Dopamine and L-Dopa as Selective Endogenous Neurotoxins

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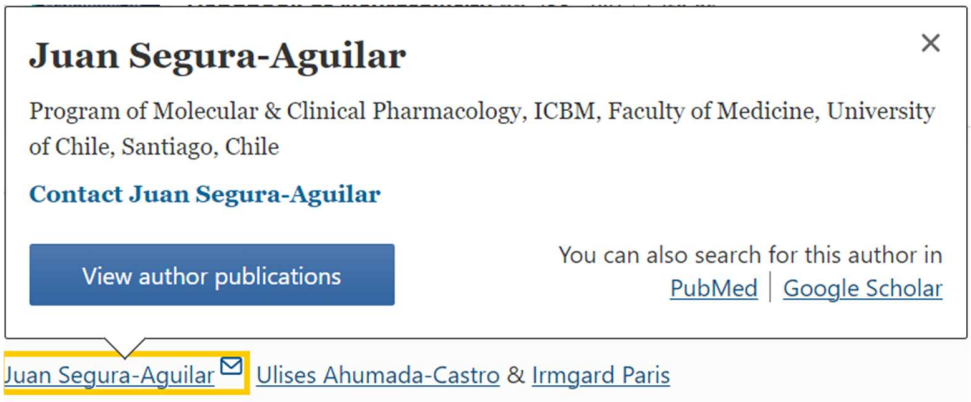
Abstract

Selective neurotoxins have the ability to exert their neurotoxic effects in dopaminergic neurons. This could depend on their affinity to the dopamine transporter. The possible molecular mechanisms involved in dopamine and L-dopa neurotoxicity in dopaminergic neurons are discussed. Dopamine seems to be neurotoxic in dopaminergic neurons by undergoing oxidation to aminochrome, which is the precursor to neuromelanin. However, aminochrome can be neurotoxic when it forms adducts with proteins such as alpha-synuclein, alpha- and beta-tubulin, and H-type ATPase, or when aminochrome is one-electron reduced by flavoenzymes that use NADH, generating redox cycling, depletion of energy, and the formation of reactive oxygen species. L-dopa is also neurotoxic in cell cultures after oxidizing to a quinone species, but L-dopa seems to be a transient precursor of dopamine in that it is not able to induce neurotoxicity in vivo due to the efficient decarboxylation to dopamine catalyzed by amino acid decarboxylase. L-dopa is used in Parkinson's disease treatment. It seems that L-dopa itself does not accelerate dopaminergic neuron degeneration because L-dopa is efficiently converted to dopamine. However, L-dopa induces dyskinesias in approximately 40% patients with 4–6 years of treatment. It is also unclear whether L-dopa modifies the course of the disease, although protective effects have recently been described. It is possible that the majority of dopamine release to the striatum is mediated by serotonergic neurons without regulation, resulting in dyskinesias. This chapter also discusses L-dopa's role in the formation of melanoma in the skin of patients treated chronically with this drug.

Keywords

Aminochrome | Dopamine | Dyskinesia | L-dopa | Metabolism | Neurotoxicity | Neurotoxins | Orthoquinones | Oxidation | Parkinson's disease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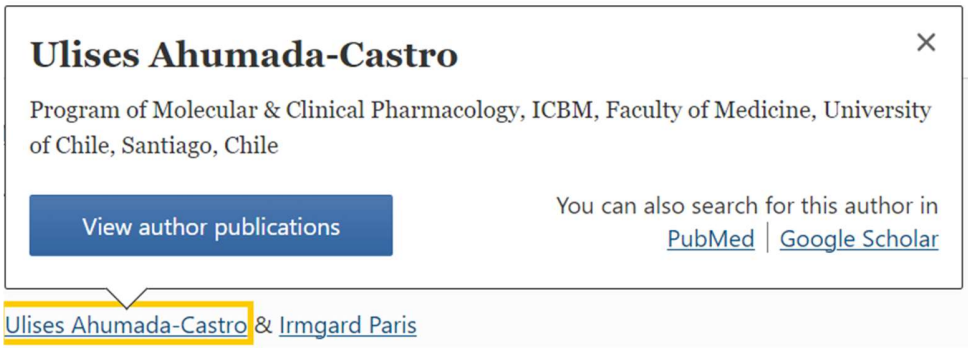
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