Figure 1. Either a μ -opioid receptor partial agonist, a full 5-HT_{2C} receptor (5-HT_{2C}R) agonist, or a combination may afford gains in reducing relapse vulnerability and extending abstinence in opioid use disorder (OUD). Partial agonist actions at the μ -opioid receptor reduce the rewarding effects of opioids and withdrawal. The selective 5-HT_{2C}R full agonist lorcaserin suppresses oxycodone intake and associated cue reactivity as well as impulsivity. Low-dose combinations of a μ -opioid receptor partial agonist plus the non-opioid lorcaserin may provide an additional new avenue to support recovery in OUD patients. While the brain locus for a potential receptor–receptor interaction is unknown, both the μ -opioid receptor and 5-HT_{2C}R are co-expressed in nodes of the limbic-corticostratial circuitry engaged in drug reward and relapse vulnerability. The FDA-approved OUD medication buprenorphine is a μ -opioid receptor partial agonist, but is not selective given its complex actions at δ -, κ -, and nociceptin/opioid receptor-like receptors (NOP or ORL-1) (Lutty and Cowan, 2004). Thus, other μ -opioid partial agonists may be needed to test the hypothesis that low-dose combinations with lorcaserin may add value in OUD medication-assisted therapy.

precipitated withdrawal following chronic opioid exposure in mice (Wu *et al.*, 2015). Thus, the non-opioid medication lorcaserin acts as a 5-HT_{2C}R agonist to influence aspects of opioid-evoked behaviors, suggesting that the 5-HT_{2C}R system may play a key role in the shared mechanisms for addiction and relapse vulnerability across psychostimulant and opioid drug classes.

The development of pain medications with analgesic efficacy, but reduced abuse liability, remains a high priority. Of equally high priority is the identification of therapeutic interventions that increase the maintenance of abstinence after cessation of opioid intake, even in high drug cue environments. A selective 5-HT_{2C}R agonist, such as lorcaserin, may provide a new avenue to add value to the outcomes of medication-assisted treatment in OUD (Figure 1). The next step is to expand the present data set to definitively test the hypotheses that lorcaserin inhibits opioid withdrawal and countermands stress- and/or opioid-triggered relapse

events, for example. It is also possible that low doses of lorcaserin administered in combination with a partial μ -opioid agonist, with limited abuse liability but efficacy to suppress opioid-induced euphoria and withdrawal may reduce relapse risk via regulation of two signaling pathways. The neurochemical mechanisms and sites of action for 5-HT_{2C}R systems to control opioid-related behaviors are also of interest. Finally, preclinical studies to evaluate low-dose combinations of a partial μ -opioid agonist plus lorcaserin will provide insight into the potential for translational value in clinical trials geared to reduce the devastation of opioid overdose and OUD.

FUNDING AND DISCLOSURE

Drs Moeller and Cunningham are supported by grants NIDA U54 DA038999 and NIDA P50 DA033935. Dr Moeller is an uncompensated consultant for INDIVIOR and receives research support from Boehringer-

Ingelheim. Dr Cunningham declares no conflict of interest.

ACKNOWLEDGMENTS

We thank Ms Christina Merritt for the design of the figure.

F Gerard Moeller¹ and Kathryn A Cunningham²

¹Department of Psychiatry, Institute for Drug and Alcohol Studies, Virginia Commonwealth University, Richmond, VA, USA; ²Department of Pharmacology and Toxicology, Center for Addiction Research, University of Texas Medical Branch, Galveston, TX, USA

E-mail: frederick.moeller@vcuhealth.org or kcunning@utmb.edu

Cunningham KA, Anastasio NC (2014). Serotonin at the nexus of impulsivity and cue reactivity in cocaine addiction. *Neuropharmacology* **76 Pt B**: 460–478.

Lutty K, Cowan A (2004). Buprenorphine: a unique drug with complex pharmacology. *Curr Neuropsychopharmacol* **2**: 395–402.

Neelakantan H, Holliday ED, Fox RG, Stutz SJ, Comer SD, Haney M *et al* (2017). Lorcaserin suppresses oxycodone self-administration and relapse vulnerability in rats. *ACS Chem Neurosci* **8**: 1065–1073.

Shanahan WR, Rose JE, Glicklich A, Stubbe S, Sanchez-Kam M (2016). Lorcaserin for smoking cessation and associated weight gain: a randomized 12-week clinical trial. *Nicotine Tob Res* 2016 Nov 4. pii: ntw301. (e-pub ahead of print).

Volkow ND, Frieden TR, Hyde PS, Cha SS (2014). Medication-assisted therapies—tackling the opioid-overdose epidemic. *N Engl J Med* **370**: 2063–2066.

Wu X, Pang G, Zhang YM, Li G, Xu S, Dong L *et al* (2015). Activation of serotonin 5-HT_{2C} receptor suppresses behavioral sensitization and naloxone-precipitated withdrawal symptoms in heroin-treated mice. *Neurosci Lett* **607**: 23–28.

Neuropsychopharmacology Reviews (2018) **43**, 220–221. doi:10.1038/npp.2017.192

The Ketamine Metabolite 2R,6R-Hydroxynorketamine Blocks NMDA Receptors and Impacts Downstream Signaling Linked to Antidepressant Effects

Clinical studies have demonstrated a reproducible rapid antidepressant effect of low-dose ketamine in patients

with depressive symptoms. However, ketamine's dissociative side effects and abuse potential has led to the search for identification of alternative compounds that trigger rapid antidepressant effects without the psychotomimetic side effects. A successful effort will require elucidation of the molecular mechanisms that elicit the antidepressant effects of ketamine. In 2011, our group proposed a synaptic signaling pathway that can account for ketamine's antidepressant-like effects in preclinical animal models (Autry *et al*, 2011). Specifically, we showed that ketamine-mediated block of resting synaptic NMDA receptor (NMDAR) activity—driven by spontaneous glutamate release—leads to deactivation of eEF2 kinase resulting in dephosphorylation of its sole known target eEF2. The dephosphorylation of eEF2 results in desuppression of dendritic protein translation and a rapid subsequent increase in brain-derived neurotrophic factor (BDNF) expression. Released BDNF activates TrkB receptors and triggers a subsequent potentiation of AMPA receptor (AMPA)-mediated synaptic transmission in the hippocampus, providing a synaptic basis for the antidepressant effects of ketamine (Autry *et al*, 2011; Nosyreva *et al*, 2013). Consistent with the premise, ketamine's antidepressant effects have previously been shown to require AMPARs as NBQX, an AMPAR antagonist, attenuates the antidepressant effects in rodents (Maeng *et al*, 2008; Autry *et al*, 2011). Importantly, the model we proposed can account for the ineffectiveness of the NMDAR blocker memantine as an antidepressant in the clinic, as memantine—unlike ketamine—has a limited ability to block resting NMDAR function. However, a recent study challenged a key component of the model by suggesting that ketamine's antidepressant action is mediated by its metabolite 2R,6R-hydroxynorketamine (2R,6R-HNK), via the same signaling pathway and AMPAR-mediated synaptic potentiation as outline above (Autry *et al*, 2011) but in a NMDAR-independent manner (Zanos *et al*, 2016). Validation of the same

signaling pathway and effects on AMPAR-mediated potentiation—sans NMDAR block—prompted us to investigate the impact of 2R,6R-HNK on NMDAR-mediated neurotransmission. In recent experiments, we showed that 2R,6R-HNK can swiftly inhibit NMDAR transmission up to 50% at concentrations needed to trigger the intracellular signaling pathway involved in the potentiation of synaptic AMPAR responses, strongly supporting a role for NMDAR-blockade in this effect (Suzuki *et al*, 2017). Further characterization showed that the effect of 2R,6R-HNK on individual NMDA-mEPSCs mimicked those of ketamine, demonstrating that 2R,6R HNK—like ketamine—selectively inhibits NMDARs while they are open (Suzuki *et al*, 2017). Our study demonstrated that 50 μ M 2R,6R-HNK blocks synaptic NMDARs and thus 2R,6R-HNK is not 'NMDAR-independent' in its action. Although we used a higher concentration than the 10 μ M 2R,6R-HNK—suggested as the brain concentration in rodents following a behaviorally effective antidepressant dose of 10 mg/kg 2R,6R-HNK (Zanos *et al*, 2016)—a recent study was not able to detect antidepressant effects of 10 mg/kg 2R,6R-HNK in the same behavioral paradigms (Yang *et al*, 2017) used by Zanos and colleagues, raising questions about the dose of 2R,6R-HNK necessary to mediate antidepressant effects and the brain concentration necessary to trigger the molecular pathway. Moreover, a mechanism, other than the demonstrated NMDAR-blockade of 2R,6R-HNK, remains to be demonstrated. The selective action of 2R,6R-HNK on open NMDARs indicate its efficacy as an antidepressant will strongly depend on factors that impact synaptic NMDAR channel opening. These factors may include glutamate release-probability, subunit composition of synaptic NMDARs, as well as levels of coagonists. Future studies will need to take into account these synaptic factors to elucidate the specific circuits involved in the antidepressant action of ketamine as well as 2R,6R-HNK. Overall, our findings demonstrate a critical

role of NMDAR-block-mediated signaling in triggering the antidepressant effects of ketamine and 2R,6R-HNK.

FUNDING AND DISCLOSURE

This work was supported by National Institutes of Health Grants MH070727 (LMM) and MH066198 (ETK). LMM is a consultant for Fortress Biotech. ETK declares no conflict of interest.

Ege T Kavalali¹ and Lisa M Monteggia¹

¹Department of Neuroscience, the University of Texas Southwestern Medical Center, Dallas, TX, USA
E-mail: lisa.monteggia@utsouthwestern.edu

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng P *et al* (2011). NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* **275**: 91–95.

Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G *et al* (2008). Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry* **63**: 349–352.

Nosyreva E, Szabla K, Autry AE, Ryazanov AG, Monteggia LM, Kavalali ET (2013). Acute suppression of spontaneous neurotransmission drives synaptic potentiation. *J Neurosci* **33**: 6990–7002.

Suzuki K, Nosyreva E, Hunt KW, Kavalali ET, Monteggia LM (2017). The ketamine metabolite hydroxynorketamine impacts downstream signaling via NMDA receptor inhibition. *Nature* **546**: E1–E3.

Yang C, Qu Y, Abe M, Nozawa D, Chaki S, Hashimoto K (2017). (R)-Ketamine shows greater potency and longer lasting antidepressant effects than its metabolite (2R,6R)-hydroxynorketamine. *Biol Psychiatry* **82**: e43–e44.

Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI *et al* (2016). NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* **533**: 481–486.

Neuropsychopharmacology Reviews (2018) **43**, 221–222.
doi:10.1038/npp.2017.210

Cognitive Signaling in Cerebellar Granule Cells

The cerebellum contains over three quarters of the neurons in the human brain (Herculano-Houzel, 2010), but it has traditionally been studied mainly in sensorimotor contexts. Yet in humans, cerebellar circuits activate during and are required for verbal and spatial processing tasks (eg, Stoodley *et al* (2012)), and multiple lines of evidence point to cerebellar links