NOCICEPTIN/ORPHANIN FQ RECEPTORS AS A NOVEL TARGET FOR DEVELOPMENT OF ANTIPARKINSONIAN DRUGS

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Nociceptin/orphanin FQ (N/OFQ) and its receptor (NOP) are expressed in the substantia nigra (SN), a brain area containing dopamine (DA) neurons that degenerate in Parkinson's disease (PD). We recently provided evidence that endogenous N/OFQ transmission is up-regulated in the SNr of 6-hydroxydopamine (6-OHDA) hemilesioned (hemiparkinsonian) rats and that these plastic changes may concur in sustain symptoms and neurodegeneration associated with experimental PD (1). Indeed: i) systemic administration of the non peptide NOP receptor antagonist J-113397 or intranigral injection of the peptide NOP receptor antagonist UFP-101 attenuated akinesia in hemiparkinsonian rats (1) or in rats made cataleptic with haloperidol (1,2) possibly through the normalization of nigral GLU transmission; ii) deletion of the NOP receptor gene conferred mice resistance to the cataleptic action of haloperidol while deletion of the ppN/OFQ gene conferred mice partial protection against MPTP-induced loss of SN DA neurons (1). Moreover, we recently demonstrated that in hemiparkinsonian rats, J-113397 and L-DOPA produced additive antiakinetic effect via additive overinhibition of the nigro-thalamic GABAergic pathway (3). This evidence suggests that co-application of a NOP receptor antagonists with levodopa may be useful to reduce levodopa dosage, thereby delaying the onset of levodopa side-effects (i.e. dyskinesia). Overall, these data suggest that NOP receptor antagonists might be used in the therapy of PD not only for their symptomatic efficacy (alone or in combination with levodopa therapy) but also for their potential ability to slow degeneration of DA neurons.

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References

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