Why sigma-1 receptor dysfunction might confer vulnerability to cannabis-induced psychosis

Jonathon C. Arnold
The Brain and Mind Research Institute and Discipline of Pharmacology, University of Sydney, Sydney, Australia

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The N-methyl-D-aspartate (NMDA) receptor has long been implicated in the pathophysiology of schizophrenia. NMDA receptor antagonists induce psychotic states in humans and when administered to rodents promote lasting behavioural phenotypes relevant to schizophrenia (Javitt and Zukin, 1991; Abi-Saab et al., 1998; Javitt, 2007). Further, schizophrenia brain tissue contains reduced expression and function of NMDA receptors (Errico et al., 2013). It is well established that the use of cannabis increases the risk of psychosis in vulnerable individuals; however, our understanding of the molecular basis of this susceptibility is limited. In this issue of the International Journal of Neuropsychopharmacology Javier Garzon and colleagues delineate a mechanism of relevance to cannabis-induced psychosis by uncovering that the sigma-1 receptor prevents cannabinoids from provoking NMDA receptor hypofunction.

Garzon and colleagues have recently shown that CB1 receptors regulate NMDA receptors at the postsynaptic membrane (Sanchez-Blazquez et al., 2013, 2014; Vicente-Sanchez et al., 2013). This provides an additional CB1 receptor-mediated homoeostatic mechanism against neurotoxicity provoked by excessive glutamate activation of NMDA receptors. Most cannabinoid CB1 receptors are expressed presynaptically and excessive NMDA stimulation by glutamate triggers the synthesis of endocannabinoids like anandamide. Anandamide then behaves as a retrograde transmitter; travelling from the postsynaptic membrane to presynaptic CB1 receptors, which when activated reduce glutamate release (Brown et al., 2003; Melis et al., 2004). Garzon and colleagues’ research has shown that CB1 receptors may also offset excessive NMDA receptor activation via a postsynaptic mechanism. CB1 receptor activation inhibits NMDA receptor function at the postsynapse by CB1 and NMDA receptors forming a complex that is moved from the cell membrane to the cytosol (Sanchez-Blazquez et al., 2013; Vicente-Sanchez et al., 2013). Thus, CB1 receptor activation induces NMDA receptor hypofunction by reducing the synaptic membrane expression of NMDA receptors.

Garzon’s group has been working on detailing the molecules involved in this CB1-NMDA co-internalization process and has shown that the histidine triad nucleotide-binding protein 1 (HINT1) plays a critical role in binding CB1 and NMDA receptors together (Sanchez-Blazquez et al., 2013; Vicente-Sanchez et al., 2013). While the CB1-HINT1-NMDA receptor complex may protect against excitotoxicity, the question remained whether a molecular sensor might switch-off NMDA hypofunction—prolongation of reduced NMDA function is also detrimental to brain function and evidence suggests this is sufficient to trigger psychosis. In the present manuscript the sigma-1 receptor is identified as the molecule that helps dissociate the CB1-NMDA receptor complex, allowing the NMDA receptor to be reincorporated into the postsynaptic density thus normalizing NMDA receptor signalling.

First using cultured cortical neurons Garzon and colleagues demonstrated that the ability of the synthetic cannabinoid receptor agonist WIN 55,212-2 to protect against NMDA-induced neurotoxicity was absent in mice lacking sigma-1 receptors. Then, using biomolecular fluorescence complementation in CHO cells it was shown that the sigma-1 receptor forms physical complexes with CB1, NR1 subunits of the NMDA receptor and HINT1 proteins. The presence of the sigma-1 receptor almost abolished the association of HINT1 with NR1 subunits, which is critical for CB1-NMDA receptor binding. Further, mice lacking sigma-1 receptors displayed reduced associations between CB1, HINT1 and NR1 subunits, with the results inferring sigma-1 binds NR1 subunits and prevents the translocation of the HINT1 protein from CB1 to the NMDA receptor.

Sigma-1 receptors also regulated the ability of NMDA receptor antagonism to reduce the analgesic effects of cannabinoids via the physical postsynaptic association of CB1 and NMDA receptors. CB1 receptor internalization and recycling is critical to effective cannabinoid analgesia as it allows resensitized CB1 receptors to be replaced at the cell surface for agonist binding. NMDA...
receptor antagonists reduce the efficacy of cannabinoid-induced analgesia by disallowing CB1 receptor internalization due to the stabilization of the CB1-NMDA receptor complex at the postsynaptic membrane (Sanchez-Blazquez et al., 2013). Here Garzon and colleagues showed sigma-1 receptors were required for NMDA receptor antagonists to disrupt cannabinoid analgesia – the effect was absent in sigma-1 knockout mice and in mice treated with sigma-1 receptor antagonists. NR1 subunits of the NMDA receptor were proven to bind CB1, as NR2-specific antagonists did not reduce cannabinoid analgesia and NR1 subunits were specifically co-precipitated with CB1 receptors in synaptosomes. This provided additional evidence that the sigma-1 receptor is vital for CB1-NMDA receptor uncoupling, this time with NMDA hypofunction impacting upon CB1 receptor sensitivity.

More research is needed to progress the exciting findings of Garzon and colleagues. One major limitation of their manuscript is that they utilized cannabinoid analgesia as a behavioural measure which has little relevance to schizophrenia-related behaviours, at least as measured in animals. Repeated adolescent cannabinoid exposure in rodents promotes a schizophrenia-relevant behavioural phenotype (e.g., sensorimotor gating deficits and cognitive dysfunction) coinciding with reduced expression of NMDA receptors in the hippocampus (Schneider and Koch, 2003; Quinn et al., 2008; Rubino et al., 2009). Thus, it would be of interest to observe whether such a phenotype might be exacerbated or reduced by antagonists or agonists of the sigma-1 receptor respectively. Another limitation is that their data were generated from cortical neuronal cultures and thus could not provide information on which specific cell types or brain regions their results are relevant to. It would be of interest to observe whether CB1-NMDA receptor co-internalization occurs in GABA interneurons of the prefrontal cortex given more CB1 receptors are expressed in GABA interneurons than pyramidal neurons (Marsicano and Lutz, 1999; Eggan et al., 2010), and CB1 receptor and NMDA receptor down-regulation have been observed in the prefrontal cortex of schizophrenia patients (Eggan et al., 2008; Errico et al., 2013).

Garzon and colleagues findings are quite timely given the recent report that pregnenolone protects the brain against the psychoactive actions of cannabis (Vallée et al., 2014). Given that pregnenolone might be an endogenous ligand for the sigma-1 receptor (Zheng, 2009), this opens the possibility that THC-induced pregnenolone may activate sigma-1 receptors to protect against CB1-NMDA receptor coupling, internalization and consequent NMDA receptor hypofunction. This mechanism could be additional to that posed by Monique Vallée et al. (2014), who showed that the effects of pregnenolone were mediated by signalling-specific allosteric modulation of a unique binding pocket of presynaptically located CB1 receptors.

The manuscript by Garzon and colleagues implies any dysfunction of the sigma-1 receptor function might increase one’s risk of CB1 receptor activation-induced NMDA receptor hypofunction and consequent psychosis. The sigma-1 receptor offers a novel molecular safety switch that uncouples the internalized CB1-NMDA receptor ensemble and corrects prolonged NMDA hypofunction. The sigma-1 receptor restores NMDA synaptic signalling by disconnecting the binding of CB1 and NMDA receptors in response to reduced intracellular calcium concentrations provoked by CB1-NMDA receptor internalization. This implies that individuals with loss-of-function single nucleotide polymorphisms in sigma-1 could be at enhanced vulnerability to cannabinoid-induced psychosis. Interestingly, both HINT1 and sigma-1 receptor variation has been linked to an increased risk of developing schizophrenia, however no pharmacogenomic study has specifically associated these genes to schizophrenia promoted by cannabis (Kurotaki et al., 2011; Ohi et al., 2011; Varadarajulu et al., 2012; Watanabe et al., 2012).

Investigating which mediators protect the brain against the effects of cannabinoids has important implications for understanding why some individuals are vulnerable to the propyschotic actions of cannabis. The preclinical identification of mediators instructs pharmacogenomic studies, which aim to discover the genes that confer vulnerability to psychosis. Further, basic research provides mechanistic information that strengthen the biological plausibility of links made between genes, cannabis and schizophrenia risk. A multitude of both neuropharmacological and pharmacokinetic mechanisms likely combine in complex ways to increase the risk of cannabis-induced psychosis (Arnold et al., 2012; Spiro et al., 2012). Our prior work has shown that mice with partial genetic deletion of neuregulin 1 (Nr1), a schizophrenia-susceptibility gene, are vulnerable to the neurobehavioural effects of cannabinoids (Karl and Arnold, 2013). Repeated THC exposure in adolescence increased the expression of NMDA receptors in the hippocampus of Nr1 hypomorphic mice but not wild-type mice (Long et al., 2013). Further, we demonstrated that this was accompanied by altered regulation of proteins involved in trafficking NMDA receptors to the synaptic membrane (Spencer et al., 2013). The manuscript by Garzon and colleagues has uncovered another mediator to consider in the complex biology of cannabis-induced psychosis and further suggests that dysregulation of NMDA receptor function might be the common denominator.

References
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