PROTEASOME AND PARKIN AS DRUG TARGETS AGAINST METHAMPHETAMINE TOXICITY

https://neurodegenerationresearch.eu/survey/proteasome-and-parkin-as-drug-targets-against-methamphetamine-toxicity/

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USA

Title of project or programme

PROTEASOME AND PARKIN AS DRUG TARGETS AGAINST METHAMPHETAMINE TOXICITY

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NIH (NINDS)

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2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

parkin gene, , , ,

Research Abstract

DESCRIPTION (provided by applicant): Methamphetamine (METH) is a highly addictive psychostimulant drug that is neurotoxic when taken at high doses chronically or acutely. METH selectively damages striatal dopaminergic terminals in experimental animals and humans. Despite years of active research on METH neurotoxicity, no specific medications have been developed to counteract the damaging effects that METH has on the brain. Due to its widespread abuse, there is a compelling need for effective pharmaceuticals that can protect and/or restore the brain from the toxic effects of acute METH overdose and chronic METH abuse. Thus, it is necessary to identify molecular drug targets in order to develop novel pharmaceuticals. My long-term goal is to develop neuroprotective therapies to treat the toxic effects of METH use. The goal of the proposed research is to better understand the molecular mechanisms regulating the ubiquitin-proteasome system in the METH-exposed rat brain and to determine whether two components of this system, proteasome and the E3 ligase parkin, are potential pharmaceutical targets that can be used to promote [survival and recovery] of dopaminergic terminals in vivo after toxic doses of [binge and chronic] METH. Both proteasome and parkin are decreased shortly after binge METH administration, and those deficits are also involved in the etiology of Parkinson's disease. We hypothesize that increasing their functions will provide neuroprotection in rats chronically and acutely exposed to METH. Specific Aim 1 will evaluate the relative roles of 20S and 26S proteasomes on the [survival of dopaminergic terminals and their recovery from binge and chronic] METH by using proteasomal inhibitors and a novel approach to regulate proteasomal activity, namely, systemic injections of TAT-tagged peptides that interfere with proteasomal assembly. TAT is a domain of the human immunodeficiency virus type 1 that rapidly crosses the blood brain barrier. These two forms of the proteasome behave differently upon exposure to METH- induced oxidative stress; thus, evaluation of their respective roles in METH neurotoxicity is warranted. Specific Aim 2 will evaluate the role of parkin in the [survival of and recovery from binge and chronic] METH using wild- type, parkin-overexpressing, and parkin knock-out rats. The role of parkin in the formation of intracellular inclusions in the nigrostriatal dopamine neurons will be investigated using immunohistochemistry and confocal microscopy. Specific Aim 3 will determine whether proteasomes and parkin are functionally linked in the METH-exposed rat brain. For clinical intervention purposes, it is important to know how variations in parkin levels influence 20S and 26S function and vice versa. These aims are conceptually linked as they investigate regulatory processes within the ubiquitin-proteasome system that may be important for [endogenous survival and recovery mechanisms] in dopamine neurons and, therefore, clinically important. The findings from the proposed research may lead to novel treatments for METH users.

Lay Summary

PUBLIC HEALTH RELEVANCE: The proposed animal study will determine whether the proteasome and parkin are potential pharmaceutical drug targets that can be manipulated to promote survival [and recovery of dopaminergic terminals after binge and chronic administration of toxic doses] of the highly abused and addictive stimulant drug, methamphetamine. Findings from the proposed research may lead to novel neuroprotective therapeutic strategies to combat methamphetamine neurotoxicity and other brain disorders involving damage to the brain's dopaminergic system such as Parkinson's disease.

Further information available at:

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Investments > €500k

Member States:
United States of America

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Parkinson's disease & PD-related disorders

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2016

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