Neuropharmacology xxx (2018) 1–11

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity

Rachael Ingram [a], Heather Kang [b, c, d], Stafford Lightman [b], David E. Jane [c], Zuner A. Bortolotto [c], Graham L. Collingridge [c, d], David Lodge [c, 1], Arturas Volianskis [a, b, *, 1]

[a] Centre for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK
[b] School of Clinical Sciences, University of Bristol, Bristol, UK
[c] Centre for Synaptic Plasticity, School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK
[d] Dept Physiology, University of Toronto and Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

ARTICLE INFO

Article history:
Received 7 April 2018
Received in revised form
27 May 2018
Accepted 5 June 2018
Available online xxx

Keywords:
Psychedelics
Ketamine
Phencyclidine
PCP
NMDA receptors
GluN2D subunit
Short-term potentiation
STP
Long-term potentiation
LTP
Memory
Working memory

ABSTRACT

Ketamine, a channel blocking NMDA receptor antagonist, is used off-label for its psychedelic effects, which may arise from a combination of several inter-related actions. Firstly, reductions of the contribution of NMDA receptors to afferent information from external and internal sensory inputs may distort sensations and their processing in higher brain centres. Secondly, reductions of NMDA receptor-mediated excitation of GABAergic interneurons can result in glutamatergic overactivity. Thirdly, limbic cortical disinhibition may indirectly enhance dopaminergic and serotonergic activity. Fourthly, inhibition of NMDA receptor mediated synaptic plasticity, such as short-term potentiation (STP) and long-term potentiation (LTP), could lead to distorted memories. Here, for the first time, we compared quantitatively the effects of ketamine on STP and LTP. We report that ketamine inhibits STP in a double sigmoidal fashion with low (40 nM) and high (5.6 μM) IC_{50} values. In contrast, ketamine inhibits LTP in a single sigmoidal manner (IC_{50} value ~ 15 μM). A GluN2D-subunit preferring NMDA receptor antagonist, UBP145, has a similar pharmacological profile. We propose that the psychedelic effects of ketamine may involve the inhibition of STP and, potentially, associated forms of working memory.

Contents

* Corresponding author. Centre for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, 4 Newark Street, London, E1 2AT, UK.
E-mail addresses: A.Volianskis@qmul.ac.uk, A.Volianskis@bristol.ac.uk (A. Volianskis).
[1] DL and AV are joint senior authors.

https://doi.org/10.1016/j.neuropharm.2018.06.008
0028-3908/

1. Introduction

Shortly after the synthesis in the 1950s of phencyclidine (PCP) (Maddox et al., 1965) and later of ketamine (McCarthy et al., 1965), it became apparent that these two anaesthetics produced some bizarre central effects in both laboratory animals (Chen et al., 1959) and in man (Greifenstein et al., 1958; Meyer et al., 1959). The drugs produced a state of anaesthesia and analgesia with a good safety margin before lethality but poor muscle relaxation (White et al., 1982). This unusual anaesthetic state was termed 'dissociative' after both the disrupted electroencephalographic patterns and the sensory deprivation with detachment from the real world (Domino et al., 1965; see Domino and Luby, 2012). The central effects, following either PCP or ketamine, include dizziness, nausea, delirium, confusion, disorientation, paranoia, amnesia, dysarthria, dysphoria with agitation, unpredictable aggression and delusions of extreme strength (Allen and Young, 1978; Domino et al., 1965; Luisada, 1978; Siegel, 1978a). Both drugs were known as psychotomimetics from the outset (Luby et al., 1959), and have been used to create animal models of schizophrenia (Cadinu et al., 2017; Frohlich and Van Horn, 2014; Javitt et al., 2012) but can they also be defined as psychedelics? Psychedelics are *'drugs (especially LSD [lysergic acid diethylamide] that produce hallucinations and apparent expansion of consciousness'* and hallucinations are experiences *'involving the apparent perception of something not present'* (Oxford English Dictionary). There are hundreds of reports of hallucinations, visual, auditory and somatosensory, following exposure to ketamine and PCP.

For example, a recreational user of ketamine reported: '*… when I closed my eyes a lot of information started to happen. Colors, patterns, cross-connections in sensory perception. Like sound and inner visions sort of got confused. I got deeper and deeper into this state of realization, until at one point the world disappeared. I was no longer in my body. I didn't have a body. And I reached a point at which I knew I was going to die …. .And what incredible feelings that evoked! . . . . .I just yielded. And then I entered a space in which . . .there aren't any words ….I mean, at-one-with-the-universe, recognizing-your-godhead ….The feeling was: I was home. That's really the feeling of it. And I didn't want to go anywhere, and I didn't need to go anywhere. It was a bliss state. Of a kind I had never experienced before. I hung out there awhile, and then I came back. I didn't want to come back. I guess in the deep state it was no longer than half an hour* '. Stafford (1977), quoted in (Siegel, 1978b) who also quotes Young et al. (1977) likening *'this state to an LSD trip, only the ketamine tripper "feels as if he is floating in a dreamlike state while experiencing vivid visual images"'*. In fact, there are numerous reports noting similarities between experiences with LSD and ketamine. But ketamine, unlike classical psychedelics such as LSD, psilocybin, mescaline and dimethyltryptamine (DMT), is not a serotonin receptor agonist and its central effects in man can be distinguished from those of LSD, as described on psychonaut websites. In humans, serotonin-based hallucinogens and dissociative anaesthetics have psychedelic features in common, as well as abuse potential, and their mode of action may be linked by direct or indirect agonism of 5-HT_2 receptors (Heal et al., 2018; Sellers et al., 2017). In a standard psychometric test which scores five separate dimensions of altered states of consciousness (Dittrich, 1998), a classical psychedelic and ketamine showed similarities but clear differences (Vollenweider and Kometer, 2010). The profile following ketamine was skewed toward the dimensions of 'disembodiment' and 'experience of unity'. Furthermore, in behavioural studies in laboratory animals, the effects of LSD and PCP/ketamine are easily discriminated, suggesting a quite different mode of action (Carroll, 1990; Jones and Balster, 1998; West et al., 2000).

Drug discrimination studies in rats, monkeys, pigeons, etc, have, however found many drugs that do generalize to the PCP and ketamine cues. In the early 1980s, it became apparent that PCP and ketamine provided similar cues to other arylcyclohexylamines such as tiletamine, to benzomorphan sigma opiates such as SKF10,047 and cyclazocine, to dioxalanes such as dexoxadrol and etoxadrol, to morphinans such as dextrorphan and dextromethorphan, to benz(f)isoquinolines and to propanolamines such as 2-MDP (Brady and Balster, 1981; Brady et al., 1982a, 1982b; Herrling et al., 1981; Holtzman, 1982, 1980; Mendelsohn et al., 1984; Shannon, 1982a, 1982b; 1981; Tang et al., 1984; White and Holtzman, 1982). Such a list of compounds coincides with those also shown to displace PCP binding from rat brain tissue (Hampton et al., 1982; Murray and Leid, 1984; Quirion et al., 1981; Sircar and Zukin, 1983; Vincent et al., 1979; Zukin and Zukin, 1981; Zukin, 1982; Zukin et al., 1984; Zukin and Zukin, 1979).

Several of these compounds were already known to have similar bizarre subjective effects in man including hallucinations and were generally known as psychotomimetics (see Lodge and Mercier, 2015 for many of the chemical structures). Thus, beside arylcyclohexylamines PCP and ketamine (see above), the morphinans, dextromethorphan and dextrorphan, were originally described as producing 'toxic symptoms (dizziness, diplopia, etc)' (Isbell and Fraser, 1953). Benzomorphans including the 'sigma agonists', SKF 10.047 (Keats and Telford, 1964) and cyclazocine produce 'dose-related scores on the LSD scale' (Haertzen, 1970 quoted by Jasinski et al., 1967) and fuzzy thinking, illusions, dysphoria and frank visual hallucinations like LSD (Freedman and Fink, 1968; Jasinski et al., 1967); such features were considered to be mediated by the sigma opiate receptor (Martin et al., 1976). The dioxalanes, dexoxadrol (Lasagna and Pearson, 1965), and etoxadrol, induced 'dreams and/or visions that were pleasing.' (Frederickson et al., 1976).

Further contemporary support for this psychedelic effect of such compounds comes from a cursory examination of the web sites frequented by so-called psychonauts. This reveals that drugs such as ketamine, dextromethorphan, 2-MDP and compounds related to them are still frequently being used by humans. To avoid legal issues associated with ketamine use, new drugs for example, methoxetamine and arylethylamines, such as ephenidine, have come on to the market (Kang et al., 2016; Morris and Wallach, 2014; Wallach et al., 2016). During the last two weeks of January 2018, for example on one website, there were 35 reports of experiences with these and similar drugs (https://erowid.org/experiences/exp.cgi?New).

2. Sites of action of ketamine and PCP

So do these compounds have a mechanism of action in common with classical psychedelics such as LSD, mescaline, psilocybin and dimethyltryptamine, which are all serotonergic ligands? It is generally believed that their agonist effect on 5-HT_2 receptors, particularly 5-HT_{2A} receptors, is the basis for their psychedelic effects (Nichols, 2004; Vollenweider and Kometer, 2010). Activation of 5-HT_{2A} receptors also increases glutamate release and firing of pyramidal neurones in the cerebral cortex by both pre-and post-synaptic mechanisms (Marek and Aghajanian, 1999; Vollenweider and Kometer, 2010), a finding in common with ketamine (discussed below). One group of authors have suggested that ketamine and PCP hallucinogenic activity may result from agonism of 5-HT_2 and dopamine (D_2) receptors (Kapur and Seeman, 2002) but this appears not to be widely accepted and has not been proposed to explain the similar central effects of morphinans, benzomorphans, dioxalanes, etc. Conversely, activation of 5-HT_{2A} receptors has been proposed to antagonise some of the neurotoxic effects of ketamine and PCP (Farber et al., 1998).

Nicotinic and muscarinic acetylcholine receptors have also been

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

considered as part of ketamine's action with activity in the low micromolar range on α3β4, and α7 subtypes (Moaddel et al., 2013). Phencyclidine, dextromethorphan and dextrorphan have potencies of 7.0, 8.9 and 29.6 μM respectively on α3β4 nicotinic receptors (Hernandez et al., 2000). In addition, phencyclidine and dextromethorphan were significantly more potent than MK-801 and SKF10,047 as nicotinic antagonists (Yamamoto et al., 1992). Such data do not fit with the known potencies of these drugs in behavioural assays (see Lodge and Mercier, 2015). The stereoselectivity shown for example by dexoxadrol/levoxadrol and by the isomers of 3-methyl-PCP in behavioural assays (Browne and Welch, 1982; Marwaha et al., 1981) was not apparent in nicotine antagonism (Purifoy and Holz, 1984).

A similar argument pertains to sigma receptors. Several of the drugs producing ketamine-like psychedelic affects in man are also known as sigma agonists and their use as ligands for sigma receptors has confused the field. Nevertheless the prototypical agonists for both sigma1 and sigma2 receptors, namely haloperidol, (+)-3-PPP (*N*-*n*-propyl-3-(3-hydroxyphenyl)piperidine) and DTG (ditolylguanidine), do not have established psychedelic properties.

The common feature that does, however, link the above psychedelics is their ability to antagonise the actions of NMDA. Following the initial observations that ketamine and phencyclidine blocked both NMDA receptor-mediated polysynaptic reflexes (Lodge and Anis, 1984) and the direct agonist action of NMDA (Anis et al., 1983), the studies were extended to compounds that displace phencyclidine binding on CNS tissue and that generalize to phencyclidine cues in discrimination assays (for review and references see Lodge and Mercier, 2015). There were good correlations between potency of compounds as NMDA receptor antagonists and their potency in PCP binding assays and in drug discrimination assays (Lodge and Mercier, 2015). In particular, the stereoselectivity of compound pairs, such as dexoxadrol vs. levoxadrol, (+) vs (−)-3-methyl-PCP and (+) vs (−)-2-MDP, in both PCP binding and behavioural assays in laboratory rodents and primates was reproduced in tests of NMDA receptor antagonism (Lodge and Mercier, 2015). It seems therefore a very strong hypothesis that their psychedelic effects in man are explained by NMDA receptor antagonism. The above compounds do not act competitively as NMDA receptor antagonists (Lodge and Johnston, 1985; Martin and Lodge, 1985) but rather block the associated calcium-permeable channel function (MacDonald et al., 1987). In support of the above hypothesis, psychotomimetic effects have been reported in man following administration of competitive NMDA receptor antagonists (Davis et al., 2000; Grotta et al., 1995; Herrling, 1997; Muir, 2006).

3. Effects of ketamine on central information processing

So the question arises as to why does NMDA receptor antagonism induce psychedelic effects? Here we discuss three potential mechanisms based on NMDAR antagonism that individually or collectively could contribute to these effects.-

1. Direct and/or indirect activation of dopaminergic pathways has been proposed to underlie the psychotomimetic effects of ketamine and related compounds.
2. A reduction in synaptic transmission through afferent pathways in which NMDA receptors play an important role will alter the sensory input to primary, secondary and association cerebral cortices and result in marked changes in perceived images.
3. NMDA receptors play a critical role in synaptic plasticity, such as long term potentiation (LTP), short term potentiation (STP) and long term depression (LTD). So the encoding and recall of recent or ongoing events/experiences will be affected by changes in NMDA receptor-dependent synaptic plasticity.

3.1. Dopaminergic modulation

Hyperdopaminergic activity, probably via D_2 receptor activation, has long been considered part of the psychedelic effect of phencyclidine and ketamine (Wise, 1996). Typical and atypical antipsychotics are effective against their psychotomimetic effects (Freeman and Bunney, 1984). Ketamine is a weak agonist at D_2 receptors (Frohlich and Van Horn, 2014) and increases release and inhibits uptake of dopamine, and other monoamines (Garey and Heath, 1976; Vickroy and Johnson, 1982); burst firing of dopaminergic neurones essential for the release of dopamine, is dependent on NMDA receptor activation (Chergui et al., 1993; Zweifel et al., 2009). However, another major influence is likely to be disinhibitory changes in limbic control of dopaminergic neurones (Boley et al., 2014; Coyle et al., 2010; Jentsch and Roth, 1999; Moghaddam and Krystal, 2012; Nakazawa et al., 2012; Olney and Farber, 1995; Kokkinou et al., 2018; Lewis, 2014), as described below.

3.2. Altered sensory inputs

Disruption of signalling pathways, conveying information from sensory inputs to brain areas that are responsible for conscious perception, is an obvious candidate to explain psychedelic actions. Indeed, since the works of Edgar Adrian it has been known that sensory information is encoded in the frequency and number of action potentials (Adrian, 1928). Activity patterns of all central neurones are dependent on the balance between excitatory and inhibitory synaptic inputs, i.e. the complex temporal and spatial summation of the activity and efficacy of the afferents inputs to each neurone. The major transmitters mediating these excitatory

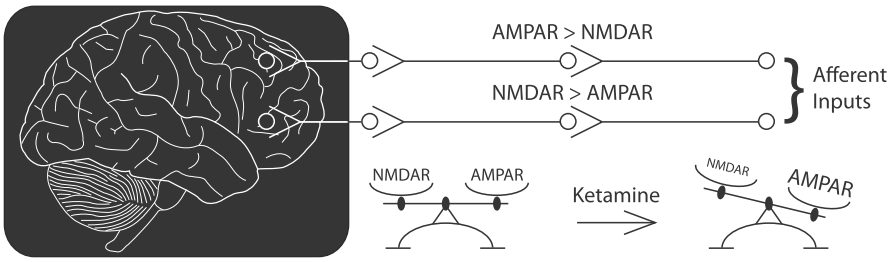

Fig. 1. The balance between NMDA and AMPA receptors. Information is transmitted from sensory receptors throughout the neuraxis by many excitatory synapses in afferent pathways. Each such glutamatergic synapse has both AMPA and NMDA receptors, the balance between relative contributions of each will depend on numerous factors. Such factors include the relative expression of each subtype, the nature of the subunits of these tetrameric receptors, temporal and spatial summation and postsynaptic membrane potential. Ketamine tips the balance and distorts the sensory information reaching higher centres by reducing the NMDA receptor contribution (D. Lodge ~1984, unpublished scheme).

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

and inhibitory inputs in higher centres of the brain are glutamate and GABA respectively, and these glutamatergic and GABAergic afferent neurones are themselves subject to the same excitatory and inhibitory influences. Glutamate receptors, and in particular NMDA receptors, due to their slow activation and deactivation kinetics, are uniquely placed to regulate patterns of neuronal firing. Excitatory synapses onto most, if not all, central neurones use both AMPA and NMDA receptors, the latter becoming more important with increasing frequency of the afferent action potentials and the depolarization of the subsynaptic membrane. Indeed, NMDA receptor antagonists are much more effective against synaptic events induced by high frequency discharges compared to low frequency ones (Herron et al., 1986; Salt, 1986). Therefore, changes in the relative contribution of subtypes of glutamate receptor throughout the neuraxis will influence the nature of the high frequency afferent signals into and between higher brain centres (Fig. 1) and thereby distort perceptual processes.

In the last few decades it has become established that NMDA

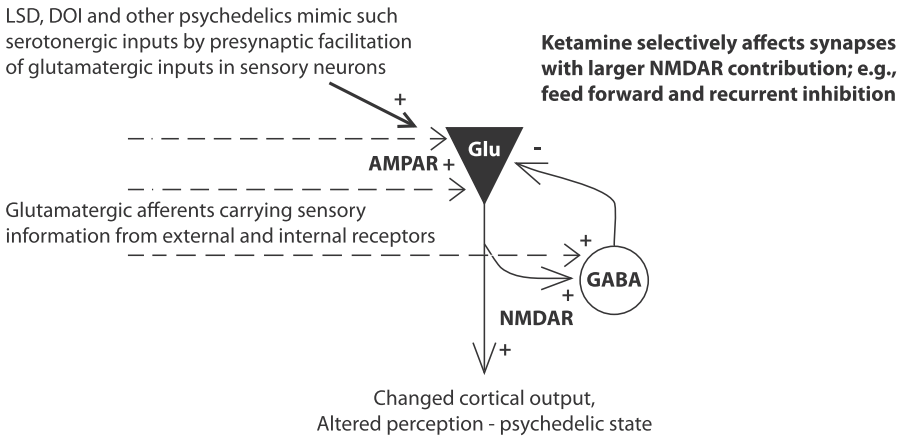

Fig. 2. Disinhibition distorts cortical processing of sensory information. Output of principal neurones in sensory, motor and limbic cortices depends on afferent information that is subject to modulation by monoaminergic fibres and by inhibitory influences, from amongst others feedforward and recurrent GABAergic interneurones. NMDA receptors play an important role in excitation of some of these inhibitory interneurones, in part because they are composed of the relatively Mg^{2+}-insensitive GluN2D subunits. Ketamine preferentially affects such receptors and results in disinhibition or overactivity of some principal neurones and as such distorts the information processing and the output of cerebral cortices. In the sensory cortex, this results in altered perception and the psychedelic state. In limbic cortices, this disinhibition can result in further increases in monoaminergic activity, potentially mimicking the effects of classical psychedelic drugs, lysergic acid diethylamide (LSD) and 2,5-dimethoxy-4-iodoamphetamine (DOI).

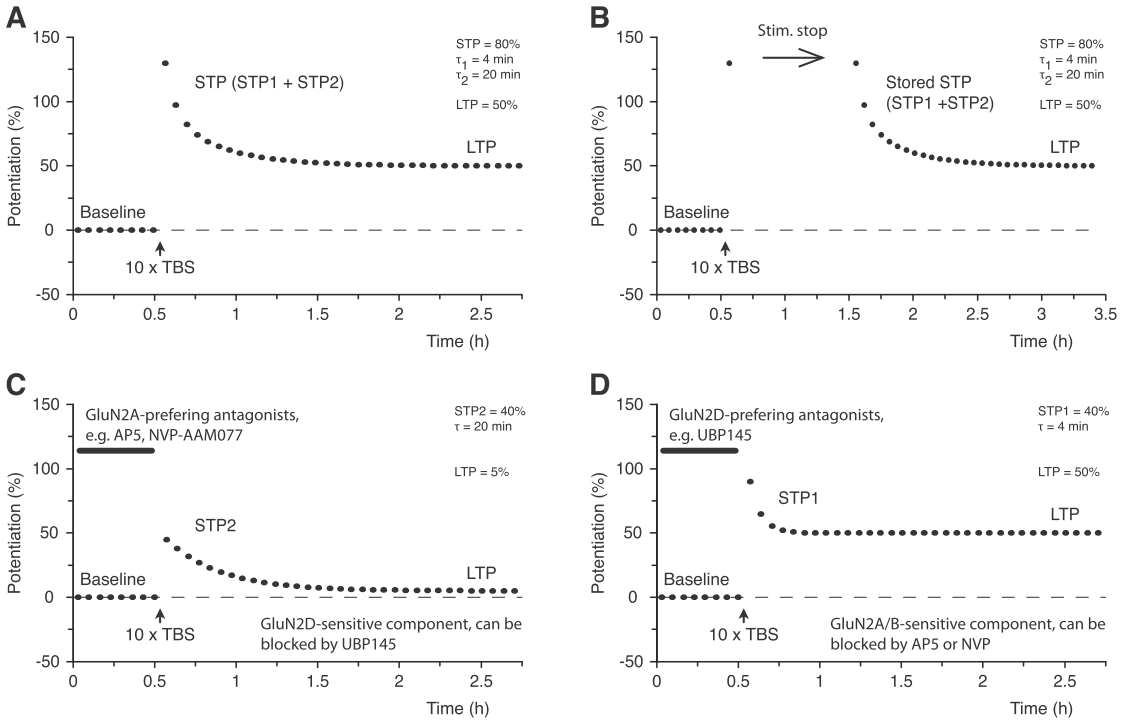

Fig. 3. STP and LTP in the CA1 area of the Schaffer-collaterals in the hippocampus (schematics based on data from Volianskis et al. (2013a,b); Volianskis and Jensen (2003)). High frequency stimulation (10 x theta-burst stimulation; TBS) induces NMDA receptor dependent short term potentiation (STP) and long term potentiation (LTP). **(A)** STP declines to a stable level of LTP in a bi-exponential manner (STP1 & STP2) with time constants such as those shown in the inset. **(B)** STP does not decline passively if low frequency testing of synaptic strength is discontinued after delivery of TBS and only starts declining after resumption of the stimulation (Volianskis et al., 2013b, 2013a; Volianskis and Jensen, 2003). **(C)** TBS in the presence of GluN2A-prefering antagonists induces mostly STP2, which declines slowly. **(D)** TBS in the presence of GluN2D-prefering antagonists induces STP1 and LTP. Synaptic potentiation can be completely blocked by combination of GluN2A and GluN2D antagonists (not shown).

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

receptors play an important role at excitatory synapses on parvalbumin (PV)-containing interneurones in the cerebral cortex (Cadinu et al., 2017; Goldberg et al., 2003; Grunze et al., 1996; Jones and Bühl, 1993; also see below). So ketamine is likely to reduce the influence of these neurones, which play an important role in fine-tuning responses of cortical pyramidal neurones (Agetsuma et al., 2017; Frohlich and Van Horn, 2014; Lee et al., 2017; Miao et al., 2017; Natan et al., 2017). Similarly ketamine-induced disinhibition via NMDA-sensitive PV-containing GABAergic neurones occurs in other brain areas including thalamus and hippocampus, disrupting their modulatory role on principal neurones (Steullet et al., 2017; Xia et al., 2017; Ye et al., 2018). Thus, changes in oscillatory function affecting cognitive ability (Uhlhaas and Singer, 2006) can result from selective inhibition of interneurone subtypes by ketamine (Middleton et al., 2008). Similar disinhibition by ketamine in the hippocampus, pallidum or pontine tegmentum could increase the number of bursting dopaminergic neurones of the ventral tegmentum (see Grace, 2010; Lodge et al., 2009).

NMDA receptors are not a homogeneous entity (Hollmann and Heinemann, 1994; Monyer et al., 1992). They are composed of tetraheteromeric assemblies containing various combinations of GluN1, GluN2 and GluN3 subunits. NMDA receptor expression is both regionally and developmentally regulated and it has been shown that the subunit composition of presynaptic, postsynaptic, perisynaptic and extrasynaptic NMDA receptors is not the same. GluN1 and GluN3 subunits bind the co-agonist glycine whereas GluN2 subunits bind glutamate itself. Relatively little is known about the functional roles of GluN3 subunits and no pharmacological tools exist that target them selectively. The functions of NMDA receptors composed of GluN1 and GluN2 subunits have been investigated in greater detail (Monyer et al., 1994; Vicini et al., 1998; Wyllie et al., 2013). Thus, diheteromeric NMDA receptors, which are composed of two GluN1 and two identical GluN2 subunits, are thought to be expressed in juvenile animals and in both synaptic and non-synaptic sites. In contrast, triheteromeric NMDA receptors contain two different GluN2 subunits in addition to the two GluN1s and are also widely expressed in the brain (Stroebel et al., 2018). Functional activation of NMDA receptors requires binding of both glutamate and glycine and, in addition to that, depolarization of the neuronal membrane is required to relieve the Mg^{2+} block from the NMDA receptor ion pore (Mayer et al., 1984; Nowak et al., 1984). It is here, close to the Mg^{2+} binding site of the tetramer, where dissociative anesthetics, such as PCP and ketamine bind (MacDonald et al., 1987; Song et al., 2018). Importantly, it is the identity of the GluN2 subunits that confers distinct pharmacological and biophysical properties to the specific NMDA receptor assemblies, such as the affinity to bind glutamate, open channel kinetics, duration of the agonist evoked currents and the susceptibility of the receptors to the Mg^{2+} block (Hollmann and Heinemann, 1994; Monyer et al., 1994; Stroebel et al., 2018; Vicini et al., 1998; Wyllie et al., 2013).

The ability of the NMDA receptor-channel blockers such as PCP and ketamine to antagonise NMDA receptors depends on the state of the receptors since the binding site for the channel blockers is less available whilst under Mg^{2+} block. At negative membrane potentials, Mg^{2+} substantially, though not fully, blocks GluN2A/2B

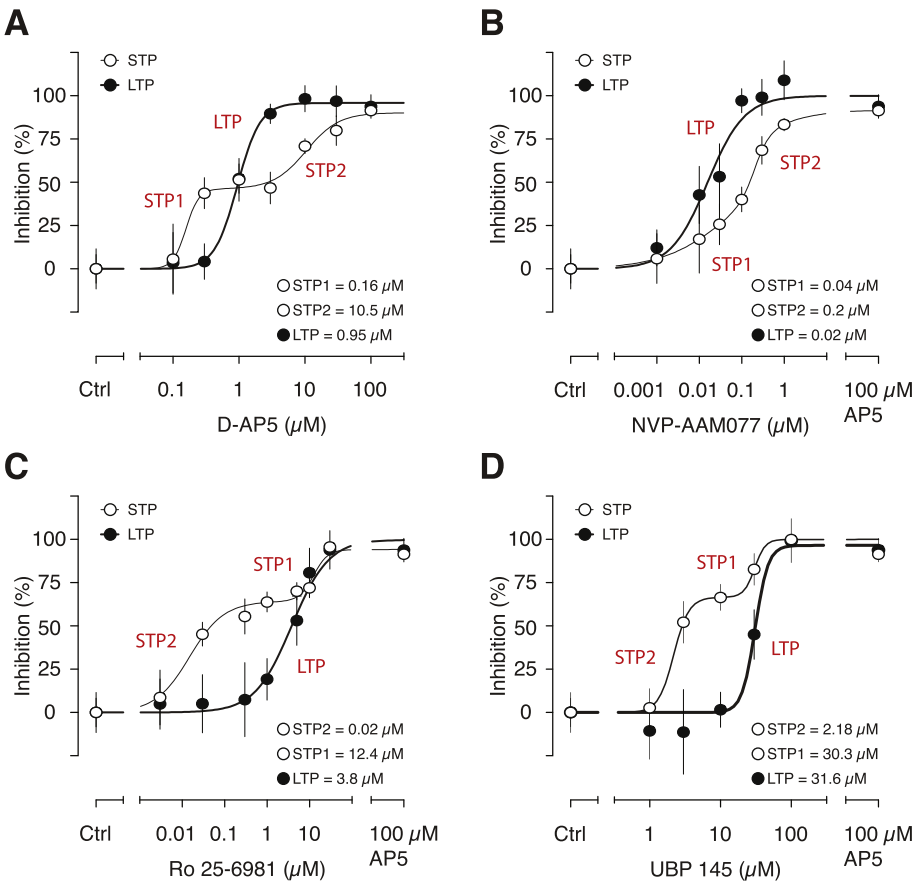

Fig. 4. NMDA receptor pharmacology of STP and LTP. STP and LTP are differentially inhibited by four, structurally different NMDA receptor antagonists (modified fromVolianskis et al. (2013a)). STP and LTP are blocked in a double- and single-sigmoidal manner respectively. STP1, STP2 and LTP components and their corresponding IC_{50} values are given in the insets. (A) Prototypical NMDA receptor antagonist D-AP5 (B) GluN2A-preferring antagonist NVP-AAM077. (C) Highly selective allosteric inhibitor of GluN2B subunits, Ro 25–6981. (D) GluN2D-prefering antagonist UBP145.

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

subunit-containing NMDA receptors and limits their contribution to synaptic transmission despite agonist availability. Pertinently, GluN2C/2D containing NMDA receptors are blocked less effectively by Mg^{2+}, and hence they contribute more appreciably to low frequency synaptic events (Schwartz et al., 2012). The competition with Mg^{2+} explains the lower IC_{50} values for the blockade of GluN2C/2D than for GluN2A/2B containing NMDA receptors by ketamine and other NMDAR channel blockers (Dravid et al., 2007; Kotermanski and Johnson, 2009; Kotermanski et al., 2009). GluN2C containing NMDA receptors are highly expressed in the cerebellum whereas GluN2Ds are prevalent throughout the brain, in both excitatory and inhibitory neurons. Thus, due to the higher affinity and due to the ability to block NMDA receptors at resting membrane potentials (Schwartz et al., 2012), both PCP and ketamine are likely to distort the processing of sensory information through inhibition of GluN2C/2D containing NMDA receptors. The finding that GluN2D subunits are relatively highly expressed in parvalbumin-expressing GABAergic interneurones helps explain the marked cortical disinhibition and hence changes in sensory inputs and processing that result from ketamine administration (Fig. 2). Interestingly, the ability of the dissociative anaesthetic, phencyclidine, to enhance striatal and prefrontal dopamine levels and to increase locomotor activity were absent in GluN2D knock-out mice (Hagino et al., 2010; Yamamoto et al., 2013) suggesting the possibility that this subunit could also be important for the psychedelic effects of ketamine. Consistent with this, ketamine-induced increases in the power of cortical gamma oscillations involves the GluN2D subunit (Sapkota et al., 2016).

3.3. Changes in synaptic plasticity

In addition to their roles as mediators of fast synaptic transmission, NMDA receptors are essential for many plasticity processes throughout the CNS, in particular LTP and LTD (Collingridge et al., 1983; Dudek and Bear, 1992; Volianskis et al., 2015). These processes are believed to be important for learning and memory (Bliss and Collingridge, 1993; Martin et al., 2000). Interestingly, unaware at the time that dissociative anaesthetics are NMDA

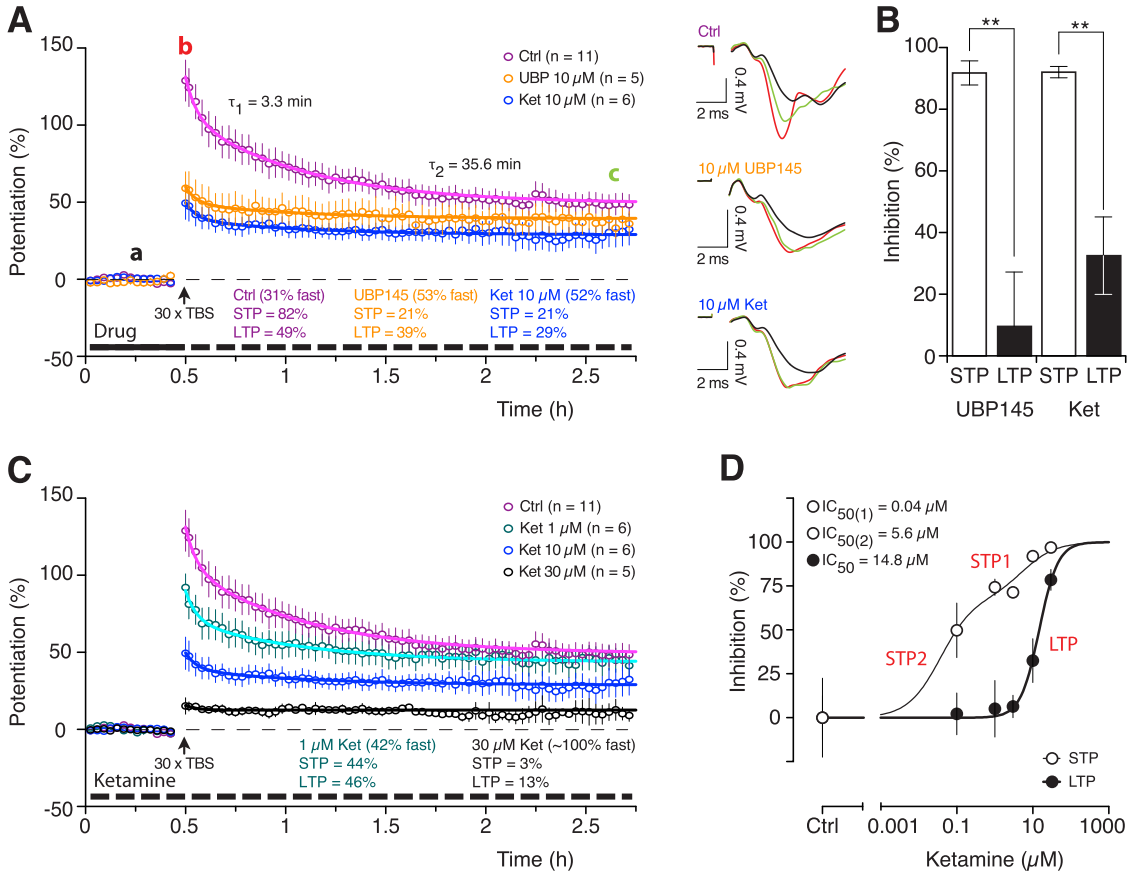

Fig. 5. Ketamine, like UPB145, is more potent at blocking STP than LTP. STP was induced by 30 x TBS (details below) and declined in a bi-exponential manner with fast (3.3 min) and slow (35.6 min) time constants to a stable level of LTP. Averaged data sets were fitted using Prism 7 (GraphPad) assuming shared decay time constants. Estimated parameters for STP and LTP are shown in the insets. **(A)** 10 μM UBP145 (orange data) and 10 μM ketamine (blue data) preferentially inhibit STP. The solid bar indicates application time for UBP145. Ketamine was pre-incubated for ~1.5 h and throughout the remainder of the experiment (dashed bar). Insets show representative f-EPSPs for the three data sets at the time points that are indicated by the coloured letters (black = baseline, red = peak STP; green = LTP). **(B)** UBP145 and ketamine inhibit STP more effectively than LTP. **P < 0.01. **(C)** Concentration dependency of the ketamine block of STP and LTP. **(D)** Ketamine is more potent at blocking STP than LTP. METHODS: Experiments were performed and analysed as described previously in detail (Volianskis et al., 2013b, 2013a; Volianskis and Jensen, 2003), using Schedule 1 methods and according to the UK Scientific Procedures Act, 1986 and EU guidelines for animal care. Briefly, transverse hippocampal slices from adult male Wistar rats (~10 weeks old, 200–220 g, Charles River) were pre-incubated for ~1.5 h prior to addition of ketamine (Ketalar©) to the perfusate. Slices were then maintained in ketamine for ~1.5 h prior to TBS and thereafter for the remainder of the experiment. UBP145 was applied for 30 min prior to TBS. Slices were kept submerged at (~32 °C) and superfused at a rate of 2.5 ml/min with aCSF (in mM: 124 NaCl, 3.5 KCl, 1.25 NaH_2PO_4, 26 $NaHCO_3$, 2 $CaCl_2$, 2 $MgSO_4$ and 10 glucose), which was saturated with 95% O_2 and 5% CO_2. Field excitatory postsynaptic potentials (f-EPSPs) were recorded in the CA1-B area of stratum radiatum. After a stable period of at least 30 min (baseline) theta-burst stimulation (TBS, a burst of 4 pulses at 100 Hz repeated 30 times with an inter-burst interval of 200 ms) was given. Data were recorded using WinLTP software (Anderson and Collingridge, 2007; www.winltp.com). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

receptor blockers, Guyenet's group found that both phencyclidine and ketamine (Stringer and Guyenet, 1983) and cyclazocine (Stringer et al., 1983) prevent the induction of LTP. This effect of ketamine on LTP, first described in the hippocampal CA1 region, has been observed in other brain regions, including the prefrontal cortex (Rame et al., 2017) visual cortex (Fathollahi and Salami, 2001) dentate gyrus (Zhang and Levy, 1992) and spinal cord (Benrath et al., 2005).

Importantly, there is differential involvement of NMDA receptor subunits in the various aspects of synaptic plasticity. For example, it has been shown that induction of LTP in the CA1 region of adult rodents requires mainly activation of GluN2A/2B containing triheteromeric NMDA receptors (Volianskis et al., 2013a).

In contrast, STP, which is frequently co-induced with LTP (see Fig. 3), comprises two pharmacologically and kinetically distinct components (termed STP1 and STP2), the latter of which involves the activation of GluN2B and GluN2D containing NMDARs (Fig. 4, France et al., 2017; Volianskis et al., 2013a). It can be predicted that ketamine, due to its greater ability to block GluN2D containing NMDA receptors, may, therefore, preferentially inhibit the GluN2D sensitive STP2 over LTP. Consistent with this hypothesis, it has been demonstrated that MK-801 is more potent at blocking STP than LTP (Coan et al., 1987). Although the effects of ketamine on LTP have been examined in detail (e.g. Ribeiro et al., 2014), its ability to block STP has never been determined quantitatively. We have therefore assessed ketamine's inhibition of STP and LTP in dorsal hippocampal slices from adult rats in the presence of 2 mM Mg^{2+} (Fig. 5).

Application of theta-burst stimulation (TBS) in control experiments induced bi-exponential STP that declined slowly to a stable level of LTP (Fig. 5A, Ctrl, pink). STP was highly sensitive to the GluN2D-preferring antagonist UBP145 (10 μM). UBP145 abolished the majority of STP whilst largely sparing LTP (Fig. 5A, orange). STP can be defined both by its amplitude and its decay time constants. From these values we calculated the STP "area" for individual experiments (Fig. 5B). STP was inhibited >90% and LTP was inhibited <10% by UBP145.

Due to the very slow, use-dependent, block of NMDA receptors by ketamine (Kang et al., 2016) the slices were pre-incubated in ketamine-containing ACSF (2 mM Mg^{2+}) for 1.5 h before the start of the experiments at concentrations indicated in Fig. 5. The same concentration was then perfused throughout the experiments. 10 μM ketamine's effects on STP were remarkably similar to those of UBP145 abolishing majority of STP while preserving most of the LTP (blue curve Fig. 5A and 5B). This was further examined by determining full concentration response relationships for ketamine's effects on STP and LTP (Fig. 5C and D). Ketamine inhibited STP in a bi-sigmoidal fashion with low (40 nM) and high (5.6 μM) IC_{50} values that differed 140-fold. Higher concentrations of ketamine were needed for inhibition of LTP, which was blocked in a single sigmoidal fashion, with an IC_{50} value of 14.8 μM. Maximal inhibition of STP was achieved before inhibition of LTP, confirming that ketamine blocks STP more potently than LTP.

Ketamine was ~370 fold more potent at inhibiting STP2 than LTP. We have anticipated a smaller difference based on the selectivity of ketamine for GluN2D vs GluN2A and GluN2B subunits in recombinant systems, in the presence of physiological concentrations of Mg^{2+} (described above). However, the block of synaptically-activated NMDA receptors by ketamine is highly voltage-dependent (Davies et al., 1988). Given that the GluN2A/2B containing NMDA receptors are located postsynaptically whereas the GluN2D containing NMDA receptors are most probably located presynaptically (Volianskis et al., 2013a), these receptor populations could readily experience differing degrees of depolarization.

Individual excitatory synapses have been shown to express STP, LTP or both (Debanne et al., 1999) and STP is observed in many cortical regions, including the visual cortex (Harsanyi and Friedlander, 1997a, 1997b) and the hippocampus (Malenka, 1991; Schulz and Fitzgibbons, 1997; Volianskis and Jensen, 2003). It has been shown that STP and LTP modulate synaptic transmission differently (Volianskis et al., 2013b). Because STP involves an increase in the probability of neurotransmitter release (P(r)) it alters the firing pattern within a high frequency burst discharge. In contrast, LTP does not affect P(r) and increases the responses within a high frequency burst discharge proportionately (Pananceau et al., 1998; Selig et al., 1999; Volianskis et al., 2013b).

The functions of STP in the CNS have not been extensively studied. However, STP has been observed during exploratory learning in rats (Moser et al., 1993, 1994). In contrast to LTP, which is thought to be involved in long-term storage of information in the brain, STP may be the physiological correlate of short-term/working memory (Volianskis et al., 2013b, 2015). STP has a unique property that could be exploited for certain forms of working memory (Fig. 3B). Notably, once induced at a synapse STP does not decay passively but can be stored during periods of synaptic inactivity (Volianskis et al., 2013b, 2013a; Volianskis and Jensen, 2003). When the synapse is re-activated, and dependent on the frequency of the incoming inputs, STP will be either be re-induced and maintained (during high-frequency activity) or depleted (during low frequency activation), leading to a decrease in synaptic efficacy back to initial values (Volianskis and Jensen, 2003). Interestingly, storage of information in inactive and silent neuronal networks has been recently suggested to mediate working memory in humans (Rose et al., 2016). STP may mediate the form of working memory that we use to remember an event in time and space, such as where we have placed our keys, or cell phone, or parked our car (Fig. 6). That is, a memory that we need to retain until accessed and then quickly forgotten, so that we can remember a different location for a similar activity.

The dissociation between the working and the long-term memories has been debated since the infamous discussion at the end of 19th century between William James and Charles Richet (see James, 1890; Richet, 1886). It was Richet who suggested that working memory processes are vital for perception of reality and also self-perception. *"Without memory no conscious sensation, without memory no consciousness"*, he said. Ketamine's disruption of working memory, a classical feature of schizophrenia, is well

Fig. 6. The K-Hole. Ketamine blocks STP and may, in this way, interfere with processes of working memory leading to distorted thoughts (background artwork by thejowking, https://thejowking.deviantart.com).

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

documented in both animals and humans (Adler et al., 1998; Kotermanski et al., 2013; Moghaddam and Krystal, 2012; Morgan and Curran, 2006) and on this basis, together with ketamine's high potency against STP, we hypothesize here that the psychedelic effects of ketamine are mediated in part by inhibition of STP and hence some aspects of working memory.

4. Conclusions

Ketamine is a relatively selective NMDA receptor antagonist. Because NMDA receptors are known to contribute to synaptic events throughout the brain and spinal cord, ketamine will distort afferent information, processing in the cerebral cortex and output pathways. Specifically, because of their biophysical properties, NMDA receptor heteromers containing the GluN2D subtype are particularly sensitive to ketamine. This relatively high potency of ketamine at GluN2D subunits and their importance in parvalbumin-containing GABAergic neurones and in STP at excitatory synapses provide a potential basis for the psychedelic actions of ketamine.

Conflicts of interest

The authors have no competing interests to declare.

Acknowledgments

Supported by The Royal Society (RSG\R1\180384), the MRC (MR/K023098/1) and CIHR.

References

Adler, C.M., Goldberg, T.E., Malhotra, A.K., Pickar, D., Breier, A., 1998. Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. Biol. Psychiatry 43, 811–816.

Adrian, E.D., 1928. The Basis of Sensation: the Action of the Sense Organs. Christophers, London.

Agetsuma, M., Hamm, J.P., Tao, K., Fujisawa, S., Yuste, R., 2017. Parvalbumin-Positive interneurons regulate neuronal ensembles in visual cortex. Cereb. Cortex 1–15. https://doi.org/10.1093/cercor/bhx169.

Allen, R.M., Young, S.J., 1978. Phencyclidine-induced psychosis. Am. J. Psychiatry 135, 1081–1084. https://doi.org/10.1176/ajp.135.9.1081.

Anderson, W.W., Collingridge, G.L., 2007. Capabilities of the WinLTP data acquisition program extending beyond basic LTP experimental functions. J. Neurosci. Methods 162, 346–356. https://doi.org/10.1016/j.jneumeth.2006.12.018.

Anis, N.A., Berry, S.C., Burton, N.R., Lodge, D., 1983. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br. J. Pharmacol. 79, 565–575. https://doi.org/10.1111/(ISSN)1476-5381.

Benrath, J., Brechtel, C., Stark, J., Sandkühler, J., 2005. Low dose of S+-ketamine prevents long-term potentiation in pain pathways under strong opioid analgesia in the rat spinal cord in vivo. Br. J. Anaesth. 95, 518–523. https://doi.org/10.1093/bja/aei215.

Bliss, T.V., Collingridge, G.L., 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361, 31–39. https://doi.org/10.1038/361031a0.

Boley, A.M., Perez, S.M., Lodge, D.J., 2014. A fundamental role for hippocampal parvalbumin in the dopamine hyperfunction associated with schizophrenia. Schizophr. Res. 157, 238–243. https://doi.org/10.1016/j.schres.2014.05.005.

Brady, K.T., Balster, R.L., 1981. Discriminative stimulus properties of phencyclidine and five analogues in the squirrel monkey. Pharmacol. Biochem. Behav. 14, 213–218.

Brady, K.T., Balster, R.L., May, E.L., 1982a. Stereoisomers of N-allylnormetazocine: phencyclidine-like behavioral effects in squirrel monkeys and rats. Science 215, 178–180.

Brady, K.T., Woolverton, W.L., Balster, R.L., 1982b. Discriminative stimulus and reinforcing properties of etoxadrol and dexoxadrol in monkeys. J. Pharmacol. Exp. Ther. 220, 56–62.

Browne, R.G., Welch, W.M., 1982. Stereoselective antagonism of phencyclidine's discriminative properties by adenosine receptor agonists. Science 217, 1157–1159.

Cadinu, D., Grayson, B., Podda, G., Harte, M.K., Doostdar, N., Neill, J.C., 2017. NMDA receptor antagonist rodent models for cognition in schizophrenia and identification of novel drug treatments, an update. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2017.11.045.

Carroll, M.E., 1990. PCP and hallucinogens. Adv. Alcohol Subst. Abuse 9, 167–190. https://doi.org/10.1300/J251v09n01_10.

Chen, G., Ensor, C.R., Russell, D., Bohner, B., 1959. The pharmacology of 1-(1-phenylcyclohexyl) piperidine-HCl. J. Pharmacol. Exp. Ther. 127, 241–250.

Chergui, K., Charléty, P.J., Akaoka, H., Saunier, C.F., Brunet, J.L., Buda, M., Svensson, T.H., Chouvet, G., 1993. Tonic activation of NMDA receptors causes spontaneous burst discharge of rat midbrain dopamine neurons in vivo. Eur. J. Neurosci. 5, 137–144.

Coan, E.J., Saywood, W., Collingridge, G.L., 1987. Mk-801 blocks Nmda receptor-mediated synaptic transmission and long-term potentiation in rat hippocampal slices. Neurosci. Lett. 80, 111–114.

Collingridge, G.L., Kehl, S.J., McLennan, H., 1983. Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. J. Physiol. (Lond.) 334, 33–46.

Coyle, J.T., Balu, D., Benneyworth, M., Basu, A., Roseman, A., 2010. Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia. Dialogues Clin. Neurosci. 12, 359–382.

Davies, S.N., Alford, S.T., Coan, E.J., Lester, R.A., Collingridge, G.L., 1988. Ketamine blocks an NMDA receptor-mediated component of synaptic transmission in rat hippocampus in a voltage-dependent manner. Neurosci. Lett. 92, 213–217.

Davis, S.M., Lees, K.R., Albers, G.W., Diener, H.C., Markabi, S., Karlsson, G., Norris, J., 2000. Selfotel in acute ischemic stroke : possible neurotoxic effects of an NMDA antagonist. Stroke 31, 347–354.

Debanne, D., Gähwiler, B.H., Thompson, S.M., 1999. Heterogeneity of synaptic plasticity at unitary CA3-CA1 and CA3-CA3 connections in rat hippocampal slice cultures. J. Neurosci. 19, 10664–10671.

Dittrich, A., 1998. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry 31 (Suppl. 2), 80–84. https://doi.org/10.1055/s-2007-979351.

Domino, E.F., Chodoff, P., Corssen, G., 1965. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin. Pharmacol. Ther. 6, 279–291.

Domino, E.F., Luby, E.D., 2012. Phencyclidine/schizophrenia: one view toward the past, the other to the future. Schizophr. Bull. 38, 914–919. https://doi.org/10.1093/schbul/sbs011.

Dravid, S.M., Erreger, K., Yuan, H., Nicholson, K., Le, P., Lyuboslavsky, P., Almonte, A., Murray, E., Mosely, C., Barber, J., French, A., Balster, R., Murray, T.F., Traynelis, S.F., 2007. Subunit-specific mechanisms and proton sensitivity of NMDA receptor channel block. J. Physiol. (Lond.) 581, 107–128. https://doi.org/10.1113/jphysiol.2006.124958.

Dudek, S.M., Bear, M.F., 1992. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc. Natl. Acad. Sci. U.S.A. 89, 4363–4367.

Farber, N.B., Hanslick, J., Kirby, C., McWilliams, L., Olney, J.W., 1998. Serotonergic agents that activate 5HT2A receptors prevent NMDA antagonist neurotoxicity. Neuropsychopharmacology 18, 57–62. https://doi.org/10.1016/S0893-133X(97)00127-9.

Fathollahi, Y., Salami, M., 2001. The role of N-methyl-D-aspartate receptors in synaptic plasticity of rat visual cortex in vitro: effect of sensory experience. Neurosci. Lett. 306, 149–152.

France, G., Fernández-Fernández, D., Burnell, E.S., Irvine, M.W., Monaghan, D.T., Jane, D.E., Bortolotto, Z.A., Collingridge, G.L., Volianskis, A., 2017. Multiple roles of GluN2B-containing NMDA receptors in synaptic plasticity in juvenile hippocampus. Neuropharmacology 112, 76–83. https://doi.org/10.1016/j.neuropharm.2016.08.010.

Frederickson, E.L., Longnecker, D.E., Allen, G.W., 1976. Clinical investigation of a new intravenous anesthetic–etoxadrol hydrochloride (CL-1848; U-37862A). Anesth. Analg. 55, 335–339.

Freedman, A.M., Fink, M., 1968. Basic concepts and use of cyclazocine in the treatment of narcotic addiction. Br. J. Addiction Alcohol Other Drugs 63, 59–69.

Freeman, A.S., Bunney, B.S., 1984. The effects of phencyclidine and N-allylnormetazocine on midbrain dopamine neuronal activity. Eur. J. Pharmacol. 104, 287–293.

Frohlich, J., Van Horn, J.D., 2014. Reviewing the ketamine model for schizophrenia. J. Psychopharmacol. 28, 287–302. https://doi.org/10.1177/0269881113512909.

Garey, R.E., Heath, R.G., 1976. The effects of phencyclidine on the uptake of 3H-catecholamines by rat striatal and hypothalamic synaptosomes. Life Sci. 18, 1105–1110.

Goldberg, J.H., Yuste, R., Tamas, G., 2003. Ca2+ imaging of mouse neocortical interneurone dendrites: contribution of Ca2+-permeable AMPA and NMDA receptors to subthreshold Ca2+dynamics. J. Physiol. (Lond.) 551, 67–78. https://doi.org/10.1113/jphysiol.2003.042598.

Grace, A.A., 2010. Dopamine system dysregulation by the ventral subiculum as the common pathophysiological basis for schizophrenia psychosis, psychostimulant abuse, and stress. Neurotox. Res. 18, 367–376. https://doi.org/10.1007/s12640-010-9154-6.

Greifenstein, F.E., Devault, M., Yoshitake, J., Gajewski, J.E., 1958. A study of a 1-aryl cyclo hexyl amine for anesthesia. Anesth. Analg. 37, 283–294.

Grotta, J., Clark, W., Coull, B., Pettigrew, L.C., Mackay, B., Goldstein, L.B., Meissner, I., Murphy, D., LaRue, L., 1995. Safety and tolerability of the glutamate antagonist CGS 19755 (Selfotel) in patients with acute ischemic stroke. Results of a phase IIa randomized trial. Stroke 26, 602–605.

Grunze, H.C., Rainnie, D.G., Hasselmo, M.E., Barkai, E., Hearn, E.F., McCarley, R.W., Greene, R.W., 1996. NMDA-dependent modulation of CA1 local circuit inhibition. J. Neurosci. 16, 2034–2043.

Haertzen, C.A., 1970. Subjective effects of narcotic antagonists cyclazocine and

nalorphine on the Addiction Research Center Inventory (ARCI). Psychopharmacologia 18, 366–377.
Hagino, Y., Kasai, S., Han, W., Yamamoto, H., Nabeshima, T., Mishina, M., Ikeda, K., 2010. Essential role of NMDA receptor channel ε4 subunit (GluN2D) in the effects of phencyclidine, but not methamphetamine. PLoS One 5, e13722–e13727. https://doi.org/10.1371/journal.pone.0013722.
Hampton, R.Y., Medzihradsky, F., Woods, J.H., Dahlstrom, P.J., 1982. Stereospecific binding of 3H-phencyclidine in brain membranes. Life Sci. 30, 2147–2154.
Harsanyi, K., Friedlander, M.J., 1997a. Transient synaptic potentiation in the visual cortex. I. Cellular mechanisms. J. Neurophysiol. 77, 1269–1283.
Harsanyi, K., Friedlander, M.J., 1997b. Transient synaptic potentiation in the visual cortex. II. Developmental regulation. J. Neurophysiol. 77, 1284–1293.
Heal, D.J., Gosden, J., Smith, S.L., 2018. Evaluating the abuse potential of psychedelic drugs as part of the safety pharmacology assessment for medical use in humans. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2018.01.049.
Hernandez, S.C., Bertolino, M., Xiao, Y., Pringle, K.E., Caruso, F.S., Kellar, K.J., 2000. Dextromethorphan and its metabolite dextrorphan block alpha3beta4 neuronal nicotinic receptors. J. Pharmacol. Exp. Ther. 293, 962–967.
Herrling, P.L., 1997. Excitatory Amino Acids: Clinical Results with Antagonists. Academic, London.
Herrling, P.L., Coale, E.H., Hein, D.W., Winger, G., Woods, J.H., 1981. Similarity of the discriminative stimulus effects of ketamine, cyclazocine, and dextrorphan in the pigeon. Psychopharmacology (Berl) 73, 286–291.
Herron, C.E., Lester, R.A., Coan, E.J., Collingridge, G.L., 1986. Frequency-dependent involvement of NMDA receptors in the hippocampus: a novel synaptic mechanism. Nature 322, 265–268. https://doi.org/10.1038/322265a0.
Hollmann, M., Heinemann, S., 1994. Cloned glutamate receptors. Annu. Rev. Neurosci. 17, 31–108. https://doi.org/10.1146/annurev.ne.17.030194.000335.
Holtzman, S.G., 1982. Phencyclidine-like discriminative stimulus properties of opioids in the squirrel monkey. Psychopharmacology (Berl) 77, 295–300.
Holtzman, S.G., 1980. Phencyclidine-like discriminative effects of opioids in the rat. J. Pharmacol. Exp. Ther. 214, 614–619.
Isbell, H., Fraser, H.F., 1953. Actions and addiction liabilities of dromoran derivatives in man. J. Pharmacol. Exp. Ther. 107, 524–530.
James, W., 1890. The Principles of Psychology. Dover Publications Inc., Henry Holt and Company, New York.
Jasinski, D.R., Martin, W.R., Haertzen, C.A., 1967. The human pharmacology and abuse potential of N-allylnoroxymorphone (naloxone). J. Pharmacol. Exp. Ther. 157, 420–426.
Javitt, D.C., Zukin, S.R., Heresco-Levy, U., Umbricht, D., 2012. Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. Schizophr. Bull. 38, 958–966. https://doi.org/10.1093/schbul/sbs069.
Jentsch, J.D., Roth, R.H., 1999. The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 20, 201–225. https://doi.org/10.1016/S0893-133X(98)00060-8.
Jones, H.E., Balster, R.L., 1998. Muscimol-like discriminative stimulus effects of GABA agonists in rats. Pharmacol. Biochem. Behav. 59, 319–326.
Jones, R.S., Bühl, E.H., 1993. Basket-like interneurones in layer II of the entorhinal cortex exhibit a powerful NMDA-mediated synaptic excitation. Neurosci. Lett. 149, 35–39.
Kang, H., Park, P., Bortolotto, Z.A., Brandt, S.D., Colestock, T., Wallach, J., Collingridge, G.L., Lodge, D., 2016. Ephenidine: a new psychoactive agent with ketamine-like NMDA receptor antagonist properties. Neuropharmacology 112, 144–149. https://doi.org/10.1016/j.neuropharm.2016.08.004.
Kapur, S., Seeman, P., 2002. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. Mol. Psychiatry 7, 837–844. https://doi.org/10.1038/sj.mp.4001093.
Keats, A.S., Telford, J., 1964. Studies of analgesic drugs. Viii. A narcotic antagonist analgesic without psychotomimetic effects. J. Pharmacol. Exp. Ther. 143, 157–164.
Kokkinou, M., Ashok, A.H., Howes, O.D., 2018. The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. Mol. Psychiatry 23, 59–69. https://doi.org/10.1038/mp.2017.190.
Kotermanski, S.E., Johnson, J.W., 2009. Mg2+ imparts NMDA receptor subtype selectivity to the Alzheimer's drug memantine. J. Neurosci. 29, 2774–2779. https://doi.org/10.1523/JNEUROSCI.3703-08.2009.
Kotermanski, S.E., Johnson, J.W., Thiels, E., 2013. Comparison of behavioral effects of the NMDA receptor channel blockers memantine and ketamine in rats. Pharmacol. Biochem. Behav. 109, 67–76. https://doi.org/10.1016/j.pbb.2013.05.005.
Kotermanski, S.E., Wood, J.T., Johnson, J.W., 2009. Memantine binding to a superficial site on NMDA receptors contributes to partial trapping. J. Physiol. (Lond.) 587, 4589–4604. https://doi.org/10.1113/jphysiol.2009.176297.
Lasagna, L., Pearson, J.W., 1965. Analgesic and psychotomimetic properties of dexoxadrol. Proc. Soc. Exp. Biol. Med. 118, 352–354.
Lee, K., Holley, S.M., Shobe, J.L., Chong, N.C., Cepeda, C., Levine, M.S., Masmanidis, S.C., 2017. Parvalbumin interneurons modulate striatal output and enhance performance during associative learning. Neuron 93, 1451–1463. https://doi.org/10.1016/j.neuron.2017.02.033 e4.
Lewis, D.A., 2014. Inhibitory neurons in human cortical circuits: substrate for cognitive dysfunction in schizophrenia. Curr. Opin. Neurobiol. 26, 22–26. https://doi.org/10.1016/j.conb.2013.11.003.
Lodge, D., Anis, N.A., 1984. Effects of ketamine and three other anaesthetics on spinal reflexes and inhibitions in the cat. Br. J. Anaesth. 56, 1143–1151.
Lodge, D., Johnston, G.A., 1985. Effect of ketamine on amino acid-evoked release of acetylcholine from rat cerebral cortex in vitro. Neurosci. Lett. 56, 371–375.
Lodge, D., Mercier, M.S., 2015. Ketamine and phencyclidine: the good, the bad and the unexpected. Br. J. Pharmacol. 172, 4254–4276. https://doi.org/10.1111/bph.13222.
Lodge, D.J., Behrens, M.M., Grace, A.A., 2009. A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. J. Neurosci. 29, 2344–2354. https://doi.org/10.1523/JNEUROSCI.5419-08.2009.
Luby, E.D., Cohen, B.D., Rosenbaum, G., Gottlieb, J.S., Kelley, R., 1959. Study of a new schizophrenomimetic drug; sernyl. AMA Arch. Neurol. Psychiatry 81, 363–369.
Luisada, P.V., 1978. The phencyclidine psychosis: phenomenology and treatment. NIDA Res. Monogr. 241–253.
MacDonald, J.F., Miljkovic, Z., Pennefather, P., 1987. Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. J. Neurophysiol. 58, 251–266. https://doi.org/10.1152/jn.1987.58.2.251.
Maddox, V.H., Godefroi, E.F., Parcell, R.F., 1965. The synthesis of phencyclidine and other 1-arylcyclohexylamines. J. Med. Chem. 8, 230–235.
Malenka, R.C., 1991. Postsynaptic factors control the duration of synaptic enhancement in area CA1 of the hippocampus. Neuron 6, 53–60.
Marek, G.J., Aghajanian, G.K., 1999. 5-HT2A receptor or alpha1-adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. Eur. J. Pharmacol. 367, 197–206.
Martin, D., Lodge, D., 1985. Ketamine acts as a non-competitive N-methyl-D-aspartate antagonist on frog spinal cord in vitro. Neuropharmacology 24, 999–1003.
Martin, S.J., Grimwood, P.D., Morris, R.G., 2000. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. 23, 649–711. https://doi.org/10.1146/annurev.neuro.23.1.649.
Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., Gilbert, P.E., 1976. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. J. Pharmacol. Exp. Ther. 197, 517–532.
Marwaha, J., Palmer, M., Hoffer, B., Freedman, R., Rice, K.C., Paul, S., Skolnick, P., 1981. Differential electrophysiological and behavioral responses to optically active derivatives of phencyclidine. Naunyn Schmiedeberg's Arch. Pharmacol. 315, 203–209.
Mayer, M.L., Westbrook, G.L., Guthrie, P.B., 1984. Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. Nature 309, 261–263.
McCarthy, D.A., Chen, G., Kaump, D.H., Ensor, C., 1965. General anesthetic and other pharmacological properties of 2-(o-chlorophenyl)-2-methylamino cyclohexanone hcl (ci-581). J. N. Drugs 5, 21–33.
Mendelsohn, L.G., Kerchner, G.A., Kalra, V., Zimmerman, D.M., Leander, J.D., 1984. Phencyclidine receptors in rat brain cortex. Biochem. Pharmacol. 33, 3529–3535.
Meyer, J.S., Greifenstein, F., Devault, M., 1959. A new drug causing symptoms of sensory deprivation. J. Nerv. Ment. Dis. 129 (1), 54–61.
Miao, C., Cao, Q., Moser, M.-B., Moser, E.I., 2017. Parvalbumin and somatostatin interneurons control different space-coding networks in the medial entorhinal cortex. Cell 171, 507–521. https://doi.org/10.1016/j.cell.2017.08.050 e17.
Middleton, S., Jalics, J., Kispersky, T., Lebeau, F.E.N., Roopun, A.K., Kopell, N.J., Whittington, M.A., Cunningham, M.O., 2008. NMDA receptor-dependent switching between different gamma rhythm-generating microcircuits in entorhinal cortex. Proc. Natl. Acad. Sci. U.S.A. 105, 18572–18577. https://doi.org/10.1073/pnas.0809302105.
Moaddel, R., Abdrakhmanova, G., Kozak, J., Jozwiak, K., Toll, L., Jimenez, L., Rosenberg, A., Tran, T., Xiao, Y., Zarate, C.A., Wainer, I.W., 2013. Sub-anesthetic concentrations of (R,S)-ketamine metabolites inhibit acetylcholine-evoked currents in α7 nicotinic acetylcholine receptors. Eur. J. Pharmacol. 698, 228–234. https://doi.org/10.1016/j.ejphar.2012.11.023.
Moghaddam, B., Krystal, J.H., 2012. Capturing the angel in "angel dust": twenty years of translational neuroscience studies of NMDA receptor antagonists in animals and humans. Schizophr. Bull. 38, 942–949. https://doi.org/10.1093/schbul/sbs075.
Monyer, H., Burnashev, N., Laurie, D.J., Sakmann, B., Seeburg, P.H., 1994. Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron 12, 529–540.
Monyer, H., Sprengel, R., Schoepfer, R., Herb, A., Higuchi, M., Lomeli, H., Burnashev, N., Sakmann, B., Seeburg, P.H., 1992. Heteromeric NMDA receptors: molecular and functional distinction of subtypes. Science 256, 1217–1221.
Morgan, C.J.A., Curran, H.V., 2006. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology (Berl) 188, 408–424. https://doi.org/10.1007/s00213-006-0572-3.
Morris, H., Wallach, J., 2014. From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. Drug Test. Anal. https://doi.org/10.1002/dta.1620 n/a–n/a.
Moser, E., Moser, M.B., Andersen, P., 1993. Synaptic potentiation in the rat dentate gyrus during exploratory learning. Neuroreport 5, 317–320.
Moser, E.I., Moser, M.B., Andersen, P., 1994. Potentiation of dentate synapses initiated by exploratory learning in rats: dissociation from brain temperature, motor activity, and arousal. Learn. Mem. 1, 55–73.
Muir, K.W., 2006. Glutamate-based therapeutic approaches: clinical trials with NMDA antagonists. Curr. Opin. Pharmacol. 6, 53–60. https://doi.org/10.1016/

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

j.coph.2005.12.002.
Murray, T.F., Leid, M.E., 1984. Interaction of dextrorotatory opioids with phencyclidine recognition sites in rat brain membranes. Life Sci. 34, 1899–1911.
Nakazawa, K., Zsiros, V., Jiang, Z., Nakao, K., Kolata, S., Zhang, S., Belforte, J.E., 2012. GABAergic interneuron origin of schizophrenia pathophysiology. Neuropharmacology 62, 1574–1583. https://doi.org/10.1016/j.neuropharm.2011.01.022.
Natan, R.G., Rao, W., Geffen, M.N., 2017. Cortical interneurons differentially shape frequency tuning following adaptation. Cell Rep. 21, 878–890. https://doi.org/10.1016/j.celrep.2017.10.012.
Nichols, D.E., 2004. Hallucinogens. Pharmacol. Ther. 101, 131–181. https://doi.org/10.1016/j.pharmthera.2003.11.002.
Nowak, L., Bregestovski, P., Ascher, P., Herbet, A., Prochiantz, A., 1984. Magnesium gates glutamate-activated channels in mouse central neurones. Nature 307, 462–465.
Olney, J.W., Farber, N.B., 1995. NMDA antagonists as neurotherapeutic drugs, psychotogens, neurotoxins, and research tools for studying schizophrenia. Neuropsychopharmacology 13, 335–345. https://doi.org/10.1016/0893-133X(95)00079-S.
Pananceau, M., Chen, H., Gustafsson, B., 1998. Short-term facilitation evoked during brief afferent tetani is not altered by long-term potentiation in the Guinea-pig hippocampal CA1 region. J. Physiol. (Lond.) 508 (Pt 2), 503–514.
Purifoy, J.A., Holz, R.W., 1984. The effects of ketamine, phencyclidine and lidocaine on catecholamine secretion from cultured bovine adrenal chromaffin cells. Life Sci. 35, 1851–1857.
Quirion, R., Hammer, R.P., Herkenham, M., Pert, C.B., 1981. Phencyclidine (angel dust)/sigma "opiate" receptor: visualization by tritium-sensitive film. Proc. Natl. Acad. Sci. U.S.A. 78, 5881–5885.
Rame, M., Caudal, D., Schenker, E., Svenningsson, P., Spedding, M., Jay, T.M., Godsil, B.P., 2017. Clozapine counteracts a ketamine-induced depression of hippocampal-prefrontal neuroplasticity and alters signaling pathway phosphorylation. PLoS One 12. https://doi.org/10.1371/journal.pone.0177036 e0177036–20.
Ribeiro, P.O., Tomé, N.R., Silva, H.B., Cunha, R.A., Antunes, L.M., 2014. Clinically relevant concentrations of ketamine mainly affect long-term potentiation rather than basal excitatory synaptic transmission and do not change paired-pulse facilitation in mouse hippocampal slices. Brain Res. 1560, 10–17. https://doi.org/10.1016/j.brainres.2014.03.004.
Richet, C., 1886. Les origines etles modalités de la memoire. Revue Philosophique XXI, 570 (quoted in James, W., 1890. The Principles of Psychology. New York, Dover Publications Inc., Henry Holt and Company).
Rose, N.S., LaRocque, J.J., Riggall, A.C., Gosseries, O., Starrett, M.J., Meyering, E.E., Postle, B.R., 2016. Reactivation of latent working memories with transcranial magnetic stimulation. Science 354, 1136–1139. https://doi.org/10.1126/science.aah7011.
Salt, T.E., 1986. Mediation of thalamic sensory input by both NMDA receptors and non-NMDA receptors. Nature 322, 263–265. https://doi.org/10.1038/322263a0.
Sapkota, K., Mao, Z., Synowicki, P., Lieber, D., Liu, M., Ikezu, T., Gautam, V., Monaghan, D.T., 2016. GluN2D N-Methyl-d-Aspartate receptor subunit contribution to the stimulation of brain activity and gamma oscillations by ketamine: implications for schizophrenia. J. Pharmacol. Exp. Ther. 356, 702–711.
Schulz, P.E., Fitzgibbons, J.C., 1997. Differing mechanisms of expression for short- and long-term potentiation. J. Neurophysiol. 78, 321–334.
Schwartz, E.J., Rothman, J.S., Dugué, G.P., Diana, M., Rousseau, C., Silver, R.A., Dieudonné, S., 2012. NMDA receptors with incomplete Mg^{2+} block enable low-frequency transmission through the cerebellar cortex. J. Neurosci. 32, 6878–6893. https://doi.org/10.1523/JNEUROSCI.5736-11.2012.
Selig, D.K., Nicoll, R.A., Malenka, R.C., 1999. Hippocampal long-term potentiation preserves the fidelity of postsynaptic responses to presynaptic bursts. J. Neurosci. 19, 1236–1246.
Sellers, E.M., Romach, M.K., Leiderman, D.B., 2017. Studies with psychedelic drugs in human volunteers. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2017.11.029.
Shannon, H.E., 1982a. Pharmacological analysis of the phencyclidine-like discriminative stimulus properties of narcotic derivatives in rats. J. Pharmacol. Exp. Ther. 222, 146–151.
Shannon, H.E., 1982b. Phencyclidine-like discriminative stimuli of (+)- and (-)-N-allylnormetazocine in rats. Eur. J. Pharmacol. 84, 225–228.
Shannon, H.E., 1981. Evaluation of phencyclidine analogs on the basis of their discriminative stimulus properties in the rat. J. Pharmacol. Exp. Ther. 216, 543–551.
Siegel, R.K., 1978a. Phencyclidine, criminal behavior, and the defense of diminished capacity. NIDA Res. Monogr. 272–288.
Siegel, R.K., 1978b. Phencyclidine and ketamine intoxication: a study of four populations of recreational users. NIDA Res. Monogr. 119–147.
Sircar, R., Zukin, S.R., 1983. Characterization of specific sigma opiate/phencyclidine (PCP)-binding sites in the human brain. Life Sci. 33 (Suppl. 1), 259–262.
Song, X., MØ, Jensen, Jogini, V., Stein, R.A., Lee, C.-H., Mchaourab, H.S., Shaw, D.E., Gouaux, E., 2018. Mechanism of NMDA receptor channel block by MK-801 and memantine. Nature 556, 515–519.
Stafford, P., 1977. Psychedelics Encyclopedia. And/Or Press, Berkeley (quoted in Siegel chapter NIDA Research Monograph 21 August 1978).
Steullet, P., Cabungcal, J.-H., Coyle, J., Didriksen, M., Gill, K., Grace, A.A., Hensch, T.K., LaMantia, A.-S., Lindemann, L., Maynard, T.M., Meyer, U., Morishita, H., O'Donnell, P., Puhl, M., Cuenod, M., Do, K.Q., 2017. Oxidative stress-driven parvalbumin interneuron impairment as a common mechanism in models of schizophrenia. Mol. Psychiatry 22, 936–943. https://doi.org/10.1038/mp.2017.47.
Stringer, J.L., Greenfield, L.J., Hackett, J.T., Guyenet, P.G., 1983. Blockade of long-term potentiation by phencyclidine and sigma opiates in the hippocampus in vivo and in vitro. Brain Res. 280, 127–138.
Stringer, J.L., Guyenet, P.G., 1983. Elimination of long-term potentiation in the hippocampus by phencyclidine and ketamine. Brain Res. 258, 159–164.
Stroebel, D., Casado, M., Paoletti, P., 2018. ScienceDirect Triheteromeric NMDA receptors: from structure to synaptic physiology. Curr. Opin. Psychol. 2, 1–12. https://doi.org/10.1016/j.cophys.2017.12.004.
Tang, A.H., Cangelosi, A.A., Code, R.A., Franklin, S.R., 1984. Phencyclidine-like behavioral effects of 2-methyl-3,3-diphenyl-3-propanolamine (2-MDP). Pharmacol. Biochem. Behav. 20, 209–213.
Uhlhaas, P.J., Singer, W., 2006. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 52, 155–168. https://doi.org/10.1016/j.neuron.2006.09.020.
Vicini, S., Wang, J.F., Li, J.H., Zhu, W.J., Wang, Y.H., Luo, J.H., Wolfe, B.B., Grayson, D.R., 1998. Functional and pharmacological differences between recombinant N-methyl-D-aspartate receptors. J. Neurophysiol. 79, 555–566.
Vickroy, T.W., Johnson, K.M., 1982. Similar dopamine-releasing effects of phencyclidine and nonamphetamine stimulants in striatal slices. J. Pharmacol. Exp. Ther. 223, 669–674.
Vincent, J.P., Kartalovski, B., Geneste, P., Kamenka, J.M., Lazdunski, M., 1979. Interaction of phencyclidine ("angel dust") with a specific receptor in rat brain membranes. Proc. Natl. Acad. Sci. U.S.A. 76, 4678–4682.
Volianskis, A., Bannister, N., Collett, V.J., Irvine, M.W., Monaghan, D.T., Fitzjohn, S.M., Jensen, M.S., Jane, D.E., Collingridge, G.L., 2013a. Different NMDA receptor subtypes mediate induction of long-term potentiation and two forms of short-term potentiation at CA1 synapses in rat hippocampus in vitro. J. Physiol. (Lond.) 591, 955–972. https://doi.org/10.1113/jphysiol.2012.247296.
Volianskis, A., Collingridge, G.L., Jensen, M.S., 2013b. The roles of STP and LTP in synaptic encoding. PeerJ 1, e3. https://doi.org/10.7717/peerj.3.
Volianskis, A., France, G., Jensen, M.S., Bortolotto, Z.A., Jane, D.E., Collingridge, G.L., 2015. Long-term potentiation and the role of N-methyl-D-aspartate receptors. Brain Res. 1621, 5–16. https://doi.org/10.1016/j.brainres.2015.01.016.
Volianskis, A., Jensen, M.S., 2003. Transient and sustained types of long-term potentiation in the CA1 area of the rat hippocampus. J. Physiol. (Lond.) 550, 459–492. https://doi.org/10.1113/jphysiol.2003.044214.
Vollenweider, F.X., Kometer, M., 2010. The Neurobiology of Psychedelic Drugs: Implications for the Treatment of Mood Disorders, vol. 11. Nature Publishing Group, pp. 642–651. https://doi.org/10.1038/nrn2884.
Wallach, J., Kang, H., Colestock, T., Morris, H., Bortolotto, Z.A., Collingridge, G.L., Lodge, D., Halberstadt, A.L., Brandt, S.D., Adejare, A., 2016. Pharmacological investigations of the dissociative "legal highs" diphenidine, methoxphenidine and analogues. PLoS One 11, e0157021. https://doi.org/10.1371/journal.pone.0157021.
West, W.B., Lou, A., Pechersky, K., Chachich, M.E., Appel, J.B., 2000. Antagonism of a PCP drug discrimination by hallucinogens and related drugs. Neuropsychopharmacology 22, 618–625. https://doi.org/10.1016/S0893-133X(99)00163-3.
White, J.M., Holtzman, S.G., 1982. Properties of pentazocine as a discriminative stimulus in the squirrel monkey. J. Pharmacol. Exp. Ther. 223, 396–401.
White, P.F., Way, W.L., Trevor, A.J., 1982. Ketamine–its pharmacology and therapeutic uses. Anesthesiology 56, 119–136.
Wise, R.A., 1996. Addictive drugs and brain stimulation reward. Annu. Rev. Neurosci. 19, 319–340. https://doi.org/10.1146/annurev.ne.19.030196.001535.
Wyllie, D.J.A., Livesey, M.R., Hardingham, G.E., 2013. Neuropharmacology. Neuropharmacology 74, 4–17. https://doi.org/10.1016/j.neuropharm.2013.01.016.
Xia, F., Richards, B.A., Tran, M.M., Josselyn, S.A., Takehara-Nishiuchi, K., Frankland, P.W., 2017. Parvalbumin-positive interneurons mediate neocortical-hippocampal interactions that are necessary for memory consolidation. eLife 6, e27868. https://doi.org/10.7554/eLife.27868.
Yamamoto, H., Kamegaya, E., Sawada, W., Hasegawa, R., Yamamoto, T., Hagino, Y., Takamatsu, Y., Imai, K., Koga, H., Mishina, M., Ikeda, K., 2013. Involvement of the N-methyl-D-aspartate receptor GluN2D subunit in phencyclidine-induced motor impairment, gene expression, and increased Fos immunoreactivity. Mol. Brain 6, 56.
Yamamoto, H., Sagi, N., Yamamoto, T., Goji, Y., Okuwa, M., Yoshii, M., Moroji, T., 1992. Inhibitory effects of psychotomimetic sigma ligands on nicotine-induced K+ flux from differentiated PC12 cells. Neurosci. Lett. 147, 97–100.
Ye, J., Witter, M.P., Moser, M.-B., Moser, E.I., 2018. Entorhinal fast-spiking speed cells project to the hippocampus. Proc. Natl. Acad. Sci. U.S.A. 115, E1627–E1636. https://doi.org/10.1073/pnas.1720855115.
Young, L.A., Young, L.G., Klein, M.M., Klein, D.M., Beyer, D. (Eds.), 1977. Recreational Drugs. Collier Books, New York (quoted in Siegel chapter NIDA Research Monograph 21 August 1978).
Zhang, D.X., Levy, W.B., 1992. Ketamine blocks the induction of LTP at the lateral entorhinal cortex-dentate gyrus synapses. Brain Res. 593, 124–127.
Zukin, R.S., Zukin, S.R., 1981. Demonstration of [3H]cyclazocine binding to multiple

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008

opiate receptor sites. Mol. Pharmacol. 20, 246–254.
Zukin, S.R., 1982. Differing stereospecificities distinguish opiate receptor subtypes. Life Sci. 31, 1307–1310.
Zukin, S.R., Brady, K.T., Slifer, B.L., Balster, R.L., 1984. Behavioral and biochemical stereoselectivity of sigma opiate/PCP receptors. Brain Res. 294, 174–177.
Zukin, S.R., Zukin, R.S., 1979. Specific [3H]phencyclidine binding in rat central nervous system. Proc. Natl. Acad. Sci. U.S.A. 76, 5372–5376.
Zweifel, L.S., Parker, J.G., Lobb, C.J., Rainwater, A., Wall, V.Z., Fadok, J.P., Darvas, M., Kim, M.J., Mizumori, S.J.Y., Paladini, C.A., Phillips, P.E.M., Palmiter, R.D., 2009. Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. Proc. Natl. Acad. Sci. U.S.A. 106, 7281–7288. https://doi.org/10.1073/pnas.0813415106.

Please cite this article in press as: Ingram, R., et al., Some distorted thoughts about ketamine as a psychedelic and a novel hypothesis based on NMDA receptor-mediated synaptic plasticity, Neuropharmacology (2018), https://doi.org/10.1016/j.neuropharm.2018.06.008