Sestrin2 modulator NV-5138, shows ketamine-like rapid antidepressant effects via direct activation of mTORC1 signaling

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Introduction

In preclinical rodent models the antidepressant actions of ketamine are dependent on mTORC1 signaling. The mTORC1 pathway is modulated by neuronal activity, endocrine and metabolic signals, including amino acids, notably leucine, which activates mTORC1 signaling via binding to sestrin2 (Wolfson and Sabatini, 2017). Here, we examine the influence of NV-5138, a small molecule modulator of sestrin2 that penetrates the blood brain barrier and causes activation of mTORC1 on antidepressant behaviors and spine synapses in the prefrontal cortex (PFC).

The results demonstrate that a single dose of NV-5138 produced rapid antidepressant effects in rodent models and rapidly reversed the anhedonia caused by chronic unpredictable stress. The effects of NV-5138 were long-lasting (up to 7 days) following a single dose. As expected, NV-5138 activated mTORC1 and the antidepressant actions of NV-5138 were blocked by inhibition of the selective mTORC1 inhibitor rapamycin into mPFC. We also found that NV-5138 rapidly increased the number and function of spine synapses of mPFC apical dendrites. Taken together, the results demonstrate that NV-5138 produces rapid synaptic and antidepressant behavioral responses via direct activation of mTORC1 signaling, supporting the possibility that sestrin2 modulation is a novel target for development of rapid acting antidepressants.

Materials & Methods

Animals: Male Sprague-Dawley rats were used. NV-5138 was dosed in 0.9% (w/v) saline and administered orally in a volume of 10 ml/kg body weight. All procedures were approved by the Yale University Animal Care and Use Committees.

Surgery and intracranial infusions: Rats were anesthetized with 80 mg ketamine/kg i.p. and administered daily for 3 days. Rats were fitted with a stereotaxic instrument and recumbent in a small cage with wire mesh floor. The rat was placed in a stereotaxic instrument (David Kopf) and a small bone flap was made in the skull over the injection site. A 26-gauge needle was inserted into the skull and the NV-5138 solution was infused into the lateral ventricle at a rate of 5 μl/min for 20 min. The solution was then removed, and the needle was left in place for an additional 5 min. The needle was then removed, and the incision was closed with surgical thread. The rats were then allowed to recover for at least 1 h before recording. Pyramidal neurons in layer V were patched under visual control using a patch pipette filled with pontamine sky blue dye and a high-impedance patch pipette (4 MΩ to 6 MΩ).

Behavioral testing: Conventional open field tests were used to determine the behavior of rats in response to NV-5138. Animals were placed in an open field and allowed to explore for 30 min. The number of beam breaks and number of footstrokes were counted and recorded using an automated system.

Fig. 1. NV-5138 shows ketamine-like antidepressant actions in rodent models of depression

Results

1. NV-5138 increases synaptic proteins, spine number, and hypocretin- and 5-HT-induced EPSCs in mPFC pyramidal neurons

2. NV-5138 reverses the behavioral and synaptic deficits caused by CUS

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