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Molecular pathology 2020: Antiparkinsonian potential of certain quinolone derivatives: insights into Nurr-1 and autophagy roles

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Abstract

Background:
Nuclear receptor related-1 (Nurr1) orphan receptor has emerged as a promising contender in ameliorating Parkinson's disease, thus finding a suitable activator of Nurr1 receptor is an attracting target for treating PD. Meanwhile, the deregulation of autophagy, along with other processes such as; inflammation, apoptosis and mitochondrial dysfunction is believed to contribute to the pathogenesis of the disease. The aim of this study is to explore the neuroprotective effect of cilostazol and hydroxychloroquine in rotenone-induced PD model in rats. Both drugs managed to enhance the dopaminergic neurons functionality and integrity as depicted by the increase in the striatal tyrosine hydroxylase content, as well as the improved locomotion and muscle coordination in rotarod and open field. However, this improvement was opposed by hydroxychloroquine induced autophagic inhibition as manifested by enhancing both LC3-II and P62 levels possibly through the prominent decline in sirtuin 1 level and enhanced apoptosis evidenced by cytochrome C and caspase-3 elevation. In conclusion, cilostazol could be a promising candidate for PD treatment through modulating Nurr1 expression, as well as SIRT-1/autophagy, and GSK-3β/apoptosis cross-regulation. Where, hydroxychloroquine successfully ameliorated PD motor dysfunction in spite of the fact that both autophagy and apoptosis were deregulated through Nurr1 modulation.

The nuclear orphan receptor (Nurr1) has recently received a perceivable solicitude as a target for the therapeutic intervention against PD. Meanwhile, the dysregulation of autophagy, along with other processes is believed to contribute massively to PD pathophysiology. Hydroxychloroquine, a hydroxy derivative of chloroquine, is an antimalarial agent which is also used as an anti-rheumatic drug. The neuroprotective potential of hydroxychloroquine and chloroquine remained controversial until recently a study showed that chloroquine exhibited an antiparkinsonian activity through Nurr1 modulation. The aim of this work is to identify whether the less toxic derivative, hydroxychloroquine, could show a similar pattern. In rat rotenone model, hydroxychloroquine effectively boosted Nurr-1 expression, exhibited an anti-inflammatory effect as verified by hindering certain pro-inflammatory cytokines and successfully reduced GSK-3β activity. Consequently, an increase in the striatal tyrosine hydroxylase content, as well as improved locomotion and muscle coordination was shown. However, this improvement was opposed by hydroxychloroquine in
duced autophagic inhibition as manifested by enhancing both LC3-II and P62 levels possibly through the prominent decline in sirtuin 1 level and elevated apoptotic biomarkers. In conclusion, hydroxychloroquine successfully ameliorated PD motor dysfunction in spite of the fact that both autophagy and apoptosis were deregulated through Nurr1 modulation.

Parkinson's disease (PD) is a chronic progressive, yet incurable neurological disorder affecting mainly the elder population . The most prominent hallmark of the disorder is dopaminergic neurons degeneration in the substantia nigra pars compacta (sNpc) and subsequent exhaustion of the dopamine content (DA) in the striatum . This depletion in DA results in the cardinal motor manifestations afflicting PD patient including tremors, rigidity and bradykinesia among others . The pathogenesis of the disorder is intricate as several interconnected factors influence the disease including; apoptosis, abnormal protein aggregates, inflammation and mitochondrial dysfunction . Thus finding a suitable agent that amends these complex interrelated factors remains a challenge.
The orphan nuclear receptor (Nurr1) up-regulation is proved to preserve the dopaminergic neurons functionality and integrity in the sNpc thus, it can be considered as a pivotal target for the intervention against PD. This receptor was shown to trigger tyrosine hydroxylase (TH) transcription along with other genes crucial for dopamine synthesis and normal development of dopaminergic neurons. Moreover, pro-inflammatory cytokines release was mitigated by Nurr1 expression
in astrocytes and microglia, an effect that could protect the dopaminergic neurons against inflammation induced neuronal death.Noteworthy showed that treatment with rotenone, a known pesticide used to induce symptoms resembling PD, was associated with a heightened inflammatory response and release of inflammatory cytokines such as interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) mediated by nuclear factor-kappa B (NF-κB), an effect that was associated with Nurr1 down-regulation. Thus, drugs activating Nurr1 over- expression have received a perceivable interest as potential candidates providing protection against PD.Lately, activated glycogen synthase kinase-3 beta (GSK-3β) has been PD is characterized by the accumulation of abnormal protein aggregates preceding the neurological damage. One of the natural physiological procedures responsible for removing those aggregates is autophagy. Accordingly, autophagy dysregulation is believed to contribute massively to PD pathogenesis.The neurotoxic pesticide rotenone was found to result

in autophagic flux inhibition through lysosomal dysfunction, an effect that could be reversed by autophagic activators providing a protective effect against rotenone cytotoxicity. On the other hand, dopaminergic cell death in PD is proved to be a direct result of an enhanced apoptosis.Previous reports showed that dopaminergic neurons may survive and their function and morphology could be preserved after using apoptosis inhibitors.Therefore, it is of an utmost importance to keep normal balanced cell death mechanisms to maintain the normal homeostasis without causing irreparable damage. Hydroxychloroquine (HCQ), a chloroquine hydroxy-derivative, is an anti-malarial and anti-rheumatic drug.HCQ neuroprotective potential is still questionable. A previous study failed to prove HCQ efficacy against Alzheimer's disease.On the other hand, a recent study suggested that some anti-malarial drugs including chloroquine succeeded in ameliorating PD motor disturbances in 6-OHDA-treated rats.Moreover, HCQ managed to alleviate neurological sarcoidosis manifestations, an effect that could support the claims around its neuroprotective potential. Hence, this study aims to unveil the discrepancy regarding the possible Nurr1 mediated neuroprotective effects of hydroxychloroquine versus autophagy and apoptosis dysregulation, in a rat model of PD. claimed to participate significantly in pathogenic mechanisms of neurodegenerative diseases including, PD and Alzheimer's disease.It was shown that GSK-3β regulates various components of the complex network involved in PD such as, inflammation and abnormal protein aggregates formation.Hence, GSK-3β inhibition can exhibit a beneficial outcome in PD treatment. Normal turnover of proteins and cells within an organism is controlled by various processes including, apoptosis and autophagy

Keywords:
Nurr-1, Rotenone, Parkinson's disease, Autophagy, Tyrosine hydroxylase. GSK-3β LC3-II Nurr1 Rotenone SIRT-1 Hydroxychloroquine

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