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Is there a role for curcumin in the treatment of bipolar disorder?

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ABSTRACT

Curcumin is a polyphenolic nonflavonoid compound extracted from the rhizome of turmeric (*Curcuma longa*), a plant commonly used in Indian and Chinese traditional medicine to treat rheumatism, cough, inflammation and wounds. Curcumin putative targets, known based on studies of diverse central nervous system disorders other than bipolar disorders (BD) include several proteins currently implicated in the pathophysiology of BD. These targets include, but are not limited to, transcription factors activated by environmental stressors and pro-inflammatory cytokines, protein kinases (PKA, PKC), enzymes, growth factors, inflammatory mediators, and anti-apoptotic proteins (Bcl-XL). Herein, we review previous studies on the anti-inflammatory and anti-oxidant properties of curcumin and discuss its therapeutic potential in BD.

Introduction

Bipolar disorder (BD) is a chronic, severe and prevalent mental disorder associated with high rates of non-recovery, recurrence, and chronicity [1,2]. Morbidity, mortality, and cost of illness studies indicate that BD is related to significant burden [3,4]. Moreover, for many affected individuals, BD is a progressive and accelerating condition associated with neurostructural changes and cognitive deterioration [5–7]. In addition to brain abnormalities, BD has been linked to several metabolic alterations, including obesity, arterial hypertension, and changes in glucose metabolism [8,9]. In fact, metabolic syndrome and cardiovascular morbidity are one of the most relevant causes of mortality in this population [10].

Evidence-based treatments for BD include the use of lithium, several anticonvulsants, and atypical antipsychotics [11]. Studies evaluating efficacy and effectiveness indicate that most individuals with BD fail to achieve symptomatic remission and functional recovery with existing treatments alone or in combination [12]. Moreover, high rates of treatment discontinuation and switching in BD are consequences of the limited efficacy of available agents [13]. Furthermore, tolerability concerns (e.g., weight gain) are major limitations of current treatments [13].

It is generally accepted that existing treatments for BD are capable of suppressing symptoms but have not been proven to modify the underlying disease course and progression of the illness. In addition to phenotypic/behavioral progression (e.g., shorter symptom-free intervals as a function of episode frequency), pathological progression in BD has been reported at the brain circuits, synaptic, cellular, intracellular, and neurochemical levels [14]. In fact, BD is characterized by progressive neuronal atrophy, cognitive deterioration functioning along with shorter symptom-free intervals and lower treatment response rates [15]. Mechanisms underlying neuroprogression are related to imbalances between neurotoxicity and neuroprotection (i.e., neuroplasticity) [14].

The search for new, more efficient, and safer drugs to treat BD are an unmet need in psychiatry. For instance, the use of complementary and alternative medicines (CAM) offers a potentially interesting resource [16]. Although the development of pragmatic clinical trials for CAM in mood disorders began approximately 20 years ago, their off-label administration dates back to hundreds or thousands of years [17]. Traditional cultures explored which plants were useful for what conditions and passed information on species, preparation, and dose through the ages [17]. There appears to be a high level of patient acceptance of this treatment modality, notwithstanding the relative paucity of evidence supporting their usage, as well as concerns regarding bioavailability and manufacturer quality assurance [18]. Some CAM treatments exhibit neurobiological effects that suggest possible application in BD [19]. For example, over 3000 preclinical reports have described pleotropic properties attributable to the herbal component curcumin [20].

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Curcumin is a polyphenolic nonflavonoid compound extracted from the rhizome of turmeric (*Curcuma longa*), a member of the ginger family, and is commonly used as a culinary season in different regions of India, China and other Asiatic countries [21]. In addition to its culinary use, turmeric has been used in these countries as an anti-inflammatory agent [22], being used in traditional Indian medicine for rheumatism, cough, inflammation and wound [23]. Turmeric has been studied in detail and all active ingredients were isolated, including curcumin, which was described as the most effective bioactive component [24]. As curcumin has low toxicity, it has been explored in medicine, based on its anti-oxidants and anti-inflammatory properties. Accordingly, curcumin has been studied in several diseases where inflammation and oxidative stress imbalances are related to the pathophysiological mechanisms, such as, Alzheimer's and Parkinson's disease [25], as well as cardiovascular diseases and cancer [20,26,27].

Curcumin is often regarded as pleiotropic compound whose the putative mechanisms of action are directed to several targets [28], such cell proteins, including transcription factors (ATF-3, AP-1, STAT-3, NF-κB), protein kinases (PKA, PKC), enzymes, growth factors, inflammatory mediators, and anti-apoptotic proteins (i.e., Bcl-XL) [21]. Because several of these targets have been implicated in the pathophysiology of BD [29–31] or in the mechanisms of action of current mood stabilizers [32,33], we postulated that curcumin could have therapeutic potential for the treatment of BD. In this work, we review current evidences of the anti-inflammatory and anti-oxidant properties of curcumin and propose that these effects may offer advantage for BD therapeutics.

Neurotrophins, oxidative species and inflammation in bipolar disorder: possible targets for curcumin

Although the pathophysiology of BD remains elusive, in the last decade, findings from different modalities of research have converged to demonstrate alterations in neuroplasticity, neuronal interconnectivity, apoptosis regulation, cell survival and resilience as critical processes in the patho-etiology and neuroprogression of BD [34]. The balance between neuronal survival and death is regulated or influenced by several mediators. Alterations in levels of these substances in the periphery have been postulated as possible biomarkers of BD [35]. The reproduction of abnormalities in neurotrophins, inflammatory mediators and oxidative species in independent studies lead to the postulation that this combination can be considered a viable biosignature and marker of progression in BD [35]. Throughout this section, we discuss these mediators and report the effects of curcumin on these potential therapeutic targets.

Neurotrophins

Neurotrophins are a family of proteins involved in neuronal development, survival and neuronal functioning. The neurotrophin called brain-derived neurotrophic factor (BDNF) is considered a key mediator of neuroplasticity, being implicated in processes such as neuronal differentiation, survival and synaptic plasticity [36]. Decreased serum BDNF levels in acute mood episodes of either polarity in BD were recently confirmed in a comprehensive a meta-analysis [37]. Furthermore, clinical recovery is associated with a corresponding increase in BDNF levels [38]. The pathophysiological role of BDNF BD has been reviewed in detail elsewhere [38,39]. Several effective treatments for BD, such as lithium, electroconvulsive therapy and atypical antipsychotics are known to increase BDNF levels [40–42]. Moreover, polymorphisms of the BDNF gene were shown to confer vulnerability to develop BD [43–45]. A special attention has been given to the Val66Met polymorphism, as it appears to be significantly associated with greater risk for BD [43].

Curcumin and BDNF

Several preclinical studies revealed that curcumin is able to: (i) induce widespread increases in brain BDNF levels; (ii) enhance the expression of this neurotrophin and (iii) modulate the second messengers in BDNF signaling pathway [46].

Induction of stress and activation of hypothalamus–pituitary–adrenal (HPA) axis in animals promotes a reduction in BDNF levels. Curcumin restored BDNF levels in the hippocampus and prefrontal cortex of rats when compared to control animals submitted to corticosterone-induced animal models of depression [47]. In addition, administration of curcumin completely reversed the alterations in BDNF and its mRNA expression in the hippocampus of pigs submitted to stress [47]. The BDNF signaling pathway in the hippocampus has been implicated in the neurogenesis and neuroprotection machinery that maintains homeostasis and ensure neuronal survival in humans [48]. The hippocampus is also suggested as a major target for curcumin's anti-stress activity in rodents and humans [49].

Studies in primary neuronal cultures found that curcumin enhanced neuronal survival by 21% by day 6 when compared to control cells [50]. To investigate if the BDNF receptor activation was involved in these neuroprotective effects, Wang and cols [50] blocked the BDNF receptor TrkB with a specific antibody. The application of an anti-TrkB IgG inhibited curcumin's effects upon neuronal survival *in vitro* [50]. Curcumin also stimulates the synthesis of BDNF in a dose-dependent manner [50]. In addition, curcumin increased the phosphorylation of TrkB, indicating that the BDNF/TrkB signaling pathway was activated by this compound. Two well-known downstream mediators of BDNF intracellular effects, MAPK–ERK and PI-3K/AKT were also investigated as putative curcumin targets. Curcumin treatment led to the phosphorilation (i.e., activation) of both mediators, thereby indicating that this substance act on important points in the BDNF signaling cascade [50]. Furthermore, curcumin upregulates cAMP response element-binding (CREB) phosphorylation, a pathway known to regulate BDNF transcription, in cortical neurons reaching a maximum effect after 6 h [50]. Finally, pretreatment with curcumin reverses the downregulation of BDNF and phosphorylated-TrkB induced by glutamate in cultured cortical neurons [51].

Oxidative stress

An excessive production of reactive oxygen species (ROS) or deficiency in antioxidant mechanisms leads to oxidative stress, which, in turn, may promote apoptosis or necrosis [52], along with brain damage [14]. Several lines of evidences relate oxidative stress mechanisms to BD [53,54]. Previous studies demonstrate both reduction and overactivity of defenses against oxidative damage as well as increases in ROS [54]. Although the findings are heterogeneous, alterations in antioxidant enzymes, such as an increase in superoxide dismutase (SOD) in both depressive and manic episodes were demonstrates (2). Catalase was found to be increased in mania [55] and decreased in euthymia (2). Markers of lipid peroxidation, like thiobarbituric acid reactive substances (TBARS), as well as nitric oxide (NO), have also been shown to be increased in major mood episodes of BD, regardless of polarity [54]. *Post mortem* brain investigations revealed that SOD and catalase expression are consistently decreased in the hippocampus of BD patients [56]. Furthermore, a down-regulation of several mitochondrial-related genes, such as the ATP synthase and cytochrome-c oxidase genes in the hippocampus [57] and dorsolateral prefrontal cortex of BD patients were reported [53]. These reductions in gene expression could lead to mitochondrial dysfunction, shifting metabolism