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LETTERS AND COMMENTS

The need of a new and more physiological preclinical model for Parkinson's disease

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The review of Lindholm et al. [1] is very interesting and raised a very important point which require a more deeply discussion. This publication reveals the failure of both the scientific community and the pharmaceutical companies to discover new treatments for Parkinson's disease (PD) despite the intensive research performed during the last five decades. L-Dopa, introduced to PD treatment in 1967, continues to be the gold drug in PD treatment despite the severe side effects observed after 4–6 years treatment such as dyskinesia. Lindholm et al. [1] review the possible use of neurotrophic factors to halt the degenerative process in PD. However, most of the research that aim to discover new drugs to treat Parkinson's have the focus on finding drugs to alleviate the side effects of L-dopa rather than to seek drugs that halt the loss of dopaminergic neurons containing neuromelanin.

One possible explanation for the failure to find drugs that halt the loss of dopaminergic neurons containing neuromelanin seems depends on (a) the fact that the molecular mechanism that triggers this degenerative process is still unknown. However, there is general agreement in the scientific community that the loss of dopamine neurons containing neuromelanin is related to protein degradation dysfunction of the proteasomal and lysosomal systems, mitochondrial dysfunction, formation of alpha synuclein neurotoxic oligomers, oxidative stress, neuroinflammation and endoplasmic reticulum stress; and (b) preclinical models for PD probably does not reflect what is happening in the disease since as successful preclinical studies in animals treated with 6-hydroxydopamine and MPTP fail in clinical studies [2]. All these neurotoxins induce a rapid and extensive loss of dopaminergic neurons, for example, MPTP induces a severe Parkinsonism in just 3 days, contrasting the very slow degeneration observed in the nigrostriatal neurons of PD patients which take years to develop motor symptoms.

We consider that it is time to open the question about the convenience to continue to use preclinical model based on exogenous neurotoxins when successful results obtained in preclinical studies fail in clinical studies. Aminochrome has been proposed as a new preclinical model for Parkinsońs disease [3]. Aminochrome is one of the products formed during dopamine oxidation to neuromelanin in the substantia nigra. Dopamine oxidizes to dopamine *o*-quinone, which is only stable at pH lower than 2 and therefore, immediately cyclizes to aminochrome with a constant rate of 0.15 s^{-1}. Aminochrome the most stable *o*-quinone formed during dopamine oxidation undergo intramolecular rearrangement to form 5,6-indolequinone with a constant rate of 0.06 min^{-1}, which finally polymerize to neuromelanin. Interestingly, aminochrome induces protein degradation dysfunction of both proteasomal and lysosomal

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systems; mitochondria dysfunction; alpha synuclein aggregation to neurotoxic oligomers; oxidative stress and endoplasmic reticulum stress [3] and therefore, it seems to be plausible that aminochrome is the endogenous neurotoxin that triggers the neurodegeneration of the nigrostriatal system, which results in the motor symptoms in PD. Aminochrome is formed inside the dopaminergic neurons containing neuromelanin that are lost during the neurodegeneration of the nigrostriatal system in PD and therefore, aminochrome can be a more physiological preclinical model to find new pharmacological treatment for PD.

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