Volume 9, Issue 4, 2019, 4085 - 4089 ISSN 2069-5837

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

https://doi.org/10.33263/BRIAC94.085089

Review Article Open Access Journal

Received: 27.06.2019 / Revised: 28.07.2019 / Accepted: 05.08.2019 / Published on-line: 15.08.2019

Curcumin effect on non-amyloidogenic pathway for preventing Alzheimer's disease

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ABSTRACT

Amyloid beta (Aβ) plaque deposition is a pathological feature of Alzheimer's disease (AD) that is characterized by dementia. Therapies approaches affecting Aβ synthesis and accumulation are necessary for improving AD. The present review, as the future prospective study, focuses on the possible effect of curcumin on the non-amyloidogenic pathways for inhibiting the Aβ plaque in AD. Activators of non-amyloidogenic pathways emerge as a novel strategy in attenuating Aβ. Drugs and natural compounds can affect neurotrophic signaling pathways including protein kinase C (PKC), tyrosine kinase (TK), mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK) signaling, and Ca^{2+} signaling as wells serotonergic and acetylcholine systems, resulting to stimulate non-amyloidogenic pathways. Curcumin, active constituent of Curcuma longa L. (turmeric), has a potent effect against AD through prevention Aβ generation and deposition. With attention to the effect of curcumin on the molecular mechanism behind the non-amyloidogenic pathways, we suggest designing more studies to identify curcumin as a therapeutic restricting AD agent via its impact on the non-amyloidogenic pathway.

Keywords: *Curcumin; Alzheimer's disease; non-amyloidogenic pathways; amyloid beta.*

1. INTRODUCTION

Amyloid beta (Aβ) plaque accumulation is a major hallmark of Alzheimer's disease (AD). The cleavage of amyloid precursor protein (APP) by β- and γ-secretase leads to produce Aβ2 [1]. Activation of α-secretase as non-amyloidogenic pathway produces sAPPα. α-secretases consist of zinc metalloproteases, the members of disintegrin and metalloprotease (ADAM) families, including ADAM9, ADAM10, and ADAM17 which stimulate the non-amyloidogenic APP processing [2]. They are membrane-bound, cell-surface glycoproteins that involved in cell adhesion, protein ectodomain shedding, matrix protein degradation, and cell fusion. It has been indicated that the modulation of α-secretase activity is very complex [2]. The activated α–secretase pathway competitively inhibits amyloidogenesis via proteolytic cleavage within the Aβ peptide sequence of APP [2]. Additionally, sAPPα is confirmed to have memory-enhancing and neuroprotective effects [3]. Modulation of the non-amyloidogenic pathway may be as a suitable therapeutic strategy for AD, though the family of all α-secretase members and their functions have not been understood [3]. It was indicated that some natural products were effective against AD via stimulating the activity of α-secretase [3]. Curcumin, the major ingredients of the turmeric spice, has been recognized for two centuries ago [4]. It is obtained from the dry rhizomes of Curcuma longa L [5] from the ginger family. The cultivation of Turmeric is mostly done in South America and Asian [6]. Traditionally, curcumin is used to cure various diseases such as wounds, skin diseases, rheumatism, liver diseases, diarrhea, colic, urinary discharges, constipation, dyspepsia, amenorrhea, pyrexia, etc [6].

In addition, turmeric is a suitable food additive and the coloring agent [6]. Curcumin, a phenolic compound, has a yellow pigment and an aromatic smell [6]. Today, curcumin has been increasingly investigated due to its several pharmacological impacts including anti-inflammatory, antioxidant, anti-microbial, and anti-tumor [7]. Curcumin affects several molecular pathways involved in inflammation, oxidative stress, and neurodegenerative disorders [7]. Although curcumin has numerous biomedical activities, however, its usage is limited due to its low bioavailability [7]. Curcumin is an insoluble water and soluble oil agent [8]. Curcumin is a safe and well-tolerated compound [9]. The bioavailability of curcumin is affected by low solubility, poor absorption, rapid metabolism and elimination [9]. Therefore, several investigations have been performed to increase curcumin bioavailability. Synthesis of a phospholipid, liposome and nanoparticles curcumin formulations have been found to effective for elevating its bioavailability [10]. Curcumin, especially its novel formulations have been reported as a suitable treatment for several neurological disorders such as AD [11]. Recent experimentations on the efficacy of curcumin against AD. They have shown that curcumin inhibited AD progression by inhibition of Aβ formation and accumulation, oxidative stress, neuroinflammation, hippocampal neurogenesis, mitochondrial dysfunction and apoptosis modulation of cholinergic systems [11]. This study reviewed the neuroprotective activities of curcumin and its novel formulations by mostly focusing on curcumin effects on the non-amyloidogenic APP processing.

2. MATERIALS AND METHODS

Methods.

Google Scholar, Scopus, Medline and ISI Web of Science were searched by terms of (curcumin OR turmeric) AND (non-amyloidogenic OR Amyloid beta OR Alzheimer's disease) from the beginning to May 2019. All references in the selected articles were also reviewed to obtain more related studies. Only published English language articles were selected in the present study.

3. RESULTS

3.1. Curcumin, inflammation and Alzheimer's disease.

Neuroinflammation is responsible for the induction of amyloidogenic and non-amyloidogenic pathways in the AD, as evident by the activation of microglial cells and the production of inflammatory mediators [12]. Microglia cells are composed of M1 and M2 phenotypes. The M1 type releases toxic inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, reactive oxygen and nitrogen species (ROS and RNS) and prostaglandins, however, the M2 type secretes anti-inflammatory cytokines that preserve the neuronal hemostasis [13]. Under AD condition, microglia cells are shifted to the M1 phenotype [14]. A close link was seen between inflammation, Aβ aggregation and activated glial cells. The inhibition of this association may be a suitable target to treat the progression of AD [15]. Curcumin can be effective for AD treatment via modulating molecular signaling pathways involved in the activation of M1 microglial. Extracellular signal-regulated kinase 2 (ERK1/2) and p38 kinase signaling are the two molecular pathways that activate M1 glial cells. Curcumin could suppress microglia activity by blocking these pathways, resulting in a decrease in inflammatory cytokines [16]. Curcumin administration to microglia cells exposed to lipopolysaccharide (LPS) markedly ameliorated the secretion of inflammatory mediators and nitric oxide [17]. Curcumin also modulated the activities of nuclear factor kappa B (NF-kβ) and phosphoinositide kinase (PI3K)/Akt pathways, leading to inhibition glial activity and inflammation [17].

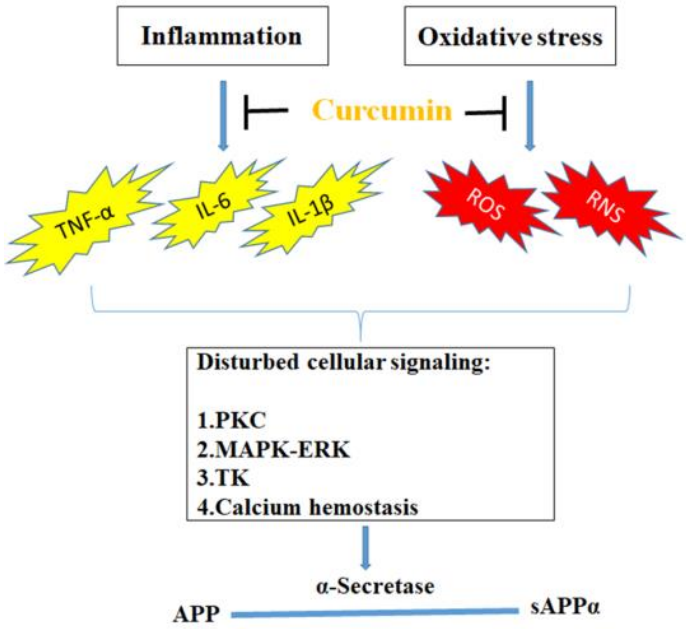

Figure 1. The impact of curcumin on inflammation and oxidative stress and release of sAPPa.

Curcumin stimulated the activation of peroxisome proliferator-activated receptor gamma (PPARγ), leading to inhibition of neuroinflammation. PPAR can suppress the activities of the NF-B and ERK pathways and decrease inflammation. Additionally, curcumin could enhance the protective impact of M2 microglia, leading to a decrease in Aβ aggregation. Finally, curcumin can stimulate signaling pathways involved in sAPPα release by inhibition oxidative stress (Figure 1).

3.2. Curcumin, oxidative stress, and Alzheimer's disease.

Oxidative stress is a key mechanism in the pathogenesis of diseases including AD [18]. It is caused due to an imbalance between oxidant-antioxidant content in cells [18]. The brain has a high sensitivity to oxidative damage due to its high amount of lipid in the cellar membrane and the high rate of oxygen consumption [19]. Oxidative stress also can affect the proteins and DNA structures, resulting in the apoptotic cell death [19]. Curcumin combats against oxidative stress directly via scavenging free radicals and indirectly via enhancing antioxidant content [20]. Oxidative stress can initiate and progress the AD process through activating both amyloidogenic and non-amyloidogenic pathways [21]. Therefore, modulation of the redox cycle may be a suitable approach for AD therapy. It was indicated that curcumin can be effective against AD through modulating oxidative stress in the brain. Curcumin attenuated increased lipid peroxidation, calcium concentration, caspase 3 and 9 in SH-SY5Y neuronal cells exposed to hydrogen peroxide [22]. Curcumin also blocked mitochondrial apoptosis induced by AB through regulation of PARP, caspase activation and DNA oxidation [23]. In addition, curcumin has also a beneficial impact on synaptic damage through modulating oxidant-antioxidant system. In vitro studies suggested that since pre-treated with curcumin was effective than post-treated in cells, therefore, this agent may be suitable for prevention of AD [24].

Therefore, curcumin can stimulate signaling pathways involved in sAPPα release by inhibition inflammation (Figure 1).

3.3. Activation of the non-amyloidogenic pathway.

sAPPα increases neuronal survival by stimulating several neurotrophic signaling pathways. The protein kinase C (PKC) signaling is the most pathway that increases the levels of anti-apoptotic BCl2 and Bcl-xL proteins and caspase-mediated apoptosis in the AD brain [25]. Other mechanisms involved in the anti-apoptotic mechanism of sAPPα include tyrosine kinase (TK), mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK) signaling, and Ca^{2+} signaling. Additionally, serotonergic and acetylcholine systems increase sAPPα release [25].

3.4. Stimulating sAPPα signaling pathways by curcumin.

3.4.1. Curcumin and PKC pathway. Stimulation of PKC signaling is considered as the main strategy to promote α-secretase cleavage of APP [26]. Indeed, all pharmacological pathways enhancing sAPPα release induced by PKC activators [26]. Curcumin, tetrahydrocurcumin, amino acid conjugates curcumin-isoleucine, curcumin-phenylalanine and curcumin-valine stimulates sAPPα signaling pathways [27]. Curcumin and tetrahydrocurcumin stimulate sAPPα signaling pathways in association with muscarinic (M1) receptors. However, other derivatives of curcumin could stimulate ADAM10 through activation PKC pathway [27]. The finding indicated the effects of curcumin and its derivatives on the PKC activation is different and more studies should be done in this context [27]. However, previous findings showed that PKC signaling preferentially stimulates regulated sAPPα secretion and affects only 30-40% of constitutive secretion. The effect of PKC signaling on α-secretase activity needs deep investigations. Muscarinic (M1/M3) acetylcholine receptors are as functional activators of PKC signaling that PKC binding to muscarinic receptors promotes sAPPa release [28]. Inhibition of acetylcholinesterase activity stimulates PKC signaling and increases sAPPa release leads to improve cognitive function [29]. Thus, cholinergic inhibition is one of the major factors causing cognitive deficiency [29]. It was indicated that supplementation with the curcuminoids mixture inhibited AChE activity in the reducing order as bisdemethoxycurcumin, demethoxycurcumin and curcumin in the ex-vivo model [29]. It is needed to study the association between curcumin, AChE inhibition and sAPPa pathways to understanding how curcumin and its derivatives improve AD.

3.4.2. Curcumin and TrK Pathway. Platelet-derived growth factor (PDGF), brain-derived neurotrophic factor (BDNF), EGF and FGF activate TrK signaling and leads to Aβ suppression via α-secretase pathway [30]. Suppressed TK signaling was observed in the hippocampus and frontal cortex of AD [30]. Activation of TrK signaling through non-amyloidogenic APP-processing protected against AD pathology [30]. It was indicated that curcumin dose- and time-dependently protected against neurotoxicity via up-regulation of BDNF expression and TrkB signaling pathway in rat primary cortical neuron [31]. Lipid-nanoparticle (NP)-encapsulated curcumin activated TrkB signaling pathways following neurotrophin binding and resulting in phosphorylation of the transcription factor CREB and release of BDNF in SH-SY5Y cells [30]. Curcumin ameliorated AD like behavior in aged human tau transgenic mice via decreasing the soluble Tau dimers levels, Tau/Fyn linking and binding the TrkB with NMDA receptors [32]. The above-mentioned findings propose that curcumin may induce Aβ inhibition via activating BDNF/TrkB signaling-mediated α-secretase pathway stimulation [31].

3.4.3. Curcumin and MAPK Pathway. MAPK-ERK pathway is suggested as the main modulator of α-secretase activity [33]. Binding of ERK1 to threonine-735 (T735) of ADAM17 induced the translocation of ADAM17 to the membrane [33]. The complex relation between PKC-modulated α-secretase processing and ERK has been also observed [34]. The inhibition of monoamine oxidase B (MAO B) for treating AD has also done through suppression of MAPK signaling pathway that resulted in the sAPPα secretion inhibition [34]. However, the interaction between PKC-modulated α-secretase pathway and ERK and ADAM17 has been reported, but this interaction should be more investigation. Additionally, ERK is involved in the activation of α-secretase by TrK pathway [34]. Altogether, the above findings indicated that the activation of three pathways including PKC, MAPK, and TrK are necessary for a-secretase activation and sAPPα release. It was indicated that curcumin could improve AD through modulating BDNF/TrkB-MAPK/PI-3K-CREB signaling pathway in cultured rodent cortical neurons [35]. Chronic administration of curcumin improved AD-related cognitive deficits by up-regulating BDNF-ERK signaling in the hippocampus of a rat model of AD ([36]).

3.4.4. Curcumin and Ca^{2+} Signaling. Homeostasis of calcium is necessary for the normal function of sAPPα, as it affects neuronal development and neurotransmitters release [37]. The calcium ionophore could elevate the release of sAPPα and reduce the expression of Aβ in primary neurons and B104 neuroblastoma cells [38]. The curcumin modulated cytoplasmic Ca2+ signaling and calcium-dependent cysteine protease activity in SH-SY5Y neuroblastoma cells [39]. According to this potent association between calcium homeostasis and normal function of sAPPα, it is hypothesized that curcumin may be effective for the normal function of sAPPα by modulating calcium homeostasis.

3.4.5. Curcumin and acetylcholine and serotonergic receptors, and sAPPa. The loss of cholinergic neurons causes memory and cognitive impairment, the main characterization of AD [40]. Therefore, inhibition of cholinesterase is one of the pharmacologic targets that activates non-amyloidogenic APP processing, resulting in the improvement of cognitive function [40]. It is reported that curcumin can act as an acetylcholinesterase inhibitor, resulting in AD improvement [29]. It is assumed that inhibition of acetylcholinesterase activity by curcumin leads to enhance the non-amyloidogenic processing of APP, and thereby down-regulation of Aβ levels in the brain. Activation of the serotoninergic system increases sAPPα release [41]. When the brain neurotransmitter levels were assessed after curcumin treatment, it was observed that the levels of serotonin increased in the mouse brain [42]. Figure 2 indicates the impact of curcumin on factors stimulating a-secretase cleavage and release of sAPPa.

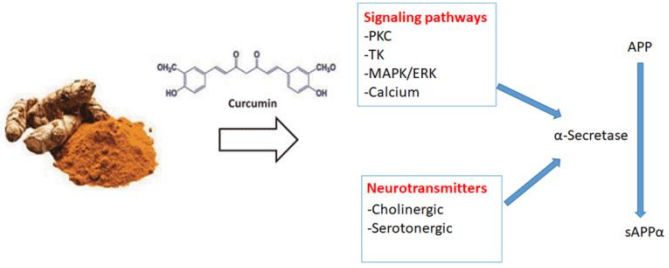

Figure 2. The impact of curcumin on factors stimulating α-Secretase cleavage and release of sAPPa.

4. CONCLUSIONS

Molecular pathways activating the non-amyloidogenic APP processing were increasingly focused in recent years. ADAMs, especially ADAM10, 9 and 17 are the key a-secretase members that are being responsible for increasing the sAPPa synthesis. Nevertheless, more investigations are necessary to clarify the specific molecular mechanism of ADAM members. One approach for inducing the activity of a-secretase is activation of ADAM-trafficking along the plasma membrane. Since sAPPa acts as neurotrophins, natural and chemical agents directly affect its elevation may also be found. Natural agents including flavonoids may be suitable for this purpose. Curcumin may be behaving like an a-secretase activator by targeting the PKC, TK, PI3K, and MAPK signaling pathways. Additionally, curcumin may stimulate APP non-amyloidogenic pathway by affecting Ca^{2+} signaling, acetylcholine, and serotonergic receptors. However, curcumin needs to be further studied, so that it introduced as a novel drug ameliorating AD via activation of APP non-amyloidogenic pathway. Although curcumin is well found in improving the neurodegenerative diseases, however; it may be studied for its effects on APP metabolism. According to the effect of curcumin on the molecular mechanisms involved in the activation of APP non-amyloidogenic pathway, this natural compound may be considered as a novel and less toxic a-secretase activators for reducing cerebral Aβ deposition.

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