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PERSPECTIVE

Optimizing psychedelic compounds for neuropsychiatric therapy

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Psychedelic compounds have engendered considerable excitement for the treatment of a range of psychiatric diseases [1]. Rapid and persistent beneficial effects of psilocybin have been reported for depression, alcohol use disorder, nicotine addiction, and OCD. The FDA has given psilocybin a fast-track designation for depression and entrepreneurs are investing heavily in psychedelic medicine, with a focus on novel non-hallucinogenic compounds with unique non-canonical pharmacological properties. There is currently a vigorous debate regarding the optimal properties of such compounds in terms of their receptor selectivity, signaling, and pharmacokinetic properties.

One barrier to the widespread utilization of psychedelic compounds is the characteristic intense alterations in sensory perception and consciousness that they produce. This response necessitates a costly 6–8 h of full-time psychological support in an inpatient setting [2]. The hallucinatory state produced by psychedelic compounds in humans results from 5HT2AR activation. These powerful alterations of consciousness are described as intensely spiritual and emotionally meaningful and are thus thought by many to be essential to the antidepressant response [3]. If they are not essential, however, then the cost of treatment, acceptance, and ultimate utility of psychedelic compounds could be greatly improved by developing therapies that maximize antidepressant properties and minimize the psychedelic response. This development is contingent on deeper understanding of the specific mechanisms of action of psychedelic compounds.

The recent report in *Nature* from Cameron et al. [4] offers tantalizing evidence that non-hallucinogenic psychedelic compounds may possess beneficial actions. The authors started with ibogaine, a powerful hallucinogenic plant alkaloid with low affinity for serotonin and dopamine transporters, as well as kappa opioid receptors [4, 5]. They then synthesized a novel analog of ibogaine called tabernanthalog (TBG). TBG is shown to have unique pharmacological properties and to lack many of the negative side effects of ibogaine. TBG is a partial agonist of the 5HT2AR (EC_{50} = 150 nM) and produces roughly half of the 5HT2AR activation as serotonin. Similar to other psychedelic compounds, TBG is nonselective and has high affinities for several 5HTRs including 5HT1BRs (EC_{50} = 34 nM), where it is a full agonist. 5HT1BR activation promotes dopamine release in the reward system [6], strengthens excitatory synapses, and is implicated in the antidepression-like actions of SSRIs [7], making it unclear which receptor type is critical to its antidepressant-like properties. TBG also has a high affinity for the serotonin transporter and monoamine oxidase, suggesting that it may elevate endogenous serotonin levels like conventional antidepressants. Even at high doses, TBG did not induce a head twitch response in mice, a 5HT2AR-dependent behavior predictive of psychedelic responses in humans.

The authors tested the behavioral effects of TBG in the forced swim test and observed decreased immobility time a day after injection, as was also seen with the fast-acting antidepressant ketamine. Unlike the persistent effects elicited by ketamine, however, these effects were no longer observed 7 days post injection. Although these data are consistent with potential antidepressant activity, additional evidence is needed using assays with greater parallels to human depressive symptoms, such as the reversal of an anhedonic state [8]. Despite the lack of a 5HT2AR-dependent head twitch response to TBG, the effects of TBG in the forced swim test were blocked by a 5HT2AR antagonist. TBG did not induce a conditioned place preference, suggesting a low risk for addiction. These results offer hope that TBG and other partial 5HT2AR agonists may ultimately provide the means to elicit a therapeutic antidepressive response in the absence of a psychedelic response.

Cameron et al. provide evidence that TBG may exert its behavioral actions through changes in synaptic function. In developing neurons in culture, TBG promoted neurite outgrowth by stimulation of 5HT2Rs, as shown previously for other psychedelic compounds [9]. Whether psychedelic compounds can exert such a profound morphological effect in a fully developed adult nervous system remains to be demonstrated, however. They also observed that TBG promoted the persistence of newly formed dendritic spines in cells in the prefrontal cortex, suggestive of an increase in the number of excitatory synapses formed onto these cells. Whether 5HT2ARs are required for this response to TBG was not tested, but selective 5HT2AR agonists produce similar effects [9, 10]. Ketamine also promotes increases in dendritic spine number after chronic stress [11], perhaps because they convergence onto common signaling pathways. Potential increases in the number of synapses raise interesting questions about the identity of the neuronal populations that contribute the presynaptic terminals to these newly formed spines, how synapse specificity is maintained during this process, and whether there are concomitant physiological changes in synaptic strength. Regardless, increases in connectivity should promote the function of the stress-sensitive reward circuits in which these cells are embedded, a mechanism of action shared with conventional and fast-acting antidepressant drugs [12]. Indeed, successful treatment with SSRIs has recently been shown to correlate with a strengthening of reward circuits in human

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depression [13]. Perhaps pan-serotonergic psychedelic compounds *rapidly* induce the same effects that SSRIs induce *slowly*.

Because psychedelic compounds have beneficial effects in various substance use disorders, the authors tested the effects of TBG in a mouse model of alcohol 'binge' drinking. A transient (24–48 h) decrease in alcohol consumption was observed after a single injection, but there was no lasting decrease. TBG did not elicit a corresponding decrease in water consumption, suggesting it was due to a specific change in the drive to consume alcohol. The data suggest that the ethanol solution became unpalatable or aversive after TBG by changing the weight of rewarding and aversive stimuli. They also tested TBG in rats in a heroin self-administration paradigm. Lever pressing for heroin was acutely and transiently decreased 3 h after TBG injection, whether given during the initial self-administration phase, during the extinction process, or during reinstatement of previously withdrawn heroin. Interpretation of these results is complicated by data demonstrating that rats also failed to self-administer sucrose pellets immediately after TBG injection. Although TBG did not affect the behavior of rats in an open field arena, the acute changes elicited by TBG in these models suggest it may produce subtle deficits in locomotor or cognitive performance, perhaps hinting at strong perceptual alterations despite the absence of a head twitch response. The role of the 5HT2AR in these responses was not tested.

These are exciting times for psychedelic medicine, with work like Cameron et al. offering the promise of a brand-new pharmaceutical landscape for treatment of neuropsychiatric disorders. More clinical work is clearly needed. A significant challenge for the antidepressant actions of psychedelic compounds is to distinguish placebo effects, which can be very strong in trials of fast-acting antidepressants, from true drug effects given the difficulty of identifying realistic placebos that are not readily distinguished from psychedelic compounds. It is also particularly important to determine the necessity of the subjective psychedelic response for the antidepressant response, perhaps by combining administration of a psychedelic compound with a 5HT2R antagonist in depressed subjects. Preclinical research on psychedelic compounds is also needed to better define their receptor pharmacology and establish the mechanisms underlying their therapeutic actions. Sadly, the NIH funds only four grants on these compounds at present but expect that to change soon. Stay turned on about the potential of these compounds and tuned in to new preclinical and clinical developments!

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