International Journal of Neurology and Neurotherapy

Santiago et al. Int J Neurol Neurother 2016, 3:061
DOI: 10.23937/2378-3001/3/6/1061
Volume 3 | Issue 6

ISSN: 2378-3001

Research Report: Open Access

Depression in Parkinson's Disease is Associated with a Serotoninergic System Change Secondary to Neuroinflammation

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Abstract

Depression is a common psychiatric disorder in patients with Parkinson's disease (PD), being more prevalent in PD than in any other chronic disabling disease. Its cause, nevertheless, has not yet been elucidated. According to some authors, there is a decrease in serotonin (5-HT) levels compensatory to dopaminergic release impairment, but new evidence suggests that chronic inflammation may be a more likely etiogenic factor to depression. The inflammatory hypothesis states that depression is caused by an activation of the inflammatory system, incrementing production of proinflammatory cytokines such as prostaglandin (PG) E2, and these cytokines promote changes in the metabolic pathway of tryptophan, reducing its levels and, hence, the availability of 5-HT. This establishes an important link between the levels of inflammatory cytokines and monoamines. We consider the hypothesis that depression in PD is associated with reduced serotonin levels by neuroinflammation. In conclusion, we suggest that depression associated with PD is related to a change in the serotonergic system caused by neuroinflammation.

Keywords

Depression, Parkinson's disease, Neuroinflammation

Introduction

Depression (depressive disorder) is a common psychiatric disorder in patients with Parkinson's disease (PD), being more prevalent in PD than in any other chronic disabling disease. [1]. The prevalence of depression in PD patients is higher than 40% [2], and its incidence reaches 1.86% per year [3,4]. Despite they being important comorbidities, the cause of depression in PD remains unknown. Our hypothesis is that depression in PD is caused by a decrease in central serotonin (5-hydroxytryptamine, 5-HT) levels, secondary to neuroinflammation.

Depression in Parkinson's Disease

The dopaminergic and serotonergic neurotransmitter systems are involved in regulating mood, and changes in these systems are associated with depression in the general population and in patients with neurodegenerative diseases like PD [5]. According to some authors, the 5-HT decrease is a compensatory mechanism associated with reduction in dopaminergic neurotransmission. Serotonin has an inhibitory function in DA release in the striatum [1,6]. Politis, et al. [7] reported that the occurrence of non-motor symptoms in PD patients may be associated with loss of serotonergic neurons.

The levels of 5-HT and its metabolite 5-HIAA in cerebrospinal fluid (CSF) are also reduced in depressed patients [8]. Other studies demonstrated that CSF levels of 5-HIAA in PD patients are lower than in healthy individuals [9-11] and this reduction is even larger when comparing PD plus depression to PD without depression [12]. In a previous study, our group showed that the depressive-like behaviors observed in Parkinsonian rats produced through the intranigral infusion of 6-hydroxydopamine (6-OHDA) was correlated with a reduction in the levels of hippocampal 5-HT and its metabolite [13]. We demonstrate, also, that the depressive-like behaviors are observed from day 7 until day 21 after infusion of 6-OHDA, and that the reduction of hippocampal 5-HT occurred on the 1st day after the lesion with 6-OHDA in the SN and persisted until 21 days after infusion [14].

Attempting to explain the cause of depression in PD patients, new approaches were proposed, as the inflammatory hypothesis of depression [12]. Evidence suggests that continuous activation of the immune system and/or chronic inflammation system can be one of the pathological processes associated with PD depression [15]. It is known that the formation of Lewy corpuscle, pathological feature of PD, and the death of dopaminergic neurons, promotes activation of microglia, which produces neurotoxic factors, such as cytokines [16], and increased expression of cyclooxygenase (COX-2) thus increasing the synthesis of prostaglandin (PG) [17]. In PD patients, the levels of inflammatory cytokines are increased in the substantia nigra pars compacta (SNpc), striatum and CSF [18,19]. According to Maes, et al. [20], dysfunction in serotonergic system in depression is the result of cell-mediated immune activation.

Neuroinflammation, depression and parkinson's disease

Inflammation is the first line of defense against tissue injury or infection, but an excessive inflammatory response can cause tissue damage. Neurons, as a result of its large cell differentiation, have

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Citation: Santiago RM, ABF Vital M, Sato MDO Adam GP (2016) Depression in Parkinson's Disease is Associated with a Serotoninergic System Change Secondary to Neuroinflammation. Int J Neurol Neurother 3:061. doi.org/10.23937/2378-3001/3/6/1061

Received: July 20, 2016: **Accepted:** November 28, 2016: **Published:** December 03, 2016

little or no ability to divide and a reduced ability to recovery from injury, becoming, therefore, extremely vulnerable to autoimmune and inflammatory processes [21]. According to Collins, et al. [22], in PD, when the glial cells are activated, they secrete high levels of proinflammatory mediators that may induce dopaminergic neurons death, that further increase the activation of glial cells, resulting in a vicious cycle of neurodegeneration and inflammation. Besides that, the neuronal COX-2 expression is related to apoptosis and involved in the response to stress [23].

Initial inflammatory response in innate immunity sparks a cascade that results in the activation and recruitment of adaptive immunity [16]. Therefore, proinflammatory cytokines released during the innate and adaptive immune responses can lead to the development of central nervous system disorders [24]. Stress conditions are associated with an increase in hypothalamic-pituitary-adrenal (HPA) axis activity and elevated serum corticosterone [25,26]. Studies support, also, the idea that activation of the HPA axis in response to chronic stress induces changes in the hippocampal serotonergic system, predisposing the individual to the development of depression [27,28].

Patients with depression and PD have an increase in the inflammatory processes, with increased levels of interleukin 1β, interleukin 6, tumor necrosis factor (TNF)-α and cortisol [5]. Depression patientes also have increased concentration of proinflammatory cytokines and PGE2 in blood and CSF [29-32]. Evidence suggests that depression increases neuroinflammation and that the antidepressants exert anti-inflammatory effects [33,34]. Studies in animals and humans indicate that cytokines interact with many pathophysiological grounds that characterize depression as the metabolism of neurotransmitters, synaptic plasticity and neuroendocrine function [35-37].This hypothesis is corroborated, yet, by the presence of activated microglia, increased proinflammatory cytokines and COX-2 in neuronal and glial post-mortem PD patients' brains [18,38]. The expression of COX-2 has been associated with the degeneration of dopaminergic neurons of the SNpc in both humans and in animal PD models [39,40]. Patients suffering from chronic inflammatory processes are at increased risk to develop depression, as well as patients treated with proinflammatory cytokines such as interleukins, interferons (IFN)-γ or TNF-α [41,42].

On the other hand, these cytokines promote changes in the metabolic pathway of tryptophan reducing levels and hence the availability of 5-HT. Proinflammatory cytokines are able to reduce the level of 5-HT through the activation of indoleamine 2, 3-dioxygenase (IDO) [43]. IDO is an enzyme that degrades tryptophan to a catabolite of tryptophan (TRYCATs) and nicotinamide, reducing the bioavailability of tryptophan for the synthesis of 5-HT [44]. The neurotransmitter 5-HT is derived from an essential amino acid, tryptophan, and its synthesis in the brain is highly dependent on the bioavailability of plasma tryptophan [45], so that the activation of IDO by proinflammatory cytokines, induces the tryptophan metabolism reducing its bioavailability and, consequently, the level of 5-HT in neurons [46]. Not only cytokines, but PGE2 is also able to reduce the level of 5-HT through the activation of IDO enzyme [41,47-49].

Anti-inflammatories as antidepressants in parkinson's disease

The pharmacological mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) arises from inhibition of COX, the limiting step enzyme for the synthesis of PGs from arachidonic acid [50]. COX is presented in two isoforms - a constitutive isoform (COX-1) and an inducible isoform (COX-2), both sharing a high degree of structural homology. However, COX isoforms are so pharmacologically distinct, that they are differentially inhibited by NSAIDs [51]. Traditional NSAIDs and aspirin (ASA) inhibit both isoforms and selective NSAIDs (coxibs) preferentially inhibit COX-2 [50]. Studies suggest that both isoforms are unevenly distributed among cells of the central nervous tissue, COX-1 being detected in microglial cells and COX-2 found primarily in glial cells, and at lower levels (above subject to regulation in patients PD and induction models of parkinsonism), in the dopaminergic neurons of the SNpc [52].

The investigation of potentially neuroprotective effect of NSAIDs in PD experimental models was instigated by in vitro studies developed by Grilli, et al. [53], who demonstrated that aspirin and sodium salicylate were able to prevent glutamate-induced neurotoxicity, suggesting a potential neuroprotective effect of those drugs. In a parecoxib study , itwas demonstrated that this drug has been effective in stopping PD motor and cognitive deficit and changes in the expression of tyrosine hydroxylase (TH) caused by intranigral infusion of 1,2,3,6-tetrahydropyridine (MPTP) in rats [54]. In the same line of work, Soliman, et al. [55] demonstrated that administration of piroxicam 7 days before and after the administration of MPTP (40 mg/kg) in mice was able to reduce neurodegeneration in SNpc and consequent motor disabilities. Using unilateral infusion of 6-OHDA in rats, Pernaute-Sanchez, et al. [56] evaluated the neuroprotective effect of chronic treatment with celecoxib, a selective inhibitor of COX-2, and the results demonstrated neuroprotection, reduced microglial activation and increased immunoreactivity for TH. In addition, the chronic treatment with celecoxib was also able to reverse the depressive-like behavior induced by moderate chronic stress protocol in rats, reducing the expression of COX-2 in the brain and, subsequently, the concentration of PGE2 [57].

Hunter, et al. [58] observed that celecoxib limited the inflammatory response induced by LPS by reducing the release and overproduction of cytotoxic molecules and partially restoring mitochondrial function, thus increasing dopaminergic neuronal survival. According to Bartels and Leenders [59], the observed benefit of celecoxib may also stem directly from COX-2 neuronal inhibition, which is apparently able, directly and through the inhibition of microglial activation, to reduce dopaminergic neurodegeneration.

Kohler, et al. [60] described in their recent meta-analysis that treatment with non-steroidal anti-inflammatory drugs improved depressive symptoms in PD in 9 out of the 10 studies evaluated without increasing the risk of adverse effects. Mendlewicz, et al. [61] demonstrated that PD patients treated with ASA, in addition to their antidepressant therapy, showed improvement in the first week of treatment. In addiction, patients with PD and depression treated with celecoxib adjunctive to the antidepressant drug demonstrated improvement in the Hamilton scale for Depression scores [62-65]. In conclusion, adjuvant treatment with NSAIDs may be a promising strategy for patients with depressive disorder and PD [65,66].

Finally, drugs that inhibit proinflammatory cytokine signaling such as NSAIDs represent a viable strategy for the treatment of depression, especially in patients with evidence of increased inflammatory activity as in PD [67]. According to Menza, et al. [68] inflammatory cytokines may be involved in the neurobiology of initiation and/or maintenance of depression in PD, supporting the hypothesis that neuroinflammation is involved in the depression secondary to PD.

Conclusion

In conclusion, we believe that depression associated with PD is related to alteration in the serotonergic system caused, in part, by a neuroinflammatory process. The inflammatory process leads to release of cytokines and PG that are able to activate IDO and thus reduce the availability of central 5-HT, leading, therefore to the onset of depression, as shown in (Figure 1).

Acknowledgements

This work was supported by grants from CNPq, CAPES and the Araucária Foundation, which had no further role in the study design, collection, analysis, and writing the report, or decision to submit the manuscript for publication. MABFV is recipients of CNPq fellowships.

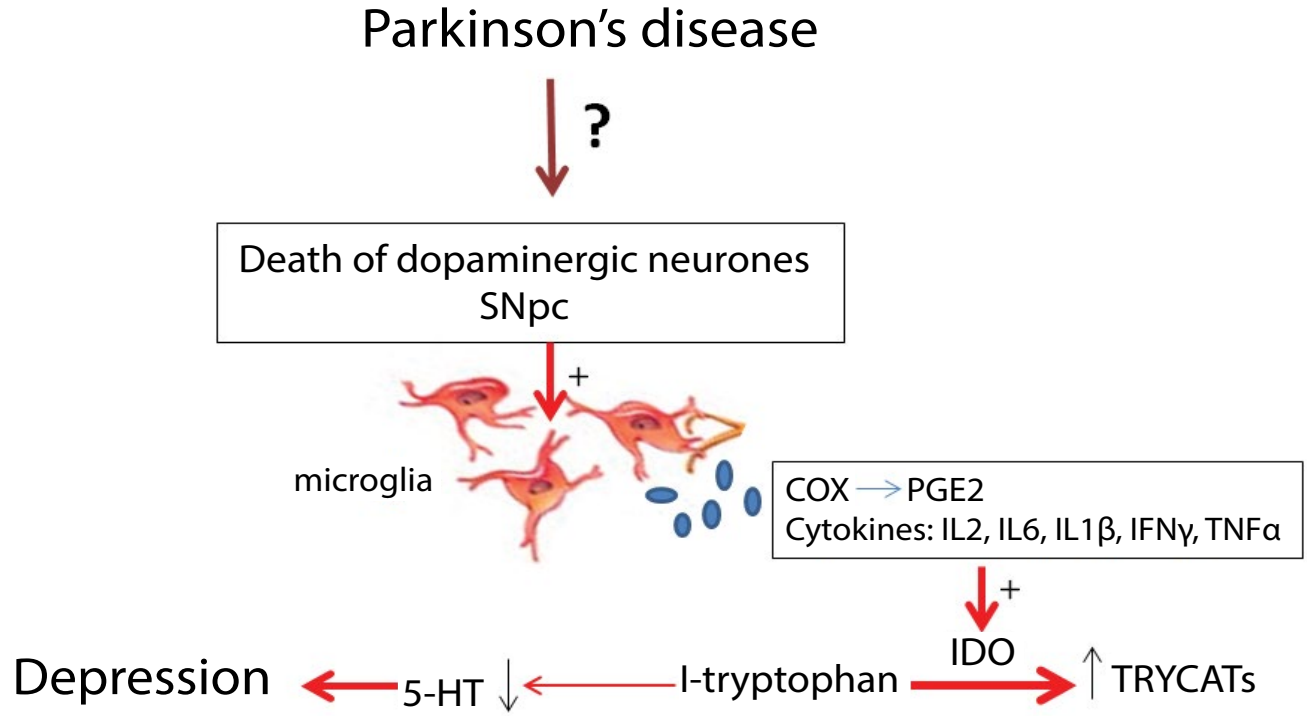

Figure 1: Scheme proposed for the cause of depression in Parkinson's disease. SNpc: substantia nigra compact part COX: cyclooxygenase; PGE2: prostaglandin E2; IL: interleukin; IFNγ: interferon gamma; TNFα: tumor necrosis factor alpha; IDO: indoleamine 2 3-dioxygenase; TRYCATs: catabolites of tryptophan; 5-HT: serotonin.

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