Deleterious effects of VEGFR2 and RET inhibition in a preclinical model of Parkinson?s disease

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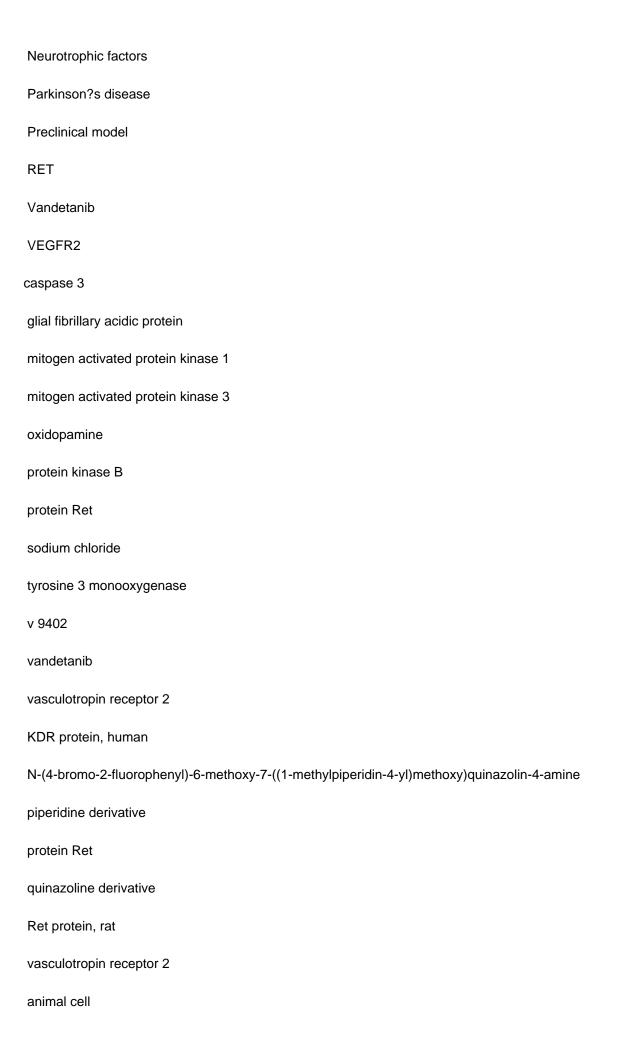
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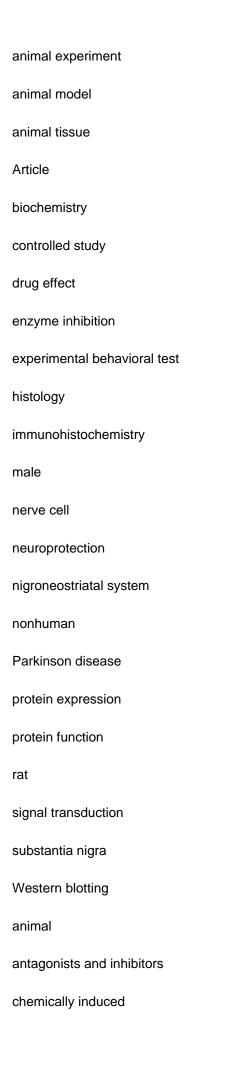
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Neurotrophic factors (NTFs) are a promising therapeutic option for Parkinson?s disease (PD). They exert their function through tyrosine kinase receptors. Our goal was to assess the effects of administering a selective tyrosine kinase inhibitor (vandetanib) that blocks VEGFR2 and RET receptors in a preclinical model of PD. Rats underwent intrastriatal injections of 6-hydroxydopamine (6-OHDA). Two weeks later, the rats received 30 mg/kg vandetanib or saline orally. The effects were assessed using the rotational behavioral test, tyrosine hydroxylase (TH) immunohistochemistry, and western blot. In 6-OHDA-lesioned rats, motor symptoms were almost undetectable, but morphological and biochemical changes were significant. Vandetanib treatment, combined with the presence of 6-OHDA lesions, significantly increased behavioral impairment and morphological and biochemical changes. Therefore, after vandetanib treatment, the TH-immunopositive striatal volume, the percentage of TH+ neurons, and the extent of the axodendritic network in the substantia nigra decreased. Glial fibrillary acidic protein-positivity significantly decreased in the striatum and substantia nigra in the vandetanib-treated group. In addition, p-Akt and p-ERK 1/2 levels were significantly lower and caspase-3 expression significantly increased after vandetanib administration. In conclusion, we demonstrate for the first time the deleterious effect of a tyrosine kinase inhibitor on the dopaminergic system, supporting the beneficial and synergistic effect of NTFs reported in previous papers. © Springer Science+Business Media, LLC 2017.

6-OHDA





metabolism
parkinsonism
pathology
Sprague Dawley rat
treatment outcome
Animals
Male
Parkinsonian Disorders
Piperidines
Proto-Oncogene Proteins c-ret
Quinazolines
Rats
Rats, Sprague-Dawley
Treatment Outcome
Vascular Endothelial Growth Factor Receptor-2