lamine. The antidepressant-like effect of AMOP-H-OH in forced swim was completely reversed by mecamylamine and the high affinity nAChR antagonist dihydro-β-erythroidine (DHβE), but not by the α7 nAChR antagonist methyllycaconitine (MLA). AMOP-H-OH was long lasting in the forced swim test with efficacy observed up to 4 h after treatment, an effect that was also completely reversed by mecamylamine. A pharmacokinetic study was carried out to determine if the duration of action of AMOP-H-OH could be correlated with plasma and brain levels. Mice were treated with 1 or 3 mg/kg of AMOP-H-OH and plasma and brains were collected 0.25, 0.5, 1, 2, and 4 h after i.p. injection. Although plasma levels showed a dose response relationship 15 min after administration, levels were nearly non-detectable by 30. Brain levels of AMOP-H-OH reached only low levels 15 min after administration and were at or below detection level at the later time points. Similar dissociations between pharmacokinetic and pharmacodynamic (PK/PD) profiles have been noted for other nicotinic compounds. The superior efficacy of AMOP-H-OH in forced swim compared to varenicline and mecamylamine suggests that this class of compounds may provide novel opportunities for the development of drugs to treat depression.

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4.7

nAChR agonists reduce L-dopa-induced dyskinesias in parkinsonian rats

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Dyskinesias are debilitating movement abnormalities that arise with L-dopa therapy in Parkinson's disease. Currently treatment options to decrease their occurrence include a reduction in L-dopa dosage or the use of drugs such as amantadine that have only limited efficacy. Our recent data show that nicotine treatment effectively attenuates L-dopa-induced dyskinesias in parkinsonian monkeys and rats. Since nicotine activates multiple nicotinic receptors (nAChRs), we initiated a series of experiments with receptor agonists to identify whether more selective receptor drugs may reduce L-dopa-induced dyskinesias. For these studies, we used a well-characterized parkinsonian animal model of dyskinesias, L-dopa-treated unilateral 6-OHDA-lesioned rats. Several nAChR agonists were tested including (1) RJR-2403 that is selective for α4β2* nAChRs, (2) A-85380 that interacts with both α4β2* and α6β2* nAChRs and (3) varenicline that targets α4β2*, α6β2*, α3β4* and α7 nAChRs. For the experiments with RJR-2403, L-dopa-treated dyskinetic lesioned rats L-dopa were given varying doses of RJR-2403 (0.1, 0.2 and 1.4 mg/kg/day) via minipump for a several week period. No significant declines were obtained in L-dopa-induced abnormal involuntary movements (AIMs) with RJR-2403, although there was a small trend for improvement. The lack of efficacy of this agonist may be because it only targets α4β2* nAChRs, or possibly due to a sub-optimal pharmacokinetic profile. After a washout period, the rats were next treated with a drug with a somewhat wider nAChR profile, the β2-directed nAChR agonist A-85380. It was injected twice daily for 4 days at doses ranging from 0.10 to 0.75 μmol/kg, as previously described. L-dopa-induced AIMs were rated on the 4th day of injection. A small (15%) but significant decline was observed in L-dopa-induced AIMs with the 0.18 μmol/kg dose. There was no decline in the antiparkinsonian effect of L-dopa, as assessed using the asymmetric forelimb or cylinder test. We then did a series of experiment with varenicline, an agonist that interacts with multiple nAChR subtypes. Varenicline (1 mg/kg) was administered to L-dopa-treated lesioned rats twice daily via sc injection for 4 days. This drug also significantly reduced L-dopa-induced AIMs (25%) without affecting parkinsonian behavior. Overall, these data show that agonists that target multiple CNS nAChR subtypes reduce L-dopa-induced AIMs with no appreciable effects on parkinsonism. The results should aid in the development of selective therapies using nAChR subtype agonists to reduce L-dopa-induced dyskinesias in Parkinson's disease.

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Section 5. Peripheral nAChRs

5.1

Importance of nicotinic acetylcholine receptors in the visual adverse effects associated with telithromycin

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Adverse effects associated with use of the macrolide antibiotic telithromycin include "blurred vision" associated with impairment of accommodation and, in myasthenia patients, exacerbated muscle weakness. A first clue about blurred vision came from the relatively high prevalence of such symptoms reported by subjects exposed to telithromycin compared to structurally related macrolides (clarithromycin or azithromycin). As macrolides do not readily cross the blood brain barrier, blurred vision must arise from disruption of function in the peripheral nervous system. Since cholinergic neurotransmission plays a determinant role in peripheral nervous transmission we evaluated the possible interaction of macrolides with neuronal nicotinic acetylcholine receptors (nAChR) and compared the effects of telithromycin, clarithromycin, azithromycin and CEM-101, a novel fluoroketolide. Effects of macrolides on the functional properties of nAChRs were evaluated using human receptors expressed in *Xenopus* oocytes. Exposure to a low concentration of telithromycin (2 μM) inhibited by 85% or more the ACh-evoked currents at α3β4 and α7 nAChR while much less inhibition was observed with azithromycin, clarithromycin or CEM-101. As the α3β4 and α7 receptors are the major constituents of ganglionic transmission, inhibition of their activity will impair or even suppress neurotransmission in peripheral ganglia. Dysfunction of the ciliary ganglion is expected to cause a loss of control of pupillary constriction and ciliary muscle contraction. Both effects thereby may combine to produce a reduction in the depth of field and of accommodation and cause a loss of focusing. This should result in profound vision disturbance and "blurred vision" for objects in the near and intermediate vision.

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