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A Novel Serotonin-2 (5-HT2) Modulator as a Candidate Drug to Treat Impulsive Behavioral Disorders and Psychoses without Weight Gain as a Side Effect

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Background: It is hypothesized that the desired serotonin 5-HT2 receptor pharmacology required to treat impulsive behavioral disorders, including, psychostimulant abuse/addiction and binge eating, as well as, psychoses, is 5-HT2A antagonism and/or 5-HT2C agonism. Currently, however, no selective 5-HT2A antagonist has demonstrated clinical efficacy to treat psychostimulant addiction or psychoses, and a clinically-acceptable 5-HT2C agonist that does not also activate 5-HT2A (hallucinations) and/or 5-HT2B (cardiopulomonary toxicity) receptors has not been reported. Negative modulation of amphetamine-induced locomotor activity in rodents is a commonly used first-stage screen for new drugs to treat amphetamines abuse/addiction, and, all effective antipsychotic compounds attenuate the robust head-twitch reponse (HTR) in mice elicited by the 5-HT2 agonist (−)−2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI), as well as, the hyperactivity elicited by the NMDA antagonist MK-801 and/or amphetamine.

Methods: The (−) and (+) enantiomers of a novel compound, (2S, 4R)-*trans*-4-(3′-bromophenyl)-*N,N*-dimethyl-2-aminotetralin (*meta*-bromo-PAT or *m*- Br-PAT), were synthesized, characterized *in vitro* for binding and function at mouse and human 5-HT2A, 2B, and 2C receptors. Subsequent studies in male C57Bl/6J mice examined these compounds in animal models predictive of activity to modulate amphetamine-induced behaviors, antipsychotic activity, and in a model of compulsive (binge) eating.

Results: Both (−) and (+)-*m*-Br-PAT bound to mouse and human 5-HT2 receptors with the (−) enantiomer being approximately 16-, 5- and 27-fold more potent at 2A, 2B, and 2C receptors respectively. (−)-*m*-Br-PAT was a relatively high efficacy 5-HT2C agonist measured by functional activation of PLC assessed by [^{3}H]-IP formation in HEK cells transiently expressing 5-HT2C receptors. Both enantiomers attenuated the HTR elicited by DOI (1.0 mg/kg) with (−)-*m*-Br-PAT being approximately 3-fold more potent. (−)-*m*-Br-PAT completely blocked MK-801-elicited (0.3 mg/kg) increases in locomotor activity, and was behaviorally active for at least 2 hours. Hyperactivity produced by amphetamine (3.0 m/kg) administration was similarly attenuated by (−)-*m*-Br-PAT. Consumption of a highly palatable food in non-food-deprived mice was decreased by ~65% and 45% following administration of the (−) and (+) enantiomers, respectively.

Conclusions: Here we report the pharmacological and initial behavioral characterization of two enantiomers of a novel 5-HT2A/2B antagonist with 5-HT2C agonist activity that may have therapeutic efficacy to treat impulsive and compulsive behavioral disorders such as

psychostimulant (amphetamines) abuse/addiction, as well as, binge eating, and, to treat psychoses without the adverse side effect of weight gain.

Keywords: animal models antipsychotic medication development serotonin 2C agonist serotonin 2A antagonist

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