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MEETING ABSTRACT

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Effects on neurochemistry and behavior of modafinil and its analogs in rodents: new clues for the next generation of medications for the treatment of psychostimulant use disorders
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Clinical trials have shown promising yet inconsistent results with oral modafinil (MOD) as a treatment for psychostimulant use disorders. MOD blocks the dopamine (DA) transporter (DAT) like abused psychostimulants, such as cocaine. However, the resulting stimulation of DA levels and its efficacy as a reinforcer are among the lowest in its class. In order to dissect the pharmacologic activity that contributes to its mechanism of action, we have recently synthesized several structural analogs of MOD, including its (R)-enantiomer ((R)-MOD). Here we show behavioral studies in rats aimed to test these analogs and their potential therapeutic effects when administered in combination with cocaine or methamphetamine under different schedules of self-administration behavior. We also have performed microdialysis and fast-scan cyclic voltammetry (FSCV) tests in the nucleus accumbens shell (NAcS), a brain area related to reward, in Sprague Dawley rats and Swiss Webster mice, in order to better understand the dopaminergic effects of these drugs alone and in combination with cocaine. We show that pretreatment with several structural analogs of MOD attenuates cocaine and/or methamphetamine self-administration behavior in rats. Also, like the atypical DAT blockers, when administered alone these MOD analogs show reduced facilitation of medial-forebrain-bundle-induced maximal stimulation of DA in the NAcS, in FSCV experiments in mice. Further, the MOD analogs reduce the maximal stimulation of DA elicited by cocaine when administered in combination with it. In microdialysis tests, we have confirmed the limited stimulation of DA levels induced by MOD and (R)-MOD and extended this finding to the MOD-analogs. So far, the MOD analogs that show atypical DAT blocker activity in FSCV tests and small, if any, increases in extracellular DA in our microdialysis studies are also those providing better results as potential blockers of cocaine or methamphetamine reinforcing effects. In conclusion, our results confirm the potential therapeutic effects of (R)-MOD for the treatment of cocaine and methamphetamine dependence. We also extend these findings to support potential therapeutic effects of selected analogs of MOD, which may provide important clues in the search for a pharmacotherapeutic treatment of psychostimulant use disorders.

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