Medical Hypotheses 124 (2019) 21–25

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Crocin may be useful to prevent or treatment of alcohol induced neurodegeneration and neurobehavioral sequels via modulation of CREB/BDNF and Akt/GSK signaling pathway

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A B S T R A C T

The neurodegeneration and neurobehavioral consequences of alcohol are serious and offering therapeutic approaches for management of these types of neurodegeneration is one of the main concerns of researchers in this manner. Alcohol-stimulated oxidative stress, apoptosis and inflammation, with modulation of involved signaling pathway in neuroprotection, was reported previously. Neuroprotective strategy for management of alcohol induced neurodegeneration through a new generation neuroprotective agent and based on modulation of some neuroprotective signaling pathway such as CREB/BDNF and Akt/GSK has always been superior to any other therapeutic interventions. Therefore, the introduction and development of potential new neuroprotective properties and clarification of their effects on major cell signaling such as CREB/BDNF and Akt/GSK is necessitated. During recent years, using new neuroprotective compounds with therapeutic probability for treatment of alcohol induced neuro-biochemical and neuro-behavioral malicious effects have been amazingly increased. Many previous studies have reported the neuroprotective roles of crocin (major active component of saffron) in multiple neurodegenerative events and diseases in animal model. But the role of crocin neuroprotective effects against alcohol induced neurodegeneration and neurobehavioral sequels and also role of CREB/BDNF and Akt/GSK in this manner remain unclear. Hence we hypothesized that by using crocin in alcohol dependent subject it would provide neuroprotection against alcohol induced neurodegeneration and neurobehavioral and probably can manage sequels of alcohol abuses. Also we hypothesized that crocin, via intonation of CREB/BDNF and Akt/GSK signaling pathway, can inhibit alcohol induced neurodegeneration. In this article, we tried to discuss our hypothesis regarding the possible role of crocin, as a potent neuroprotective agent, and also role of Akt/GSK and CREB/BDNF signaling pathway in treatment of alcohol induced neurodegeneration and neurobehavioral through its anti-inflammatory, anti-apoptotic, anti-oxidative stress and cognitive enhancer.

Introduction

Alcohol is a sedative agent, prompts neurodegeneration [1] and its pharmacological similarity to sedative and hypnotic agents, makes it a probable candidate for abuse [2]. Abuses of alcohol have been increased in recent years [2,3]. Studies has indicated that alcohol abuse can cause neurobehavioral disorder such as depression, anxiety and cognitive (learning and memory) deficiencies in human and animal subject [4–7]. Previous studies also showed that chronic abuse of alcohol can cause neurodegeneration [8,9], and experimental studies have suggested that potential effect of alcohol in neurodegeneration of some area of the brain such as the hippocampus, is responsible for its neurobehavioral sequels [9]. Previous molecualr studies have shown that alcohol abuse can lead to production of free radical and cause activation of oxidative stress [10–12]. Also other studies demonstrated that alcohol abuse can induce inflammation [13,14]. Also other works indicates that alcohol abuses can increase apoptotic proteins like Bax and caspase family proteins and therefore it can causes DNA fragmentation in some brain region such as hippocampus [15,16]. All these studies believed that this types of increase of inflammation, oxidative stress, apoptosis and mitochondrial dysfunction by alcohol is responsible for its neurodegenerative properties in brain [16]. On the other way during recent years, using new using herbal/natural neuroprotective compounds with therapeutic probability for treatment of drug abuses induced sequels have been amazingly increased [17]. Natural flavonoids and their derivatives are being extensively evaluated as therapeutic agents against neurodegenerative diseases and some neuro-disorders induced by drug abuse [17]. Saffron is a medicinal plant which Phytochemical analysis have reported it is composed of at least four active ingredients such as crocin, crocetin, picrocrocin and safranal [18]. Crocin is a carotenoid chemical compound, found in the flowers crocus and gardenia [19]. Crocin is the ingredient which mainly

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https://doi.org/10.1016/j.mehy.2019.01.017
Received 25 October 2018; Accepted 23 January 2019
0306-9877/

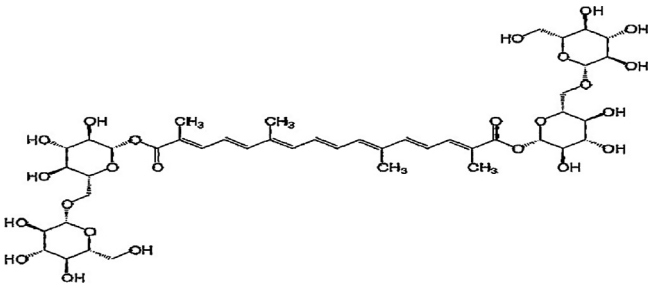

Fig. 1. Chemical structure of crocin.

is responsible for the saffron color [20–22]. Structurally it has complex molecules (Fig. 1), chemical analysis has indicated the presence of more than 150 ingredients in saffron stigmas [18,23]. Crocin, crocetin and safranal are the most important ingredients of saffron [23–25]. Crocin is the diester formed from the disaccharide gentiobiose and the dicarboxylic acid crocetin [23–25]. In other hand, crocin is a common term of a sequence of carotenoids that are either monoglycosyl or diglycosyl polyene esters of crocetin [25]. This compound is being extensively considered as a therapeutic agent against neurodegenerative diseases and events and also it can be used for management of neurobehavioral disorder [26,27]. Crocin has possible antidepressant and cognitive enhancer properties in animal and humans subjects [28–30]. The antioxidant and anti-inflammatory behavior of crocin was approved in previous studies [31,32]. Crocin treatment has shown to counteract apoptosis and reduces rise in apoptotic biomarkers levels in neurodegenerative events [33]. On the other way cyclic AMP response element binding protein (CREB) is a chief transcription factor which is a main element in regulation of genes related with synaptic and survival of neurons, neuroprotection and neural plasticity such as brain-derived neurotrophic factor (BDNF) [34,35]. BDNF is a main neurotrophic factor which predominantly supports the growth and survival of neurons. It is greatly expressed in some brain areas that are identified to adjust cognition, emotions, and rewards [36,37]. Conversely, various prior works showed that phosphatidylinositol 3-kinase (PI3K) can stimulate Akt (Protein Kinase B) in brain cells and by triggering this protein, glycogen synthase kinase 3 (GSK3), which is involved in neurodegeneration will be inhibited and cells protected from neurodegenerative effects of GSK3 [38,39]. Also previous works showed the role of Akt/GSK3 signaling pathway on cognitive activity [40]. All these properties may contribute to therapeutic potential efficacy of crocin in neurodegenerative disorders of drug abusers. However it's exact mechanism, specially role of CREB/BDNF and Akt/GSK signaling pathway in this manner remains unclear.

The hypothesis

During recent years, using new generation of therapeutic agent with neuroprotective properties for treatment of alcohol abuses induced sequels such as neurodegenerative and neurobehavioral malicious consequences of abuse have been astonishingly increased. According to mentioned neuroprotective properties of crocin in managements of oxidative stress, inflammation and apoptosis in brain areas such as hippocampus and also it's protective role as anxiolytic, antidepressant and cognitive enhancer and also due to importance of CREB/BDNF and Akt/GSK3 signaling pathway in modulation of neuroprotection and cognition performance it is suggested that crocin may protect hippocampal neurons against alcohol-induced behavioral and molecular damage. These functions may be mediated via CREB/BDNF and Akt/GSK3 signaling pathway and inhibition of oxidative stress, inflammation and apoptosis and also enhancement of cognition.

Evaluation of the hypothesis

For finding available data and information in the literature about neuroprotective properties of crocin in prevention or treatment of alcohol induced neurodegeneration and neurobehavioral sequels and involvement of CREB/BDNF and Akt/GSK3 signaling pathway in this manner we performed searches in multiples data bank such as Web of Science, PubMed, Elsevier, Science Direct, Google Scholar, Core Collection, and Cochrane with the key words crocin plus alcohol and CREB/BDNF or Akt/GSK3 signaling pathway. The search was limited to English full-text articles just about crocin effects on alcohol induced cell damages on gastrointestinal and there was no direct articles about role of crocin on alcohol prompted neurodegeneration and neurobehavioral such as anxiety, depression, cognition and involvement of CREB/BDNF or Akt/GSK3 signaling pathway.

Discussion

Alcohol as a sedative agent with a high potential for misuse and addiction [16]. According to previous studies chronic abuse of alcohol can cause neurobehavioral disorder in human and animal subjects [12,16]. These data suggested that alcohol can induce cognition disturbances [8,41]. Also some other studies demonstrated that alcohol abuses can cause anxiety and depression and can induce mood related behavior disturbance [2,5]. Previous studies demonstrated that management of these types of neurobehavioral disorder can help to manage alcohol cessation [42,43]. Some of these studies suggested some neuroprotective agent for managing this types of alcohol induced sequels [43]. About the role of alcohol in induction of biochemical molecular changes, earlier studies proved that administration of alcohol can increase MDA level in multiple brain area [10,44]. Related to former findings, showed that management of alcohol-induced lipid peroxidation in the brain can be involved in alcohol induced neurodegeneration which can result in neurobehavioral changes [44]. In consistent on alcohol effects on lipid peroxidation induction in some preceding works showed that alcohol administration can reduce mitochondrial GSH content however induce GSSG level in the brain tissues. Converting of GSH to GSSG by alcohol, is an important change that can start and prompt neurodegenerative signals in the brain [45,46]. This mechanism leads to damaging effect on glutathione cycle and as a result causes neural cell death [46]. About the role of alcohol on antioxidant enzymes many previous data demonstrated that alcohol abuses can decrease enzymes such as GPx, GR, SOD and CAT function in brain tissues [47,48], which confirmed the reports about the role of alcohol abuse in reducing antioxidant defenses and its outcomes on induction of neurodegeneration [48]. It has been shown that GR is the key enzyme which modulates glutathione circle. Thus, alcohol-prompted reduction in GR activity results in elevation of GSSG and reduction of GSH levels as reported in previous studies [48,49]. A number of novel reports displayed that alcohol intake causes mitochondrial dysfunction and lead to inhibition of antioxidant enzyme function in multiple cells, and these properties caused alcohol-stimulated degenerative effects on brain cells [49,50]. Conferring to these data, it appears that part of the damaging effects of alcohol is mediated via mitochondrial dysfunction and disturbance in oxidative and antioxidant balances [50,51]. It was demonstrated that chronic administration of alcohol significantly rises the level of pro-inflammatory cytokines like IL-β and TNF-α in the brain tissue [51]. Previous works which have stated the increase of pro-inflammatory cytokines following alcohol and other similar agents' abuse [51]. It has been proposed that alcohol-prompted rise in inflammation is responsible for the neurodegenerative properties of alcohol [44]. It can be inferred that some part of the alcohol destructive effects and its neurodegenerative properties is mediated through activation of neuroinflammation pathway [44]. Other than oxidative stress and inflammation, previous study approves alcohol-induced apoptosis and cell death in the brain [44,52]. According to these studies, alcohol

administration increased the level of an apoptotic protein, Bax, however declining an anti-apoptotic protein, Bcl-2. This data is consistent with previous works which have been demonstrated that alcohol misuse leads to brain impairment via stimulation of multiple apoptotic cascades and can result in DNA damages which is responsible for neural cell death and mentioned neurobehavioral disorders such as cognition impairment [9,49].

According to our hypothesis we suggested that crocin can be used for management of neuro behavioral and neurochemical sequels of alcohol abuses results, previous studies indicates that crocin could alter the drug abuse-induced cognition impairment [17,19]. Much previous work showed that crocin as new generation neuroprotective agent can improve learning and memory [53,54]. One study results suggest that crocin can be useful for the treatment of gastric cell degeneration in subject with alcohol abuses [55]. Also other similar studies demonstrated that crocin can act as anxiolytic and antidepressant agent and it seems that this effect can be useful in management of drug abuse such as alcohol withdrawal syndrome. In this manner previous work showed that crocin can block alcohol-induced release of dopamine in some brain areas and by possibly this mechanism can inhibit alcohol induced rewarding effects [54]. But the direct role of crocin neuroprotective effects on alcohol induced neurobehavioral effects and relation between inhibition of neurodegeneration and this type of neurobehavioral changes remain unclear. About the role of crocin on inhibition of oxidative stress previous studies indicates that crocin treatment attenuates rise in lipid peroxidation in the brain after spinal cord injury or in skin diseases [56]. Furthermore, it has been indicated by previous work that crocin exerts some parts of its neuroprotective properties by inhibiting the development of free radicals and lipid peroxidation in neurodegenerative event [21]. The function of crocin as a scavenger for free radicals is apparent in this type of disorder [17]. In consistent with this claim based on previous works crocin can increase GSH content, while decreasing GSSG level in animals subjects after cerebral edema [57]. These findings have also been reported already by previous studies specifying that crocin, by modulation of glutathione circle, can be therapeutically valuable against neurodegenerative diseases as it stimulates GSH formation [57,58]. Also some other studies demonstrated that crocin treatment can recover the function of antioxidant enzymes [58,59]. Crocin by triggering GR rises the transformation of GSSG to GSH and therefore, protects the brain against induction of oxidative stress in neurodegenerative events [59,60]. Previous experimental studies have also established such anti-oxidative properties of crocin in neurodegenerative disorder and diseases were mediated by increasing GR and GPx activity [60,61]. In addition, consistent with prior studies, treatment by crocin was found to be effective in reversing the decline in SOD and CAT function in the brain tissues [61,62]. According to protective role of crocin in management of oxidative stress in multiple situations we can suggest that crocin can inhibit alcohol prompted oxidative stress and by this inhibition possibly can protect brain from alcohol induced brain damages [62]. On the other hand, crocin has shown to have the therapeutic potential for management of neuroinflammation signaling cascades, thus maintaining the brain against inflammation and its damage [53]. Crocin is a neuroprotective agent and can improve brain function after neurodegenerative process and it can eliminate the destructive process of secondary injury which occur by neuro inflammation [59,63]. Based on this claim we can suggest that treatment of alcohol abuser by crocin can inhibit inflammatory destructive process which occurs in alcohol abuses. Alternatively, previous results confirmed the anti-apoptotic effect of crocin, as shown by reducing Bax and enhanced Bcl-2 expressions in the brain [64]. These studies revealed that crocin treatment reduces cleaved caspase-3 and production of Bax and nuclear condensation resulting from some neurodegenerative disorder and disease [64]. In fact it was demonstrated that crocin can inhibit cell death by inhibition of DNA fragmentation in apoptosis process during neurodegenerative process [65,66]. Further, most studies were related to pharmacokinetics of crocin compounds [23,67,68]. These pharmacokinetic studies have indicated that due to conversion to crocetin in intestine, crocin is not detectable after oral administration in blood circulations [23,67–69]. However after intravenous injection, the level of crocetin in plasma is low [68]. Because of weak interaction between crocetin and albumin, crocetin can distribute in different tissues [68]. Moreover it can penetrate blood-brain barrier and reach CNS by passive transcellular diffusion; therefore it can be active in neurodegenerative disorders [68]. The large portion of crocin is removed via feces [68,69]. According to these concepts it seems that some parts of crocin effects on brain maybe due to conversion to crocetin [68]. Conferring to its structure (Fig. 1), corcin itself could not pass the blood-brain barrier but many previous studies reported that this compound can act as neuroprotective agent against many kinds of neurodegenerative disease such as Alzheimer [70,71], Parkinson [72] and Epilepsy [73]. These studies show that crocin can modulate and inhibit occurrence of neuro-inflammation, oxidative stress and apoptosis in brain regions such as hippocampus, amygdalae, cerebral cortex, hypophysis and hypothalamus [25,59,60,70–72,74,75]. Its neuroprotective capability and properties showed that this agent, probably by convertion to active metabolites can pass the blood brain barrier [25,68]. Also some previous findings indicate that crocin or related antioxidants may protect and maintains integrity of blood brain barrier against cerebral ischemia, this studies showed that crocin can effect likely through repressing the activation of matrix metalloproteinase pathway [24]. On the other way there is special clarified signaling pathway for this neuroprotective effect against alcohol induced neurodegeneration [66,76]. The activated, phosphorylated, CREB (P-CREB), as a transcription factor, adjusts over hundred target genes, especially BDNF, associated in neuronal regeneration, development, survival, excitability, addiction, depression and cognition [77]. Furthermore, dysregulation of CREB transcriptional cascade has displayed to prompt oxidative stress, neurodegeneration, and apoptosis [77,78]. Various former molecular studies verified that the phosphorylated form of CREB has the key role in several herbal and chemical neuroprotective possessions [78]. Conferring to numerous studies, P-CREB (activated form of CREB) causes the creation of BDNF, ligands of TrkB receptor. These works displayed that BDNF by stimulation of its own receptor, TrkB, can prevent brain cell from degeneration and induce the existence of neurons [79]. In the present hypothesis, it appears that probably reduction in P-CREB protein level, by alcohol, impacts the mentioned cascade of BDNF/TrkB signaling path and triggers the neurodegeneration, apoptosis, inflammation and oxidative stress. On the other way crocin administration probably inhibit this property of alcohol and can trigger cascade of P-CREB/BDNF/TrkB. In consistent with our claim, it has been shown that P-CREB-BDNF signaling pathway has been associated in modification of some of the brain functions such as learning, memory, mood balances, reward mechanisms and neuroprotection [79–81]. One of the other signaling pathways which is involved in neurobehavioral and neurochemical modulation is Akt/GSK [82,83]. According to our hypothesis, alcohol can decrease Akt protein level/expression in total and phosphorylated form, while increase GSK3 in both forms. According to our claim, by activation of GSK3 with alcohol consumption some neurodegenerative events will occur in brain cells and some neurobehavioral disorders such as cognition impairment can be related to inhibition of Akt and activation of GSK3, which is involved in neurodegeneration [84]. Also we suggested that curcumin can inhibit alcohol induced decreases of Akt protein level/expression in total and phosphorylated form, while causes decreases of GSK3 in both forms in alcohol treated subject [40,85]. It has been shown by many preceding studies that neuroprotective effects of some neuroprotective agents were mediated by modulation of Akt/GSK3 and other similar signaling pathways [40,85], But the role CREB/BDNF and of Akt/GSK3 in modulation of crocin protective role in management of alcohol induced neuro-behavioral and neurochemical changes has not been clarified yet which according to the present hypothesis, crocin might act through these pathways,

CREB/BDNF or Akt/GSK3, and rescue cell survival from alcohol induced brain cell damages and triggers neuroprotection. According to these advantages of crocin we can suggest that probably alcohol induced cell death and apoptosis can be inhibited by crocin and probably CREB/BDNF or Akt/GSK3 signaling pathway can play critical role in this manner. Thus crocin can inhibit alcohol induced neurodegeneration. Taken together, based on mentioned literatures, results suggest that crocin treatment of alcohol abuser, in both human and animal subject, possibly can decline alcohol-induced apoptosis, oxidative stress and inflammation and neurobehavioral changes and might possibly act as a neuroprotective agent against alcohol induced neurodegeneration through modulation of CREB/BDNF or Akt/GSK3. However, further studies for confirming or refusing this hypothesis are necessary.

Conflict of interest

None.

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