The antioxidant N-acetyl-L-cysteine exerts strong neuroprotective effects in both in-vitro and in-vivo models of Parkinson's disease

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Keywords: PARKINSON'S DISEASE, 6-OHDA, NEUROPROTECTION

Abstract: Parkinson's disease (PD) is a devastating neurodegenerative disorder for which there is no cure. It is caused by the loss of dopaminergic (DA) neurons in the striatum, producing disabling motor symptoms. In the present study, the neurotoxin 6-hydroxydopamine (6-OHDA) was used for the modeling of Parkinson's disease in both in-vitro and in-vivo experiments. In primary culture of mesencephalic neurons, 15µM of 6-OHDA induced selective death of the DA neuron population. Unilateral injection of 6-OHDA in the medial forebrain of the rat induced ipsilateral depletion (90% reduction) of nigrostriatal dopamine along with ipsilateral rotation of rat following injection of apomorphine. In addition, 6-OHDA-injected rats showed marked motor deficit in different behavioral tests such as beam walking and forelimb use asymmetry tests. In-vitro, Baclofen (GABAB receptor agonist), Z-vad-fmk (caspases inhibitor) and PD150606 (calpain inhibitor) elicited 30, 50 and 55% inhibition of the death of DA neurons, respectively. Complete inhibition of cell death was observed with the antioxidant N-acetyl-L-cysteine (NAC). Furthermore, treatment of 6-OHDA rats with NAC prevented the loss of nigrostriatal dopamine and markedly reduced apomorphine-induced rotation. These rats showed improved performance in beam walking and in the forelimb use asymmetry tests. The above data underline the pivotal role of the oxidative stress pathway in 6-OHDA-mediated death of DA neurons. In addition, they indicate the relevance of an in-vitro model to predict in-vivo neuroprotection.

Topic: C.03.b. Degeneration models

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Animal model of cognitive dysfunction responding to ADHD therapies

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Keywords: ADHD, METHYLPHENIDATE, ANIMAL MODEL.

Abstract: Over 90% of adults and children living with and seeking treatment for Attention Deficit Hyperactivity Disorder (ADHD) manifest cognitive dysfunction, particularly impairments in attention, working memory and executive function which provides support for a cognitive rather than psychomotor basis of ADHD pathology. The existing animal models for ADHD feature psychomotor behavior impairments (impulsivity and hyperactivity) but do not always favorably respond to the psychostimulant drugs used for the treatment of ADHD. In the present study, the potential of ADHD médications (methylphenidate, amphetamine and atomoxetine) to restore cognitive performance (spontaneous and continuous alternation in the T-maze) was tested in mice after pharmacological alteration of the central cholinergic system by injection of scopolamine. Amphetamine, Methylphenidate and Atomoxetine elicited dose-dependent reversion of cognitive deficit in scopolamine -treated mice. Seven days of subchronic treatment was required to obtain the cognitive effect of amphetamine whereas Methylphenidate and Atomoxetine were effective following a single acute or 3-day subchronic dosing regimen. Furthermore, Atomoxetine was effective after a short pretreatment period (0.5h prior to the T-maze task) whereas Amphetamine and Methylphenidate required longer pretreatment times (16h). The above results demonstrate that psychostimulant drugs with differing mechanisms of action have a positive effect in this model of scopolamine-induced cognitive dysfunction, and indicate its utility for evaluating the cognitive enhancing properties of new chemical entities for ADHD.

Topic: ++C.06.j. ADHD, SLI, dyslexia and other specific disorders of neurobehavior

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The effect of immunosuppressive and immunomodulatory drugs in a cellular model of brain inflammation: Involvement of nitric oxide-mediated neuronal death

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Keywords: INFLAMMATION, OXIDATIVE STRESS, MODEL.

Abstract: Neuroinflammation is now recognized as a critical process in different neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, stroke and multiple sclerosis. Microglia and astrocytes are key players in neuroinflammation since they release a wide variety of proinflammatory mediators, including nitric oxide (NO). In the present study, the potential neuroprotective effect of immunosuppressive (dexamethasone) and immunomodulatory (doramapimod) drugs was investigated in lipopolysaccharide (LPS) - stimulated microglia/astrocyte/neuron co-cultures, with special attention to the involvement of NO in the death of neurons. Stimulation of co-cultures with LPS produced substantial, sustained production of NO in the medium. Significant death of dopaminergic neurons was observed 5 days post-stimulation. Neuronal death was fully prevented by dexamethasone treatment but not by doramapimod although both drugs fully suppressed the production of NO. It is noteworthy that the antioxidant resveratrol markedly reduced NO production along with partial inhibition of neuronal death. These data indicates that inflammation-mediated neuronal death in microglia/astrocyte/neuron co-cultures involves both NO-dependent and NO-independent pathways.

Topic: ++C.11.g. Neuroinflammation: Neurodegeneration

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