Lysergide May Enhance Neuroplasticity by Post-Dose Upregulation of TrkB Compared to Other Compounds

Submission ID 3005851

Submission Type Poster/Individual Research Report

Topic Drug Discovery and Development

Status Submitted

Submitter Julie Tripp, MS RVT DABT

Affiliation Mind Medicine Inc.

SUBMISSION DETAILS

Request for Proposals Psychedelics

Abstract: Introduction: Psychoactive compounds that produce transient alterations in perception, cognition, and emotion partially through agonism of the serotonergic receptors (5-HT, especially 5-HT2A) are categorized as psychedelics. It was recently reported that lysergic acid diethylamide (LSD) and psilocin also directly bind to the TrkB receptor.1 MM120 (lysergide D-tartrate, a formulation of LSD) is under development as a potential treatment for generalized anxiety and major depressive disorders. As TrkB mediates brain-derived neurotrophic factor (BDNF) driven neuroplasticity, we evaluated the interaction of the TrkB receptor and several serotonergic drugs that are considered psychedelic as a key target of neuroplasticity.1-2
Methods: Activation of TrkB by BDNF was assessed by measuring inositol monophosphate 1 (IP1) accumulation. NIH/3T3 cells stably expressing human TrkB were used. Natural TrkB ligand BDNF served as positive control. We tested LSD, psilocin, N,N-dimethyltryptamine (DMT), mescaline, 2,5-dimethoxy-4-iodoamphetamine (DOI), N-2-methoxybenzyl-phenethylamine (25B-NBOMe), 4-bromo-2,5-dimethoxyphenethylamine (2C-B), methylenedioxyamphetamine (MDA), and the selective serotonin reuptake inhibitor fluoxetine. The same cells were treated with varying BDNF concentrations, combined with test drugs at fixed concentrations to assess potential allosteric modulation of TrkB activation. In a separate experiment, we assessed potential TrkB upregulating effects of LSD due to its partial antagonism.

Results: As expected, BDNF was highly potent at the TrkB receptor, activating it in the sub-picomolar range (EC50 0.2 pM). LSD, 25B-NBOMe, and fluoxetine activated TrkB (EC50 of 811, 26370, and 6040 pM respectively) with low maximal efficacies (40, 57, and 60% respectively). Psilocin, DMT, DOI, MDA, and 2C-B did not activate TrkB at concentrations up to 1 mM or, in the case of psilocin, activated it with very low efficacy.

Cotreatment with BDNF and a fixed concentration of LSD increased BDNF-induced TrkB activation (EC50 0.06 pM) and reduced activation efficacy to 60%. The other drugs tested reduced activation potency, as well as the maximal receptor activation. Fluoxetine and 25B-NBOMe did not generate

activation curves. All drugs partially antagonized the effect of BDNF at the TrkB receptor. This antagonistic effect may lead to the observed induction of neuroplasticity. Pretreatment with LSD led to reduced activation potency and efficacy of BDNF after recovery for 18 and 24 hours. After 30 hours of recovery, BDNF was similarly potent but around 30% more effective in activating TrkB than without LSD treatment. Hence, LSD seems to induce TrkB upregulation, which could lead to the described neuroplastic effects observed by other research groups.

Conclusions: LSD, 25B-NBOMe, and fluoxetine activated TrkB at pharmacologically relevant concentrations as partial agonists and psilocin, DMT, DOI, MDA, and 2C-B did not. The combination of BDNF with fixed concentrations of drugs described as psychedelic or fluoxetine led to reduced activation efficacy of BDNF. LSD increased the BDNF-induced TrkB activation. Pretreatment with LSD strongly increased the activation efficacy of BDNF at the TrkB receptor without changing the activation potency. Induced TrkB upregulation may underly and provide evidence for neuroplastic effects of LSD.

Learning Objectives:

Learning Objective 1 The TrkB receptor is a key target for neuroplasticity. Tested drugs activated TrkB with lower efficacy than BDNF and with potencies reflecting their in vivo potencies in humans.

Learning Objective 2 LSD, 25B-NBOMe, and fluoxetine, but not psilocin, DMT, mescaline, DOI, MDA, or 2C-B, activate TrkB as partial agonists.

DISCLOSURE

Financial Relationships

Disclosure Yes, I do have a financial relationship(s) to disclose.

Financial Relationships Details

Ineligible Company	Type of Financial Interest
Mind Medicine Inc.	Employee