OXFORD

International Journal of Neuropsychopharmacology (2017) 20(4): 359–361

doi:10.1093/ijnp/pyw117
Advance Access Publication: February 6, 2017
Focus Paper

FOCUS PAPER

Structural Integrity in the Sustained Antidepressant Effect of Ketamine

Pauline Belujon

INSERM, U1084, F-86022 Poitiers, France; Université de Poitiers, U1084, F-86022 Poitiers, France.

Keywords: ketamine, perineuronal nets, hippocampus, forced swim test, animal models

The discovery of antidepressant properties of ketamine has been one of the most striking revolutions in treatment-resistant depression in the last decade. The noncompetitive, glutamatergic N-methyl-d-aspartate receptor (NMDAR) antagonist exerts rapid (2 to 3 hours) and sustained (up to 2 weeks) antidepressant effects after a single dose in depressed patients (Berman et al., 2000; Zarate et al., 2006). The mechanisms of the rapid actions of ketamine are different from the majority of approved antidepressant for MDD, which act through the monoaminergic systems.

In patients, major depressive disorder (MDD) is associated with gray matter abnormalities and decreased volume in the prefrontal cortex (PFC) and the hippocampus (Price and Drevets, 2010; Kempton et al., 2011; MacQueen and Frodl, 2011), which is thought to be associated with a loss of dendrites and their synapses (Kassem et al., 2013). Neuroimaging studies in humans highlighted a specific role of the PFC in MDD. In particular, there is reduced function in the PFC (Price and Drevets, 2010), which is reversed by ketamine administration (Abdallah et al., 2016). It is now well known that ketamine rapidly increases glutamate transmission, particularly in the PFC, and multiple hypotheses have emerged as to which specific processes are involved in this rapid and sustained effect (Miller et al., 2016). One hypothesis posits that antagonism of NMDARs expressed in PFC pyramidal neurons induces disruption of basal activation of NMDARs, resulting in increased synthesis of synaptic proteins, which will ultimately induce a compensatory homeostatic synaptic plasticity leading to an increase in excitatory synaptic input (for review, see Miller et al., 2016). The other hypothesis posits that ketamine exerts its antidepressant effect through disinhibition of pyramidal neurons in the PFC. In particular, it is suggested that ketamine antagonizes NMDA receptors preferentially on cortical inhibitory neurons (Quirk et al., 2009), which would lead to disinhibition of pyramidal cortical neurons, inducing an LTP-like synaptic plasticity. Evidence supporting this hypothesis is the involvement of the loss of phenotype of parvalbumin (PV) cortical interneurons, as well as the GABA-producing enzyme GAD67 in the antidepressant effect of ketamine (Behrens et al., 2007; Zhou et al., 2015). The majority of studies investigating the cellular mechanisms of the antidepressant effect of ketamine have focused primarily on the PFC. However, functional imaging studies in MDD patients provided some information about dysfunctions of brain structure connectivity, highlighting reductions of connectivity between the PFC and the hippocampus, suggesting disruption of reciprocal connections between these 2 structures (Price and Drevets, 2010). Previous studies using the chronic mild stress animal model of depression have shown a decrease in PV-containing interneurons in the hippocampus, which was reversed by antidepressant treatment (Czeh et al., 2005). Recent studies have suggested that the perineuronal nets (PNN), a unique extracellular matrix prominently displayed around PV-expressing GABAergic interneurons, are involved in the regulation of synaptic plasticity (McRae and Porter, 2012). Considering that the hippocampus-PFC pathway has been shown to be involved in the antidepressant effect of ketamine (Carreno et al., 2016), it is suggested that PNN in the hippocampus might be involved in ketamine antidepressant properties, which is examined in the study by Donegan and Lodge in this issue (Donegan and Lodge, 2016).

Donegan and Lodge provide new evidence in the disinhibition hypothesis in the antidepressant effect of ketamine. In particular, the authors identify the involvement of PNN in the hippocampus in the sustained effect of ketamine. The authors studied changes in time spent immobile in the forced swim test after degradation of PNN with a chondroitinase treatment, 30 minutes and 1 week after ketamine administration. In control animals, after acute ketamine administration, a decrease in immobility was observed in both chondroitinase-treated and nontreated rats, suggesting that the acute effect of ketamine is not dependent on PNN function. In contrast, 1 week after

Received: December 20, 2016; **Accepted:** December 23, 2016

ketamine administration, ketamine had no effect on immobility time in chondroitinase-treated animals, suggesting that the sustained effect of ketamine is dependent on the integrity of a local inhibitory circuit in the hippocampus. While these data give another possible foundation in the involvement of GABAergic interneurons in the antidepressant effect of ketamine, there are some caveats that should be considered. First, Donegan and Lodge (2016) approached the role of an extracellular matrix structure, linked to PV-interneuron function, in the antidepressant effect of ketamine by using the forced swim test. In this procedure, immobility induced by exposure to an inescapable situation is an index of behavioral despair in normal animals. The FST is considered a predictive model of antidepressant activity when administered to normal rats, not a model of depression per se, since it lacks face and construct validity (Nestler and Hyman, 2010). Indeed, a "depressive state" is not induced, but rather a direct response to the test itself is observed. Moreover, this test was performed in normal rats, not in rats that had been exposed to a depression model. This is particularly important since, while providing important insights into the normal function and system-wide effects of drugs, this test does not model some of the pathophysiology of depression, which is crucial to understand specific effects of ketamine as an antidepressant. MDD is a complex pathology with modifications in different signaling pathways, neuroendocrine regulations, synaptic plasticity, synaptogenesis, or neurogenesis (for review, see Krishnan and Nestler, 2008). To study cellular effects of a novel antidepressant that are relevant for human pathology, the model used should meet a complex set of criteria of validity. For example, it is now well known that ketamine induces rapid enhancement of synaptic structure and function in cortical regions, in parallel with antidepressant behavioral effect in animal models (Li et al., 2011). In animals, the chronic mild stress, a model of depression showing high face, construct, and predictive validity, is associated with neuronal atrophy and synaptic depression in the PFC (Liu and Aghajanian, 2008; Li et al., 2011). Furthermore, in learned helplessness, ketamine was found to act, at least in part, on a disrupted hippocampal-accumbens circuit (Belujon and Grace, 2014), a condition that is not present in the normal animal (Carreno et al., 2016). These alterations of plasticity, acutely and sustainably reversed by ketamine, involve neurotrophic factors such as brain-derived neurotrophic factor (Bramham and Messaoudi, 2005), which, coexpressed with NMDAR, plays a crucial role in excitatory synaptic synaptogenesis (Yoshii and Constantine-Paton, 2010). Then, it is likely that the intricate structural changes observed in MDD and animal models of depression with high face and construct validity might be of great importance in understanding the complexity by which ketamine exerts its acute and sustained antidepressant effect. Therefore, although PNNs are suggested to be involved in synaptic integrity and plasticity and likely play a critical role in normal system function, their role in MDD is not clearly established. Consequently, whereas the use of a simple bioassay might give certain information on possible mechanisms of a novel treatment, its use is limited in its ability to outline the multiple neural circuits, symptom dimensions, and structural changes described in depression. Moreover, whereas the hypothesis in this study posits that degradation of PNN disrupts the function of PV interneurons regulating the projecting neurons from the hippocampus to the PFC, this remains to be elucidated.

There is no question that this study provides new insights into the role of PNN of the hippocampus and its functional impact in the normal function of hippocampal-prefrontal cortical interactions. Moreover, the study may provide a unique insight into the sustained effect of ketamine on normal systems. In the future, using adequate animal models of depression and behavioral assessments, this study by Donegan and Lodge will likely open new doors for studies of the structural integrity of neurons in the hippocampus, and its possible influence on cortical information processing, in understanding some of the mechanisms of the sustained antidepressant effect of ketamine.

Acknowledgments

This work was supported by the Agence Nationale de la Recherche Grant No. ANR-15-CE37-0010.

Statement of Interest

None.

References

Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, DeWilde KE, Wong E, Anticevic A, Tang CY, Iosifescu DV, Charney DS, Murrough JW (2016) Ketamine treatment and global brain connectivity in major depression. Neuropsychopharmacology doi: 10.1038/npp.2016.186.

Behrens MM, Ali SS, Dao DN, Lucero J, Shekhtman G, Quick KL, Dugan LL (2007) Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase. Science 318:1645–1647.

Belujon P, Grace AA (2014) Restoring mood balance in depression: ketamine reverses deficit in dopamine-dependent synaptic plasticity. Biol Psychiatry 76:927–936.

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–354.

Bramham CR, Messaoudi E (2005) BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol 76:99–125.

Carreno FR, Donegan JJ, Boley AM, Shah A, DeGuzman M, Frazer A, Lodge DJ (2016) Activation of a ventral hippocampus-medial prefrontal cortex pathway is both necessary and sufficient for an antidepressant response to ketamine. Mol Psychiatry 21:1298–1308.

Czeh B, Simon M, van der Hart MG, Schmelting B, Hesselink MB, Fuchs E (2005) Chronic stress decreases the number of parvalbumin-immunoreactive interneurons in the hippocampus: prevention by treatment with a substance P receptor (NK1) antagonist. Neuropsychopharmacology 30:67–79.

Donegan JJ, Lodge DJ (2017) Hippocampal perineuronal nets are required for the sustained antidepressant effect of ketamine. Int J Neuropsychopharmacol. In press.

Kassem MS, Lagopoulos J, Stait-Gardner T, Price WS, Chohan TW, Arnold JC, Hatton SN, Bennett MR (2013) Stress-induced grey matter loss determined by MRI is primarily due to loss of dendrites and their synapses. Mol Neurobiol 47:645–661.

Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, Williams SC (2011) Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 68:675–690.

Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455:894–902.

Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS (2011) Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic

deficits caused by chronic stress exposure. Biol Psychiatry 69:754–761.

Liu RJ, Aghajanian GK (2008) Stress blunts serotonin- and hypocretin-evoked EPSCs in prefrontal cortex: role of corticosterone-mediated apical dendritic atrophy. Proc Natl Acad Sci U S A 105:359–364.

MacQueen G, Frodl T (2011) The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? Mol Psychiatry 16:252–264.

McRae PA, Porter BE (2012) The perineuronal net component of the extracellular matrix in plasticity and epilepsy. Neurochem Int 61:963–972.

Miller OH, Moran JT, Hall BJ (2016) Two cellular hypotheses explaining the initiation of ketamine's antidepressant actions: direct inhibition and disinhibition. Neuropharmacology 100:17–26.

Nestler EJ, Hyman SE (2010) Animal models of neuropsychiatric disorders. Nat Neurosci 13:1161–1169.

Price JL, Drevets WC (2010) Neurocircuitry of mood disorders. Neuropsychopharmacology 35:192–216.

Quirk MC, Sosulski DL, Feierstein CE, Uchida N, Mainen ZF (2009) A defined network of fast-spiking interneurons in orbitofrontal cortex: responses to behavioral contingencies and ketamine administration. Front Syst Neurosci 3:13.

Yoshii A, Constantine-Paton M (2010) Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. Dev Neurobiol 70:304–322.

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of general psychiatry 63:856–864.

Zhou Z, Zhang G, Li X, Liu X, Wang N, Qiu L, Liu W, Zuo Z, Yang J (2015) Loss of phenotype of parvalbumin interneurons in rat prefrontal cortex is involved in antidepressant- and propsychotic-like behaviors following acute and repeated ketamine administration. Mol Neurobiol 51:808–819.