstone in ageing research. When it comes to humans, there are several types of diseases,

which correlate with or are a result of ageing. Some of the major ones are cardiovascular diseases, diabetes, osteoporosis, cancer and neurodegeneration. Among those, neurodegeneration repeatedly escalates with age and leads to a significant increase in dementia-related diseases [2]. One prevalent example of this is the rise in overall death rates caused by Alzheimer's disease worldwide [23]. Thus, understanding in detail the process of ageing will allow a better approach to the prevention and treatment of age-related diseases.

Hallmarks of ageing

Although the incredible complexity of ageing, there have been established several hallmarks of it that give a more accurate picture, allowing for a deeper understanding of the mechanisms behind this process. These hallmarks are illustrated in Fig. 1 [31].

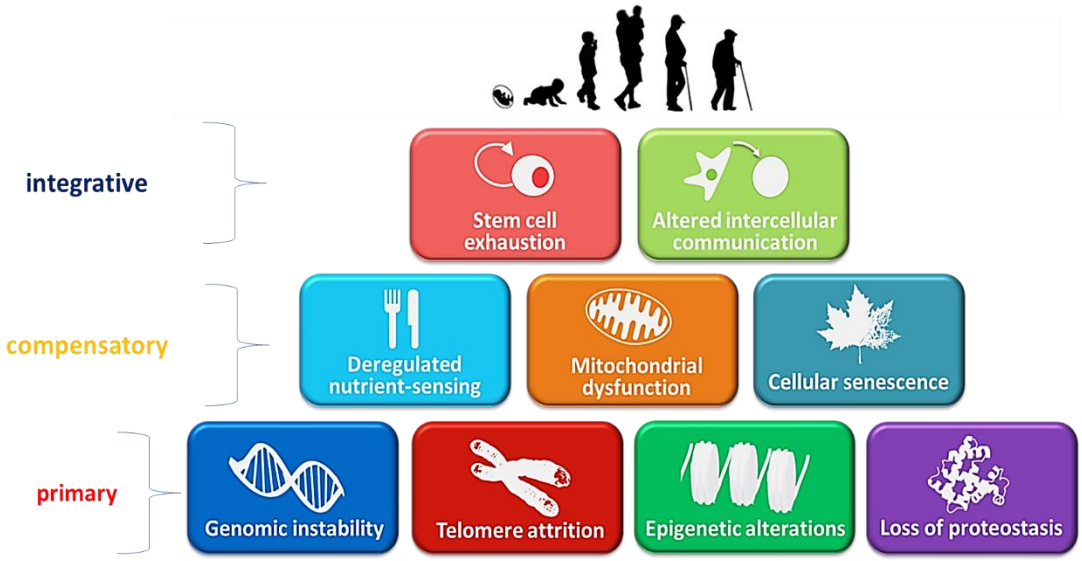

Fig. 1 Hallmarks of ageing reviewed in [1]

Cellular senescence

As discovered by Hayflick and colleagues, normal cells have a limited ability to proliferate in culture as they double their population a fixed number of times [20]. The process of stable cell cycle arrest is known as cellular senescence (CS). Even though CS plays a key role in anti-cancer and tumour-suppressive mechanisms, it also takes part in inducing degeneration of ageing tissues *via* the loss of regeneration and repair of the cells. Therefore, CS is considered one of the hallmarks of ageing [6]. Studies have shown that different kinds of intrinsic and extrinsic stimuli and stress signals lead to CS [39]. Specifically, telomere shortening or alteration, oncogenic stress, oxidative stress, radiation, genotoxic stress, mitochondrial dysfunction and different epigenetic changes are some examples of the abovementioned stimuli. Moreover, senescent cells are recognizable by their significant difference in gene expression along with chromatin remodelling, typical increased lysosomal activity, particular changes in structure and morphology in most cases, as well as the development of the senescence-associated secretory phenotype (SASP) [6, 28].

Stem cell exhaustion

A considerable body of evidence has demonstrated that stem cell exhaustion has been implicated in tissue and organ decline with age [53]. Regeneration of the tissues depends on two functions of utmost importance of the tissue-specific stem cells. Precisely, these are self-renewability and production of differentiated cells. However, stem cells have a life-long

persistence, which makes them more vulnerable to the accumulation of cellular and DNA damage and therefore eventually leading to cell death along with the loss of regenerative function. Alterations in cell signalling pathways are another major cause of stem cell exhaustion, especially in the case of extracellular signalling pathways, that occur in stem cell niches [35].

Genomic instability

DNA damage is known to accumulate with ageing due to various intrinsic and extrinsic factors and stressors [45]. The resulting genomic instability through the accumulation of DNA damage leads to the eventual deterioration of tissues and organs, which is prevalent in an ageing organism. The occurrence of DNA damage or the so-called DNA lesions is a result of different point mutations, deletions, insertions or even large chromosomal aberrations. As mentioned, there are different causes of DNA lesions. Such may be the oxidative stress when the DNA is exposed to reactive oxygen species (ROS), piled up by the cell's metabolic activity [45]. Replication errors and stress are considered also as major causes of genomic instability. Even though DNA polymerases replicate DNA with high accuracy, an insertion of incorrect nucleotides still occurs, which are then proofread and repaired. However, different types of machinery responsible for the detection and repair alternate their activity with the advancement of age. Furthermore, there are various factors such as reduced nucleotide pool, impaired nucleosome assembly and unrepaired DNA damage, which can cause the stalling of the replication fork, leading eventually to major genomic instability [45, 57].

Telomere attrition

Telomeres play an incredibly important role in cells as their main function is to protect the chromosomes from premature end-to-end degradation and chromosomal instability that occurs due to the telomeres' specific structure [18]. Moreover, telomeres can be actively transcribed despite their heterochromatic state, whereas the products from the transcription are in most cases long non-coding RNAs that have a regulatory function of the telomeres and telomerase activity. Alternatively, telomerase is a DNA polymerase responsible for telomere elongation by adding nucleotides at the 3' ends. However, telomerase is incapable of completely replicating the 3' end of the DNA strand resulting in the shortening of the telomeres at each cell division cycle. With the ageing of an organism, telomeres' length progressively shortens causing chromosomal instability. Subsequently, the length of a telomere has been identified as one of the best biomarkers of ageing [31, 55].

Epigenetic alterations

The patterns of DNA methylation have proven to be an underlying factor in the epigenetic changes of ageing. Globally, DNA methylation decreases with age except in certain specific regions where hypermethylation occurs. Diverse types of epigenetic changes like histone modifications (acetylation and deacetylation, methylation and demethylation, phosphorylation and many others) and DNA methylation have multiple and varied roles and effects on cells and tissues throughout life [9, 37, 41]. Consequently, epigenetic mechanisms are involved in the process of ageing as well. There is evidence that certain histone modifications affect ageing too [9, 19]. For example, increased acetylation of histones H4K16 and H3K9 has been recognized as age-associated epigenetic markers. Additionally, methylation and demethylation of the histones are important modifications in ageing [19]. These changes are most evident in histones H3 and H4 as H4K20 methylation and H3K16 trimethylation tend to decrease with age, while H3K27 trimethylation and H3K79 methylation and demethylation increase [37]. There are other epigenetic alterations affecting ageing such as chromatin remodelling, transcriptional alterations and changes in the expressions of microRNAs (miRNAs) [19, 31].

Mitochondrial ∂ysfunction

Mitochondrial dysfunction has been repeatedly demonstrated as one of the integral causes of ageing [52]. The main causes of decline in mitochondrial function are respiratory chain dysfunctions. They can occur through damage or mutations in the mitochondrial DNA (mtDNA). A significant body of evidence indicates the implication of mtDNA deletions in different human tissues with ageing [14, 48]. For a long time, a cause for the occurrence of mitochondrial dysfunction has been attributed to the production of ROS from the mitochondria as they are considered the main producer of ROS in the cell. Moreover, the oxidative damage induced by ROS to lipids, proteins and DNA has been identified in both model organisms and humans [36, 52]. However, the idea of ROS causing mitochondrial dysfunction remains inconclusive. Authors have reported that the observed phenomenon cannot be ascribed to the fact that the increased use of antioxidants does not decrease mitochondrial damage such as mtDNA deterioration or decreased biogenesis [36, 52].

Loss of proteostasis, deregulated nutrient sensing and changes in the intracellular communication

The stability of proteins in the cell relies on regulatory mechanisms such as the correct folding of proteins and degradation of proteins by the proteasome or lysosome. With age, these mechanisms endure alterations leading to the accumulation of unfolded, misfolded and aggregated proteins in the ageing cell. This leads to the appearance of the pathology of many age-related diseases [31].

Nutrient sensing constitutes another hallmark of ageing as it has been demonstrated that intervening with nutrient signalling pathways can attenuate ageing in various organisms [8]. The first nutrient pathway recognized to regulate ageing is the insulin/insulin-like growth factor 1 (IGF-1) signalling pathway and its effects on ageing can be most famously reduced by calorie restriction [25].

Other pathways are altered during ageing, as well. Specifically, certain intracellular communications are deregulated such as endocrine, neuroendocrine and neuronal communications. Along with the aforementioned alternations, the inflammation is increased, while the immune reactions against pathogens are decreased [31].

Ageing and age-related diseases

The hallmarks of ageing described above are signs of deterioration of the organism observed in ageing but also correlate to the occurrence of age-related diseases. As mentioned, the processes of ageing tend to be manifested in several types of diseases, which will be discussed in the following paragraphs. They include cancer, cardiovascular diseases, metabolic diseases, musculoskeletal disorders and neurodegenerative diseases on which we gather our focus.

Cancer

As the average life expectancy in most developed countries has increased to over 80 years, cancer has become an escalating health problem. According to the Global Cancer Incidence, Mortality and Prevalence Survey (GLOBOCAN, 2020), the International Agency for Research on Cancer declared a record of about 19.3 million new cancer cases and 10 million cancer deaths for 2020 and estimates a rise of 47% in cancer cases for 2040 [47]. Even though ageing is the main risk factor for cancer, the ageing cell and the cancer cell are considered to be contradictory to each other in terms of the ongoing processes. The ageing cell goes through a "loss of function and fitness", while the cancer cell has a "gain of function and fitness". Yet,

ageing and cancer cells share many characteristics. Some of the hallmarks of ageing such as genomic instability, deregulated nutrient sensing, and mitochondrial dysfunction are similar in cancer cells as well. DNA damage is what triggers cells' exhaustion. Similarly, cellular damage leads to cellular death (the final result of ageing) but when some additional mutations occur cells deviate from that pathway and transform into cancer cells [1].

Cardiovascular diseases

Cardiovascular diseases (CVDs) and especially ischemic heart disease are leading causes of death worldwide [27]. CVDs are intertwined with ageing, which is evident by the increased instances of CVDs among the population over 65 years of age. The process of ageing is suggested to be responsible for the deterioration of cardiovascular structures and functions as well as for the debilitated response to CVD. The structural deterioration of the cardiovascular system occurs due to the molecular mechanism of ageing in these tissues. An example is the accumulation of oxidative damage caused by the ROS produced from mitochondria as heart tissues are rich in them due to the consequence of high metabolic demand. Other factors such as altered proteostasis and dysregulated signalling pathways can significantly influence cardiac ageing. Some examples of affecting vascular ageing are cell senescence and dysregulated apoptosis as well as depletion of stem cells [54]. These are just a few of the mechanisms of ageing responsible for CVDs but it is evident that the process of ageing is considered the main culprit for these types of diseases [7].

Metabolic diseases

Obesity is a major risk factor for metabolic diseases such as type 2 diabetes (T2D). However, an abnormally elevated body mass index (BMI) does not encompass the whole picture, since impaired glucose homeostasis is correlated to increasing age [34]. Ageing is likewise intertwined with diseases like T2D. Virtually all of the hallmarks of ageing can potentially induce processes, which lead to T2D. An increase in age is associated not just with impaired glucose homeostasis but also impaired insulin secretion from β-cells along with a reduction in insulin sensitivity. Moreover, β-cell death is promoted *via* mitochondrial dysfunction [30, 34].

Neurodegenerative diseases

Regarding the pathology of the most common neurodegenerative diseases, it is evident that the process of ageing is a major driving force. The two most common neurodegenerative diseases that predominantly occur in the elderly are Alzheimer's (AD) and Parkinson's disease (PD). Other neurodegenerative diseases, which have an important connection to ageing, include ataxia-telangiectasia, amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). These diseases share many characteristics with the hallmarks of ageing. For instance, in ALS several pathways are dysregulated such as protein homeostasis, nucleoplasmic and endosomal transport. Concerning HD, due to the presence of the cytotoxic Huntington protein, proteostasis is affected leading to cellular impairment [21].

Alzheimer's disease

Trevisan et al. reported a positive link between Alzheimer's incidence and age and even though healthy ageing may help in avoiding the disease, it does not ensure prevention [51]. AD is manifested with clinical features like memory and learning deficits, disorientation and behavioural issues. At the molecular level, it is characterized by the aggregation of extracellular Aβ plaques and p-tau neurofibrillary tangles in the brain. The aggregation of these molecular patterns in AD is a complex combination of events, which occur in ageing as well such as DNA damage, changes in expression due to histone modifications and an increase in senescing neural cells [21, 29].

Parkinson's disease

Since the 1990s, the number of people suffering from PD has doubled, whereas ageing populations have greatly contributed to this trend [17]. A hallmark of PD is lying behind the loss of dopaminergic neurons in the *substantia nigra* resulting in dopamine deficiency. Interestingly, aggregates of α-synuclein in intracellular inclusions alongside mitochondrial dysfunction are also characteristics of PD. A risk factor for developing PD is DNA repair defects as they can affect the dopaminergic axis. Moreover, authors have found the association between CS in brain tissues with PD is based on the deposition of α-synuclein [21, 29].

Monoamine oxidases drive age-associated changes in neurotransmitters

The pathologies of neurodegenerative disorders are often associated with and influenced by the production, transport and subsequent failure in signalling [59]. Some neurotransmitters are crucial for the proliferation of new neural cells. Therefore, to fully understand the way and to what extent ageing affects the rate of neurodegenerative disorders, it is of great importance to investigate any possible alternation of levels in neurotransmitters during ageing.

Types of neurotransmitters

Monoamine neurotransmitters consist of serotonin or 5-hydroxytryptamine (5-HT) and the catecholamines dopamine, adrenaline, and noradrenaline [59]. These compounds have multiple functions including modulation of psychomotor function, cardiovascular, respiratory and gastrointestinal control, sleep mechanisms, hormone secretion, body temperature, and pain.

Dopamine is classified as one of the 7 major neurotransmitters with a significant impact on cognitive functions, learning motor and mood control. Dopamine's pivotal role in neuronal proliferation and differentiation in adults has been discussed in a previous paper by Mishra and colleagues [33]. The same was reported in another research showing that reduction in cognitive abilities in aged individuals is correlated with decreased dopamine receptors and transporters while younger individuals showcase higher synthesis capacity [3].

In the development of a wide range of neurodegenerative diseases, serotonin or 5-hydroxytryptamine (5-HT) plays a central role. Loss of 5-HT has been discovered in serotonergic neurons and receptors in the case of AD, for instance. This correlates to the fact that 5-HT is involved in most types of behaviour and physiological functions such as eating, circadian rhythmicity, etc. [13]. During ageing in humans, it has been shown that 5-HT levels decline in certain brain regions along with a decrease in the density of defined 5-HT receptors [32, 56]. However, there is evidence displaying an increase of 5-HT levels in some brain regions with ageing, as well as in specific 5-HT receptors. Overall, it is evident that 5-HT levels are influenced by the process of ageing [11].

Other notable neurotransmitters are gamma-aminobutyric acid (GABA) and acetylcholine. GABA is known as a main inhibitory neurotransmitter in the brain and interestingly, its levels alternate with ageing. GABA is important for the excitatory-inhibitory balance in the brain. Importantly, Ethiraj and colleagues have reported a decrease in GABA levels, as well as in the expression of certain subunits of GABA receptors with age. The authors hypothesized that the observed changes could be linked to the emergence of neurological conditions such as AD and depression [10]. Acetylcholine acts in motor neurons, the autonomic nervous system and in the brain as a neuromodulator. The synthesis of acetylcholine declines with age, which is accompanied by an increase in acetylcholine degradation. Notably, the same tendency as mentioned above for GABA and acetylcholine has been observed in neurodegenerative diseases like AD and PD [43].

MAO enzymes and the process of ageing

Taking into account that monoamine neurotransmitters and more specifically 5-HT, dopamine and norepinephrine have a central role in the development of many neurodegenerative disorders, it would be meaningful to look at their mechanisms of regulation. This will assist in the understanding of their role in the pathology of diseases and give some insight into potential new treatment strategies. Maybe the most fundamental regulation of monoamine neurotransmitter levels occurs via enzymatic degradation, which is mediated by the enzymes monoamine oxidases [4].

MAO-A and MAO-B

After the first isolation of the MAO enzyme from a rabbit liver in 1928 by Mary Hare, two isoenzymes in humans have been established – monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). The genes for the two isoenzymes span over 60 kb and are located on the short arm of the X-chromosome (Xp11.23). Both genes consist of 15 exons with the identical organization of exons and introns. Certain variations and mutations in these genes are correlated with different disorders and neurological conditions, as the last is relevant for MAO-A gene [4, 44]. The promoter region of the MAOA gene is an example of the aforementioned fact since a functional polymorphism of a variable number tandem repeat (VNTR) has been shown to influence certain neurological conditions. According to Samochowiec et al., the VNTR sequence is present in a different number of copies and based on these, the transcription of the gene can be more or less efficient [42].

Both MAO-A and MAO-B are expressed in most cells and are bound to the outer mitochondrial membrane. However, there are specific cells, tissues and organs of higher expression for the enzymes. Specifically, MAO-A is highly expressed in catecholaminergic neurons, while MAO-B is more prevalent in serotonergic neurons. Moreover, MAO-A is highly expressed in the liver, lungs and small intestine and MAO-B is highly expressed in histaminergic cells, the brain and also in the liver and small intestine [4, 36]. These differences are summarized in Table 1. As already mentioned, MAO enzymes' key role in the monoamine neurotransmitters' metabolism lies in their effective degradation. The last is possible due to the similar molecular structure of both enzymes. They are flavoprotein oxidases, which are characterized by a Flavin adenine dinucleotide (FAD)-binding domain. The domain allows the oxidation of the substrate of the enzyme [16]. Both participate in the degradation of major neurotransmitters like 5-HT, dopamine, adrenaline and noradrenalin, however, they have a slightly higher affinity for certain neurotransmitters. For example, MAO-A has an affinity for 5-HT and noradrenaline, while MAO-B shows an affinity for benzylamine and beta-phenylethylamine, see Table 1 [36]. Furthermore, the association of the major neurotransmitters with age-related diseases is illustrated in Fig. 2. We have outlined their role in the pathology of some common age-related diseases.

Neurological disorders associated with dysregulated MAO enzymatic activity

MAO-A and MAO-B take part in the modulation of different behaviours and cognitive functions via the regulation of levels of neurotransmitters that are directly related to those processes. MAO enzymes are considered to be key contributors to depressive disorders, especially MAO-A. It has been established that increased expression and activity of MAO-A lead to higher rates of degradation of neurotransmitters such as 5-HT, resulting in the development of depressive conditions [4, 49]. The last occurs due to the specific VNTR polymorphisms, which can lead to upregulation of gene expression. Also, MAO-A is a pro-apoptotic gene and its expression can cause neuronal cell death [26]. Reduced levels in MAO-A activity are on the other hand associated with negative outcomes such as anti-social and aggressive behaviour, most often observed in males [58].

Table 1. MAO-A and MAO-B substrates and their predominant expression sites in human tissues

	MAO-A	MAO-B
Favoured substrates for degradation	➢ serotonin ➢ noradrenalin ➢ norepinephrine ➢ dopamine	➢ benzylamine ➢ β-phenylethylamine
Shared substrates for degradation	Dopamine Adrenalin Tryptamine Tyramine	
Differential sites of expression	➢ catecholaminergic neurons ➢ liver ➢ lung ➢ placenta ➢ small intestine	➢ serotonergic neurons ➢ small intestine ➢ liver ➢ brain ➢ histaminergic cells

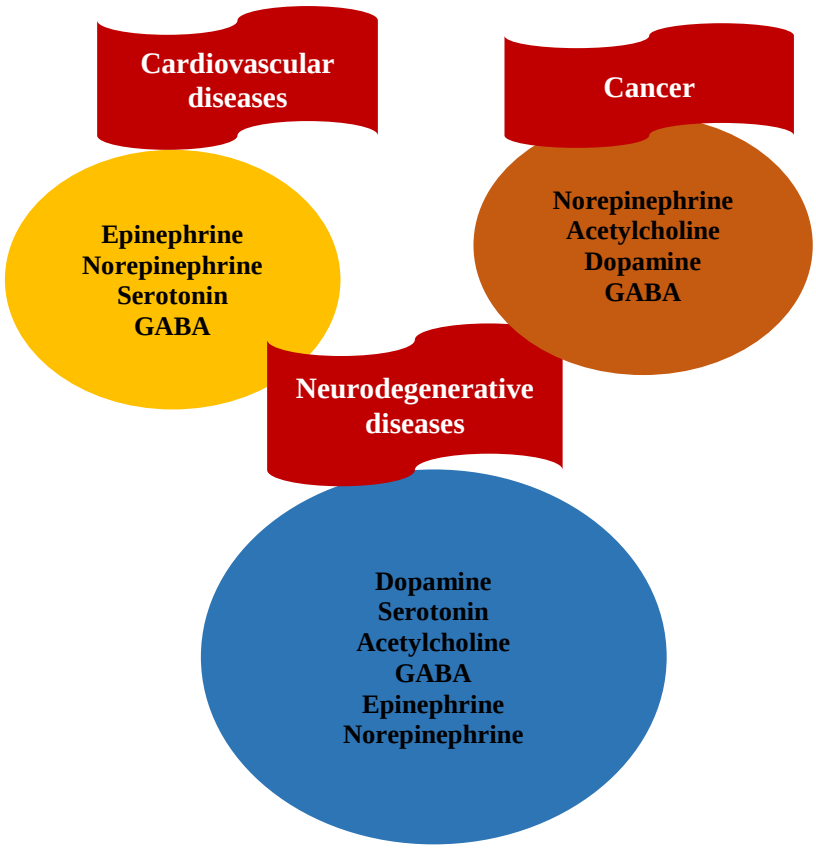

Fig. 2 Different neurotransmitters with roles in age-related diseases

In age-related neurodegenerative diseases like AD and PD, MAO enzymes have a pivotal role. Changes in the metabolism of these enzymes are also linked to these neurodegenerative pathologies. MAO-A contributes to the neuropsychiatric symptoms of AD-like depression. This is supported by the fact of the generation of hydrogen peroxide, which is essentially a byproduct of the MAO-A and B enzymatic reaction. Thus, it is a potential factor for the neuropathology of AD and PD [12, 59]. The generated peroxide induces oxidative stress, leading to cell death and/or mitochondrial dysfunctions – both of which occur during ageing. The mitochondrial dysfunction driven by the excess activity of MAO results in further production of free radicals

and therefore the oxidative stress damage is exacerbated [15]. Alternatively, MAO-B has been detected in astrocytes close to amyloid plaques (a hallmark of AD) [38]. Moreover, increased levels of MAO-A and MAO-B have been observed in the putamen in the postmortem brains of individuals struggling with PD [50]. Yet, there has not been established a specific mechanism through which the MAO enzymes affect patients diagnosed with AD and PD. However, MAO inhibitors (MAOIs) have been widely utilized and tested as part of the treatment of those neurodegenerative diseases [26].

Inhibition of MAO enzymes as therapeutic approaches in age-related diseases

Monoamine oxidases' inhibitors (MAOIs) have demonstrated excellent results in treating multiple neurological and behavioural conditions [40, 49]. Importantly, MAOIs are classified as reversible or irreversible and also as MAO-A or B selective or non-selective. Since the clear association of depressive disorders with MAO, MAOIs have commonly been used for the treatment of patients struggling with the aforementioned conditions. In that sense, it is noteworthy to mention two of the most widely used MAOIs phenelzine and isocarboxazid, which present a brilliant example of irreversible non-selective inhibitors in clinical practice. Along with their positive effects, an issue emerged related to the use of irreversible inhibitors called the "cheese effect". Abnormal use of irreversible inhibitors has been shown to reduce MAO's ability to metabolize tyramine (an amine present in some fermented foods like cheese). This may lead to the eventual access of tyramine to the circulatory system. Nevertheless, these types of inhibitors proved successful in treating depressive disorders and the "cheese effect" can be avoided by some dietary changes [12].

On the other hand, patients suffering from AD showcase elevated MAO activity. Potentially, inhibition of those enzymes could present an effective treatment strategy. In literature, a vast number of studies have provided evidence regarding the MAOIs' neuroprotective effect in AD. It has been also suggested that MAOIs can improve cognitive impairment, as they correct chemical imbalances in the brain and reduce the accumulation of Aβ plaques [5]. MAOIs neuroprotective effect is also observed in treating PD. In particular, selegiline and rasagiline (irreversible inhibitors) have been shown to improve motor symptoms in PD patients. This is most likely due to the increase in dopamine as it is not metabolized by MAO enzymes. Not only MAOIs have been regarded as a good option for early treatment of PD, but they can also improve some symptoms distinguished in mental disorders [40].

Perspectives

Inhibition of MAO-A and MAO-B has a positive effect on treating age-related neurodegenerative diseases. MAOIs have been explored substantially and even though they have proven effective in inhibiting MAO enzymes, they come with issues as well. Considering that, it would be of great benefit to explore alternative methods in alternating MAO levels to prevent age-related neurodegenerative diseases. One possible strategy is to investigate naturally the occurrence of MAOIs. In nature, MAO suppressors can be found in many plants or plant extracts such as *Curcuma longa* L., *Ginkgo biloba* L. and coffee [22]. Another strategy is by using different light treatments. It has been established for a long time that season and light influence the serotonergic system. Moreover, seasonal fluctuations in the brain's MAO-A levels have been recorded, most likely influenced by the amount of sunlight exposure in each season. Bright light therapy has shown promising results as MAO-A levels significantly reduce after the treatment [46]. Similarly, light-emitting diodes are an alternatively effective and trustworthy approach for modulating MAO levels, due to their safe and easy use. Moreover, light-emitting diodes emitting electromagnetic radiation at different wavelengths have proven to modulate also 5-HT levels, which is potentially due to the altered MAO activity [60].

Understanding both the process of ageing and the molecular mechanism responsible for the pathology of age-associated diseases could give the upper hand when exploring different treatment options. Furthermore, it can aid in the pioneering of novel treatments, which are less harmful and easier to use.

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