A hypothetic role of minocycline as a neuroprotective agent against methylphenidate-induced neuronal mitochondrial dysfunction and tau protein hyper-phosphorylation: Possible role of PI3/Akt/GSK3β signaling pathway

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A B S T R A C T

The underlining mechanism in neural mitochondrial dysfunction and consequences neurotoxicity, and cognitive behavior after methylphenidate (MPH) prolonged uses is unclear and proposing of therapeutic approaches for treatment of these types of neurotoxicity is one of the main goals of scientist in this manner. MPH-induced mitochondrial dysfunction in neural cells caused induction of oxidative stress, apoptosis, inflammation and cognition impairment, which leads to neurotoxicity, was reported previously but role of key neural cells proteins and involved signaling pathway in this manner remained indeterminate. Tau protein aggregation is a biomarker for mitochondrial dysfunction, neurodegenerative event and cognition impairment. Tau aggregation occur by stimulation effects of Glycogen synthase kinase-3(GSK3β) and phosphatidylinositol 3-kinase (PI3K) which activates protein kinase B(Akt) and causes inhibition of phosphorylation(activation) of GSK3β, thus Akt activation can cause inhibition of tau aggregation (hyper-phosphorylation). Management of mentioned MPH-induced mitochondrial dysfunction and consequences of neurotoxicity, and cognitive behavior through a new generation neuroprotective combination, based on modulation of disturbed in Akt function and inhibition of GSK3β and tau hyper-phosphorylation can be a prefect therapeutic interventions. Therefore, finding, introduction and development of new neuroprotective properties and explanation of their effects with potential capacity for modulation of tau hyper-phosphorylation via PI3/Akt/GSK signaling pathway is necessitated. During recent years, using new neuroprotective compounds with therapeutic probability for treatment of psychostimulant-induced mitochondrial dysfunction, neurotoxicity and cognitive malicious effects have been amazingly increased. Many previous studies have reported the neuroprotective roles of minocycline (a broad-spectrum and long-acting antibiotic) in multiple neurodegenerative events and diseases in animal model. But the role of neuroprotective effects of this agent against MPH induced mitochondrial dysfunction, neurotoxicity and cognitive malicious and also role of tau hyper-phosphorylation by modulation of PI3/Akt/GSK signaling pathway in this manner remain unknown. Thus we suggested and theorized that by using minocycline in MPH addicted subject, it would provide neuroprotection against MPH-induced mitochondrial dysfunction, neurotoxicity and cognitive malicious. Also we hypothesized that minocycline, via modulation of PI3/Akt/GSK and inhibition of tau hyper-phosphorylation, can inhibit MPH-induced mitochondrial dysfunction, neurotoxicity and cognitive malicious. In this article, we tried to discuss our hypothesis regarding the possible role of minocycline, as a powerful neuroprotective agent, and also role of tau hyper-phosphorylation related to PI3/Akt/GSK signaling pathway in treatment of MPH-induced mitochondrial dysfunction, neurotoxicity and cognitive disturbance.

Introduction

MPH is the selected drug for the management of attention defect hyperactive disorder (ADHD) in children [1]. Abuses of MPH (Fihure-1), as a neurostimulator agent, has been increased in latest years [2]. MPH action, pharmacologically, is similar to cocaine and this similarity causes the high potential for abuse and addiction [3,4]. Prolonged abuses of MPH can prompt behavioral changes such as cognition (learning and memory) impairment in human and animal subjects [1].

Experimental studies have confirmed the potential effect of MPH in induction of mitochondrial dysfunction, oxidative stress and inflammation in some brain areas such as the hippocampus, which is responsible for cognition, but its putative mechanism remains unknown [5–7]. Former studies have presented that MPH abuse can lead to increased apoptotic proteins production and therefore result in DNA fragmentation in some brain regions such as hippocampus [2,5,8]. In spite of all characteristic of MPH in induction of neurotoxicity and mitochondrial dysfunction, research is needed to clarify the
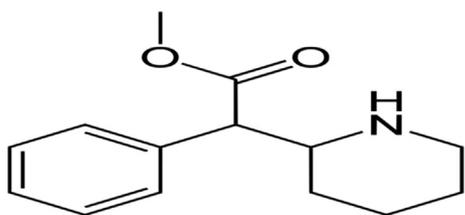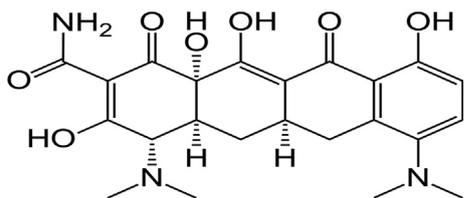
Fig. 1. Structure of Methylphenidate.

Fig. 2. Structure of Minocycline.

biochemical mechanisms [2,9] (Fig. 1).

Fortunately, the use of new neuroprotective compounds with therapeutic probability for management of drug abuse-induced neurodegeneration has increased during recent years [10,11]. Minocycline (Fig. 2), a broad-spectrum and long-acting antibiotic with anti-inflammatory and antioxidant effects [10,11], is extensively considered as therapeutic agents against neurodegenerative events [12,13]. The antioxidant, anti-inflammatory and anti-apoptotic behavior of minocycline was approved in former studies [14,15]. It is also proved to have neural protective effects [14,16]. Minocycline has possible anti-depressant and cognitive enhancer properties in animals and humans [17–19]. Minocycline neuroprotective effects modulates through its antioxidant, anti-inflammatory and anti-apoptotic properties [18]. Although various data are presented regarding neuroprotection role of minocycline and its capability for mitochondrial biogenesis and cognition enhancer, possible signaling pathway in this manner remain imprecise and necessitate for clarification.

Tau proteins act as a biomarker for neurodegenerative diseases [20]. Tau proteins stabilize microtubules [20,21]. Previous studies demonstrated that Tau aggregation (hyper phosphorylation) causes toxic effects through its accumulation inside cells [21]. According to these studies accumulation of hyper-phosphorylated form of tau in neural cell causes mitochondrial dysfunction and lead to neurotoxicity [22–24] (Fig. 3). Mechanisms including tau release and toxicity are unclear and it was demonstrated that hyper-phosphorylated form of tau is responsible for neurodegenerative disease and events such as Alzheimer disease (AD), Parkinson disease (PD). According to these studies accumulation of hyper-phosphorylated form of tau protein causes induction of oxidative stress, inflammation and apoptosis by modulation of mitochondrial performance dysfunction [22–25].

On the other way signaling pathway indicated that Tau aggregation occurs through stimulation effects of active (phosphorylated from) Glycogen synthase kinase-3(GSK3β) [26,27]. These studies demonstrated that phosphatidylinositol 3-kinase (PI3K) activation (phosphorylation) of protein kinase B (Akt) and phosphorylated Akt leads to inhibition of phosphorylation (activation) of GSK3β, and thus Akt activation can cause inhibition of tau aggregation (hyper-phosphorylation) [27,28](Fig. 3). Because of the importance of PI3/Akt/GSK signaling pathway in inhibition of tau hyper-phosphorylation and its outcomes, such as neurotoxicity and cognitive dysfunctions, it seems that this signaling pathway mediates minocycline-induced neuroprotection against MPH induced mitochondrial dysfunction (oxidative stress, inflammation, apoptosis) and cognitive disturbances. Interpretation of this concept gives us novel insight into the disorders associated with MPH abuse and neuroprotective action of minocycline against such disturbances.

The hypothesis

During preceding years, abuses of MPH and other psychostimulant concomitant with using new generation of neuroprotective agent for management (reduction of its molecular and behavioral sequels) of MPH consequences have been surprisingly increased. According to the following points:

1. Neuroprotective properties of minocycline in enhancement of mitochondrial biogenesis
2. Critical role of tau hyper-phosphorylation in activation of mitochondrial dysfunction and cognitive performance
3. Importance of PI3/Akt/GSK signaling pathway in modulation of tau performance,

It is suggested/hypothesized that minocycline may protect brain cells, possibly hippocampus, from MPH -induced probable tau hyper-phosphorylation, mitochondrial dysfunction and cognition impairment. These functions may be mediated PI3/Akt/GSK signaling pathway.

Evaluation of the hypothesis

For research and finding of accessible information and valid data in the literature about neuroprotective properties of minocycline against (prevention, treatment or management) MPH induced mitochondrial dysfunction, neurotoxicity, neurobehavioral sequels(such as cognition impairment) and involvement of tau hyper phosphorylation and PI3/Akt/GSK signaling pathway in this manner we did searches in many kind of data bank such as Web of Science, PubMed, Elsevier, Science Direct, Google Scholar, Core Collection, and Cochrane with the following key words: minocycline plus methylphenidate and tau hyper phosphorylation and PI3/Akt/GSK signaling pathway. Our searching was limited to English studies and there were no direct studies or paper about role of minocycline on MPH- induced mitochondrial dysfunction, neurotoxicity, neurobehavioral sequels (such as cognition impairment) and involvement of tau hyper phosphorylation and PI3/Akt/GSK signaling pathway in this manner.

Discussion

MPH as a psycho-stimulant agent has a high potential and capability for misuse and addiction [2,9,29,30]. According to previous studies prolonged administration of MPH can decrease spatial learning and memory in both animal and human subjects [31]. Previous data investigated that MPH abuses caused the increases in release of dopamine, serotonin, and adrenaline in the brain and this phenomenon lead to down-regulation of the mentioned amine receptors and the consequence of this phenomenon is cognition impairment [29]. According to previous studies MPH can induce depressive-like and anxiety like behavior [32]. Previous studies established that management/testament or prevention of these types of neurobehavioral disorder can help manage MPH cessation syndrome [3,5]. Some of these studies introduced some neuroprotective combination for management or prevention of these types of MPH induced cognitive sequels.

It was indicated that MPH administration raises hippocampal MDA, as lipid peroxidation biomarker, level [2,33,34]. These outcomes showed MPH- prompted lipid peroxidation in the brain [2,35]. According to previous studies it appears that some of the damaging effects of MPH is intermediated through mitochondrial dysfunction and possibly producing lipid peroxidation [2,33]. According to previous studies mitochondrial GSH, benefic forms of glutathione, play a key role in miochondrial biogenesis, while increasing GSSG, malicious forms of glutathione, can initiate mitochondrial dysfunction. Converting of GSH to GSSG by MPH, is a main change that can start and trigger neurodegenerative signals in the brain [2,36], and this mechanism causes damaging influence on the glutathione cycle and thus causes neural cell
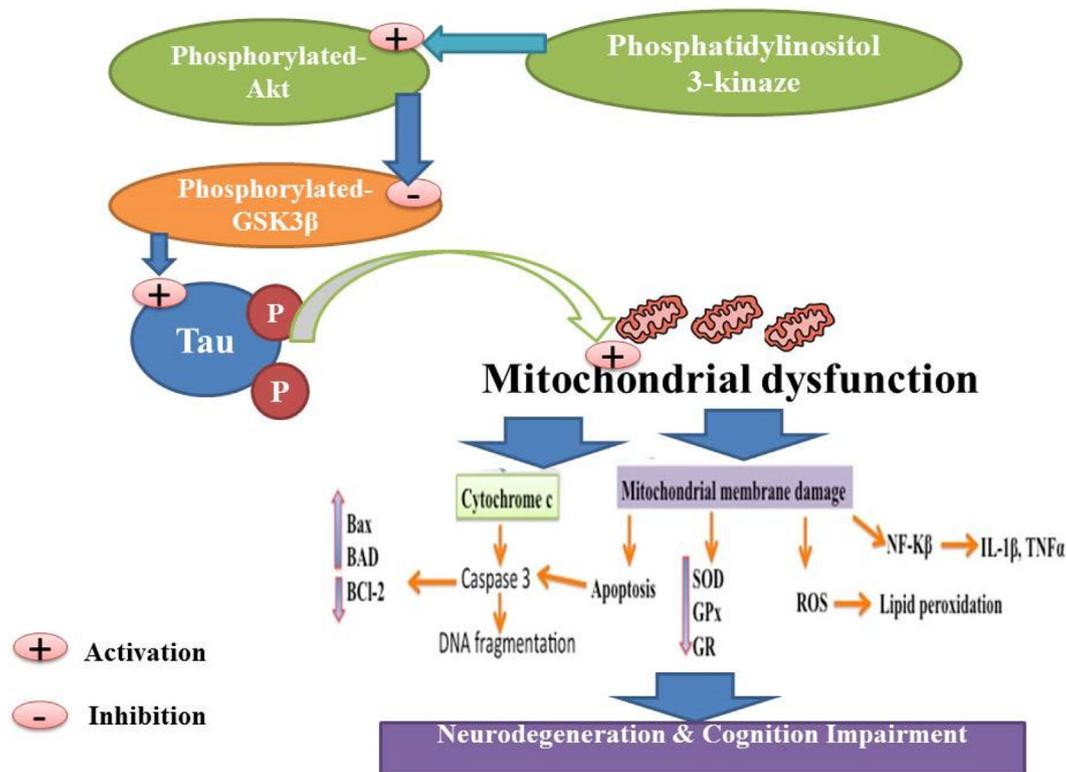
Fig. 3. Modulation of tau performance (phosphorylation) by PI3/Akt/GSK signaling pathway, Tau hyper phosphorylation prompted mitochondrial damages and neurodegeneration.

death [2,36]. Glutathione reductase (GR) is the key enzyme which modulates glutathione circle and cause conversion of GSG to GSH [2,33]. MPH prolonged abuses causes reduction of Glutathione peroxidase (GPx), GR and superoxide dismutase (SOD) actions in brain cells, which confirmed that reduction in antioxidant defenses, by MPH, may perhaps result in neurotoxicity and neurodegeneration [2]. Several new reports showed that MPH consumption leads to mitochondrial dysfunction and inhibits antioxidant enzyme activity in multiple cells, and these properties caused MPH-stimulated degenerative effects on brain cells such as the hippocampus which involved incognitive function [2,37].

New reports confirmed that chronic MPH administration significantly raises the level of pro-inflammatory cytokines like IL-β and TNF-α in the brain [33,34]. Prior works have stated the increase of pro-inflammatory cytokines following MPH and other psychostimulant agents' abuse [38]. It has been proposed that MPH-induced increase in inflammation is likely for the neurotoxicity properties of MPH [2]. MPH-prompted apoptosis and cell death in brain cell was approved in previous reports [34]. According to these studies, administration of MPH increased the level of an apoptotic protein, Bax, while declining an anti-apoptotic protein, Bcl-2. This data have been demonstrated that MPH abuse can cause brain impairment via triggering multiple apoptotic cascades [5,39,40]. In spites of all characteristic of MPH in induction of neurotoxicity and mitochondrial dysfunction, as reported based on previous data, role of tau hyper phosphorylation and PI3/Akt/GSK signaling pathway in this manner remain unclear and requires clarification.

According to our theory we proposed/hypothesized that minocycline can be benefit for management or prevention of mitochondrial dysfunction, neurotoxicity, neurobehavioral sequels (such as cognition impairment). Previous studies show that minocycline could modify the drug abuse -induced neurochemical and neurocognitive sequels [10,41]. Several former studies showed that minocycline, as a new

generation neuroprotective agent, can improve learning and memory [11,42]. According previous studies minocycline significantly improves learning and spatial memory, these data confirmed protective role of minocycline in enhancement of cognitive activity [11,42].

The inhibitory effect of minocycline on production of MDA level was indicated in previous report [43]. It appears that some part of the protective effects of minocycline is mediated through lipid peroxidation and mitochondrial biogenesis and perhaps minocycline is somehow modulating formation of lipid peroxidation [43,44]. Previous work have shown that minocycline exerts neuroprotective effects by inhibiting the formation of free radicals in neurodegenerative events [45,46], and it is well-evident that minocycline acts as a scavenger for free radicals in this type of disorders [17,46].

As it was mentioned above GSH conversion to GSSG by MPH, is a crucial change that can start and stimulate neurodegenerative signals in the brain [5,39], and this mechanism causes harmful effect on glutathione cycle and consequently causes neural cell death [5,39]. Moreover, it was found that minocycline, increase GSH content, while reducing GSSG level [2]. These findings have also been reported already by previous studies indicating that minocycline, by modulation of glutathione cycle, can be therapeutically beneficial against neurodegenerative diseases as it promotes GSH formation. According to this data minocycline can regenerates glutathione cycle [17,18].Some novel reports showed that minocycline consumption causes mitochondrial biogenesis and cause activation of antioxidant enzymes in multiple cells. These properties caused minocycline-induced protective effects on brain cells [10,11]. Previous work confirms minocycline neuroprotective role as antioxidant and free radical scavenger [10,47]. Minocycline, by activating GR, increases the conversion of GSSG to GSH and thus, protects the brain against mitochondrial dysfunction-induced oxidative stress [48]. Previous experimental studies have also established such anti-oxidative properties of minocycline in neurodegenerative disorder and diseases, mediated by increasing GR and GPx
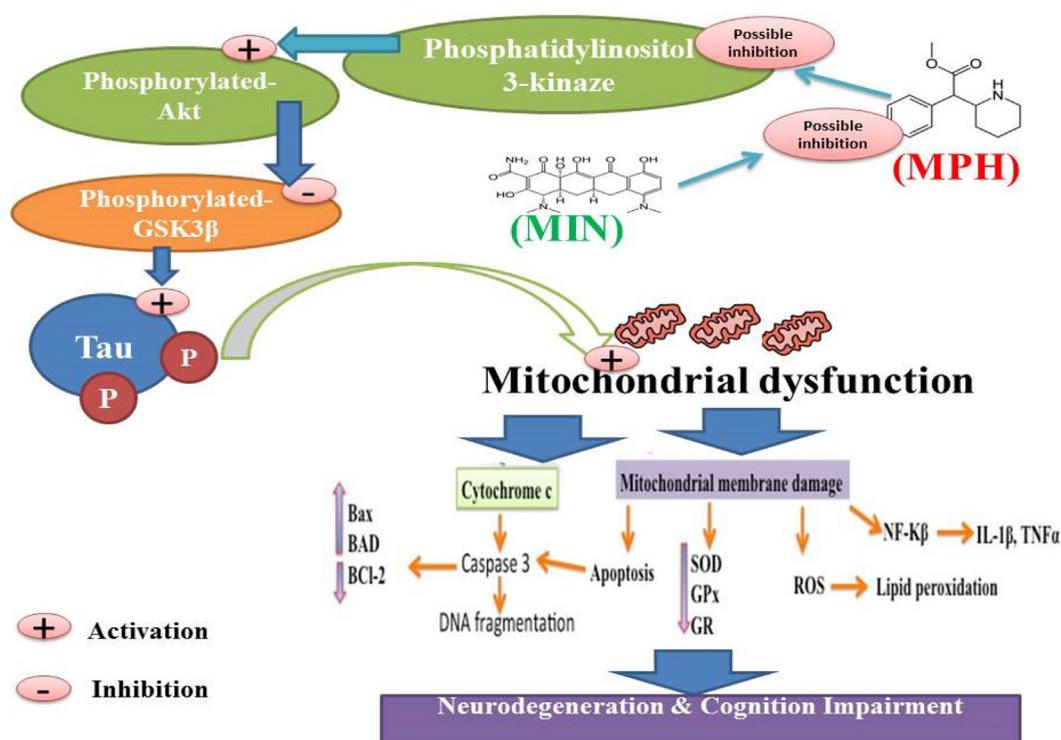
Fig. 4. Possible role of minocycline (MIN) on methylphenidate (MPH) induced possible effects on changes in modulation of tau performance (phosphorylation) by PI3/Akt/GSK signaling pathway. Tau hyper phosphorylation (by MPH) caused mitochondrial damages and neurodegeneration. Minocycline (MIN) might be act as neuroprotective agent against these malicious effects of MPH.

activity [14,18,49]. Treatment by minocycline was found to be effective in reversing the reduction in SOD activity in the brain tissues [10].

It was demonstrated that minocycline has a strong potential for suppressing neuroinflammation in a dose-dependent manner [50,51]. Research showed that treatment of animals by minocycline can attenuate IL-β and TNF-α level in the brain tissues in multiple neurodegenerative events [43,50,51]. On the other hand, minocycline has shown to have the therapeutic potential for management of neuroinflammation signaling cascades, thereby protecting the brain against inflammation and its damage [13,52]. In addition to oxidative stress and inflammation, the previous studies demonstrated the anti-apoptotic effect of minocycline against mitochondrial dysfunction prompted apoptosis as indicated by reducing Bax and improved Bcl-2 expressions in the brain [51]. Previous studies demonstrated that minocycline treatment attenuates cleaved caspase-3 and production of Bax and nuclear condensation resulting from some neurodegenerative disorders and diseases [18,52]. This indicates the role of minocycline in activation of neuroprotection [51,53]. According to these reports we tried to provide insight into neuroprotective role of minocycline based on the anti-inflammatory, anti-apoptotic and anti-oxidative effects of minocycline [51,53], But in spite of various data about neuroprotection role of minocycline and its capability for mitochondrial biogenesis and cognition enhancer, possible role of tau hyper phosphorylation and PI3/Akt/GSK signaling pathway in this regard remain vague.

As mentioned above according to previous studies it can be suggested and hypothesized that minocycline can be useful for management of MPH- stimulated seaquels but it can be proposed that some involved signaling pathways involved in this regard requires clearing up. In this regard we suggested that PI3/Akt/GSK signaling pathway by modulation of Tau proteins can be involved in minocycline neuroprotective effects against MPH induced mitochondrial dysfunction and neurotoxicity. Previous studies demonstrated that tau proteins act as a biomarker for neurodegenerative diseases [23,24]. Aggregation (hyper phosphorylation) of this protein causes toxic effects via its

accumulation inside brain cells [24]. These works suggested that accumulation of hyper-phosphorylated form of tau inside brain cell induces mitochondrial dysfunction (and cause oxidative stress, inflammation and apoptosis) by modulation of mitochondrial performance dysfunction and lead to neurotoxicity, which occurs in neurodegenerative disease such as Alzheimer disease (AD), Parkinson disease (PD) [22–25](Fig. 3). On the other way as protein based signaling pathway indicated, Glycogen synthase kinase-3(GSK3β) lead to tau aggregation (hyper-phosphorylation) [21,22,28]. These studies established that phosphatidylinositol 3-kinase (PI3K) activation (phosphorylation) of protein kinase B (Akt) and phosphorylated Akt causes inhibition of phosphorylation (activation) of GSK3β, and so Akt activation can cause inhibition of tau aggregation (hyper-phosphorylation) [23,54](Fig. 3). Regarding the critical role of PI3/Akt/GSK signaling pathway in inhibition of tau hyper-phosphorylation and because of tau hyper-phosphorylation roles in mitochondrial dysfunction and neurotoxicity and behavioral damages, we hypothesized that minocycline neuroprotective effects against MPH induced mitochondrial dysfunction, neurotoxicity and behavioral damages was mediated by tau hyperphosphorylation and PI3/Akt/GSK signaling pathway. Thus based on mentioned literatures, results of previous studies suggest that minocycline can be useful as potent neuroprotective agent for treatment/management of MPH abuser, in both human and animal subject and possibly can deteriorate MPH–stimulated mitochondrial and neurotoxicity via mediation of tau hyper-phosphorylation and PI3/Akt/GSK signaling pathway (Fig. 4), but further study designed for approving or declining of this hypothesis are essential.

Conflict of interest

None.

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