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Review article

The mechanism of neuroprotective action of natural compounds

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ABSTRACT

Disturbance of cerebral redox homeostasis is the primary cause of human neurodegenerative disorders, such as Parkinson's disease or Alzheimer's disease. Well known experimental research demonstrates that oxidative stress is a main cause of cell death. A high concentration of reactive oxygen and nitrogen species leads to damage of a lot of proteins, lipids and also DNA. Synthetic compounds used for the treatment in the neurodegenerative diseases failed to meet the hopes they had raised and often exhibit a number of side effects. Therefore, in recent years interest in natural compounds derived from plants appears to be on the rise. This review describes a few natural compounds (1MeTIQ, resveratrol, curcumin, vitamin C and Gingko biloba) which revealed neuroprotective potential both in experimental studies and clinical trials. 1MeTIQ has a privileged position because, as opposed to the remaining compounds, it is an endogenous amine synthesized in human and animal brain. Based on evidence from research, it seems that a common protective mechanism for all the above-mentioned natural compounds relies on their ability to inhibit or even scavenge the excess of free radicals generated in oxidative and neurotoxin-induced processes in nerve cells of the brain. However, it was demonstrated that further different molecular processes connected with neurotoxicity (*e.g.* the inhibition of mitochondrial complex I, activation of caspase-3, apoptosis) follow later and are initiated by the reactive oxygen species. What is more, these natural compounds are able to inhibit further stages of apoptosis triggered by neurotoxins in the brain.

Contents

Abbreviations: AD, Alzheimer's disease; Akt, protein kinase B; AMPK, AMP-activated kinase; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; 1BnTIQ, 1-benzyl-1,2,3,4-tetrahydroisoquinoline; Cat, catalase; COMT, catechol-O-methyltransferase; COX-1 and COX-2, cyclooxygenase-1 and 2; DAT, dopamine transporter; DOPAC, 3,4-dihydroxyphenylacetic acid; GSH/GSSG, glutathione/oxidized glutathione; HO-1, heme oxygenase 1; IL-1β, interleukin 1β; JNK, c-Jun N-terminal kinases; LPS, lipopolysaccharides; MAO, monoamine oxidase; MDA, malodialdehyde; 1MeTIQ, 1-methyl-1,2,3,4-tetrahydroisoquinoline; MMP-9, matrix metallopeptidase 9; MPTP, 1-methyl-2-phenyl-1,2,3,6-tetrahydropyridine; 3-MT, 3-methoxytyramine; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; Nrf2, transcription factor erythroid 2; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PEA, phenylethylamine; skPI3K, phoshoinositide 3-kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PTEN, phosphatase and tensin homolog; RNS, reactive nitrogen species; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; SOA, superoxide anion; TNF-α, tumor necrosis factor-alpha.

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Introduction

Disturbance of cerebral redox homeostasis is the primary cause of human neurodegenerative disorders. Imbalance between internal antioxidant system and toxic reactive oxygen species (ROS) is defined as oxidative stress. This phenomenon plays the main role in the pathology and progression of neurodegenerative disorders, such as Parkinson's disease (PD) [1] or Alzheimer's disease (AD) [2]. Moreover, the phenomenon of oxidative stress is considered to be an essential factor in aging process [3]. Oxidative stress is a universal mechanism causing cell death [4]. In PD oxidative stress is induced *via* different mechanisms, like modification of iron accumulation in the substantia nigra, changes in α-synuclein aggregation and proteolysis, changes in calcium channel activity, and protein mutations [5]. Furthermore, an increase in malondialdehyde, hydroperoxides and protein oxidation has been reported in the substantia nigra of PD patients [6]. In addition, the accumulation of lipid peroxidation products was observed in cerebral spinal fluid of PD patients [7]. Overproduction of ROS and reactive nitrogen species (RNS) leads to disruption of natural cellular homeostasis and is the cause of oxidative and nitrosative stress. A high concentration of ROS and RNS leads to damage of a lot of proteins, lipids and also DNA, while, low concentration of ROS and RNS during normal cellular metabolism acts as signaling molecules [8]. Dopaminergic neurons show the greatest sensitivity to oxidative stress because they contain neuromelanin [9]. Neuromelanin is a black pigment which contains ferrous ions (Fe2+). The presence of Fe2+ promotes the Fenton reaction. Beyond natural factors causing the oxidative stress, such as environmental toxins (heavy metals, herbicides, pesticides), UV radiation, heat shock, also the dopamine itself plays a considerable role in this adverse phenomenon. Namely, ROS are formed during dopamine catabolism. Dopamine at low concentrations can block mitochondrial respiration mainly by MAO-dependent oxidation pathway in which H_2O_2 is formed [10]. Dopamine can be nonenzymatically oxidized or enzymatically deaminated by monoamine oxidase (MAO). Both processes: autoxidation and MAO-mediated catabolism of dopamine lead to H_2O_2 formation. The mitochondrial complexes I, II, and III are highly sensitive to the inhibitory effect of ROS [11,12]. A deficiency in the mitochondrial complex-1 of the electron transport chain, which leads to elevation of O_2-production and adenosine triphosphate (ATP) reduction, was reported to be one of the main factors of the etiopathology of PD [13]. The reduced level of ATP causes a fall in the ratio of the reduced glutathione/glutathione-disulfide (GSH/GSSG) which is a measure of redox state of cells [14]. The redox couple GSH/GSSG acts in concert with enzymes: glutathione peroxidase/reductase, glutaredoxin and thioredoxin to maintain protein thiol redox homeostasis [15,16]. The production of free radicals during dopamine biosynthesis and catabolism causes the loss of a lot of dopaminergic neurons [17]. Moreover, these phenomena are boosted by the presence of neuromelanin in dopaminergic neurons [18]. Thus, neuromelanin promotes the Fenton reaction. Dopamine is catabolized *via* two metabolic pathways: about 80% of dopamine is intraneuronally N-oxidized by MAO_B to the intermediate metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), while 20% of dopamine is extraneuronally O-methylated by catechol-O-methyltransferase (COMT) to the intermediate metabolite 3-methoxytyramine (3-MT). Large amounts of dopamine released into the synaptic cleft are easily taken up by dopamine transporter (DAT) and catabolized by MAO_B which is located on mitochondrial membranes. In addition, dopamine is able to oxidize to ortho-quinones in the absence of metal-ion catalysts. This reaction of dopamine oxidation catalyzed by oxygen will produce dopamine o-semiquinone radical and superoxide. Next, dopamine o-semiquinone radical is converted into dopamine o-quinone, which cyclizes and autoxidizes to form aminochrome [19]. As it demonstrated by Zecca et al. [20], both dopamine o-quinone and aminochrome induces mitochondria dysfunction. α-Synuclein is the major component of Lewy bodies and mutations at gene encoding this protein are the main genetic risk factor for PD [21]. Moreover, α-synuclein can activate microglia and elevate the expression of ROS, RNS, tumor necrosis factor-alpha (TNF-α), matrix metallopeptidase 9 (MMP-9) and interleukin 1β (IL-1β) [21]. Therefore, α-synuclein induces pro-inflammatory changes in the dopaminergic neurons and in consequence, causes a progressive loss of these cells [22]. Various antioxidants, such as GSH, melatonin, coenzyme Q10 and neuromelanin act as scavengers of free radicals and simultaneously rejuvenate mitochondrial complex-1 oxidoreductase, which is an enzyme involved in ATP synthesis [22]. It is interesting, that neuromelanin has shown both toxic and protective role in dopaminergic neurons. In physiological condition it can protects neurons from harmful effects of dopamine and its metabolites. Furthermore, neuromelanin can induces chelating redox/toxic metals such as iron, copper or manganese to form stable complexes. On the other hand, when the iron is overload, neuromelanin induces exacerbation of oxidative stress [19].

In recent years, an increasing number of researchers have attempted to search for efficient drugs for neurodegenerative diseases using natural substances of plant origin. These compounds are often well known and have been used for centuries in traditional medicine and now are rediscovered by scientists and studied in detail in order to understand its molecular mechanism of action. In this review we would like to present a few interesting natural compounds with neuroprotective potential.

Natural compounds as a neuroprotectants

The origin and synthesis of 1MeTIQ

1-Methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) is a derivative from tetrahydroisoquinoline group. This compound was detected in the plants as well as in the mammalian brains, *e.g.* in rodents, monkeys and humans [23–26]. Two enantiomers (S)- and (R) of 1-MeTIQ were identified in the brain (Fig. 1) [27]. Worth of the emphasis is the fact that both stereoisomers have shown similar biological action [28,29]. What is especially worth emphases highest concentrations of 1MeTIQ was detected in dopaminergic structures mainly in the extrapyramidal system (substantia nigra and striatum) [26]. In the rat brain the concentration of 1MeTIQ was measured as 3.5 ng/g tissue [30]. 1MeTIQ as an endogenous substance can be synthesized enzymatically in the brain from biogenic amines (phenylethylamine [PEA] and pyruvate) [31]. The enzyme which is involved in this process was localized in the mitochondrial-synaptosomal fraction and is called 1MeTIQase [31,32]. Interestingly, PEA, which is a substrate for 1MeTIQ generation in the brain, is catabolized by MAO.