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Hallucinogenic Drugs: A New Study Answers Old Questions about LSD

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LSD induces profound psychedelic effects, including changes in the meaning of percepts. The subjective effects of LSD are fully blocked by a 5-HT_{2A} receptor antagonist. LSD may alter meaningfulness by increasing activity in cortical regions responsible for processing personal attribution.

Almost 75 years have passed since lysergic acid diethylamide (LSD) was discovered to act as a potent hallucinogen. Since then, LSD has been used by millions of people worldwide, including tens of thousands of research subjects. Although investigation of the clinical effects of LSD ceased in the early 1970s due to widespread nonmedical use and concerns about toxicity, human trials have resumed over the last decade [1–3], including studies using modern imaging techniques [4]. A new study published by Preller *et al.* in a recent issue of *Current Biology* [5] continues

that work by examining the mechanism of action of LSD.

The discovery of LSD helped to bring about the modern era of biological psychiatry. Serotonin (5-hydroxytryptamine, 5-HT) was initially identified by Rapport [6] as a vasoconstrictive agent in serum, but was later found to be present in the central nervous system. In 1953, Gaddum reported that LSD antagonizes the contractile effect of 5-HT on uterine smooth muscle [7]. That finding, coupled with the presence of 5-HT in the brain, led Woolley and Shaw [8] to propose that 5-HT plays a specific role in mental

processing and in nervous disorders. Their proposal is noteworthy because it was one of the first times that a neurochemical was linked to brain function.

Despite the importance of LSD to neuropsychopharmacology and its long history of human use, no one has ever conclusively identified the receptor mechanisms responsible for mediating the psychedelic effects of LSD. The failure to resolve this fundamental question was not due to a dearth of information about the pharmacology of LSD — far from it. There is compelling evidence that the characteristic effects of LSD and other

serotonergic hallucinogens (e.g., psilocybin and mescaline) are mediated by the 5-HT_{2A} receptor [9]. The 5-HT_{2A} receptor was first linked to hallucinogen effects in the early 1980s, based to a large extent on animal behavioral models as well as *in vitro* pharmacological studies [10]. A milestone occurred in 1998 when Dr. Franz Vollenweider and colleagues demonstrated that the psychedelic effects of psilocybin are blocked by ketanserin, a moderately selective 5-HT_{2A} antagonist [11]. Despite these findings, however, it has not been clear to what extent the 5-HT_{2A} receptor is responsible for mediating the hallucinogenic effects of LSD. Compared to psilocybin, the pharmacology of LSD is considerably more complex: both drugs act as nonselective serotonin receptor agonists, and LSD also binds to dopaminergic receptors. LSD has moderately high affinity for dopamine D₂ receptors [12] and the dopaminergic effects of LSD are reportedly behaviorally relevant in rodents — at least under certain conditions [13]. Some effects of LSD, such as thought disorder and ego dissolution, are reminiscent of the symptoms of psychosis [14]. It is conceivable that D₂ receptor activation by LSD contributes to its psychotomimetic effects.

The study conducted by Preller *et al.* [5] examined the contribution of 5-HT_{2A} receptors to the effects of LSD in humans. LSD was tested at a dose (100 µg p.o.) that is capable of producing robust alterations of consciousness [2]. The subjective effects of LSD were assessed using the Five-Dimensional Altered States of Consciousness (5D-ASC) rating scale, a validated self-report questionnaire frequently used in hallucinogen studies. According to the report [5], pretreatment with 40 mg ketanserin completely blocked the subjective response to LSD in 22 volunteer subjects who participated in the double-blind, placebo-controlled study. These findings confirm that the psychedelic effects of LSD are a consequence of 5-HT_{2A} receptor activation. The ability of ketanserin to fully ameliorate the response to LSD is surprising because it suggests that dopamine receptors do not play an appreciable role in the effects. As a caveat, the effects of LSD are notably dose-dependent, and higher doses are more likely to provoke psychosis-like

effects. The possibility of a dopamine system contribution to the effects of higher doses of LSD cannot be excluded based on these findings. Nevertheless, it is now apparent that the 5-HT_{2A} receptor can fully account for LSD-induced phenomenology.

Another reason these findings are significant is because they corroborate the results of animal studies with LSD. Ketanserin was first reported to antagonize the behavioral response of rodents to LSD in 1987 [15], a finding supported by subsequent studies. Hence, it has taken thirty years to confirm that the interaction between LSD and ketanserin also occurs in humans. Although by no means optimal, the use of animal models to probe the pharmacological and neurochemical actions of serotonergic hallucinogens has been necessitated by the difficulties associated with human hallucinogen research. Unfortunately, development of animal models of hallucinogen effects has been hindered by the highly subjective nature of the psychedelic state and uncertainties regarding the cross-species translational validity of animal findings. By confirming that ketanserin can block the effects of LSD in humans, the work of Preller *et al.* provides powerful evidence supporting the use of animal behavioral paradigms to experimentally model the effects of hallucinogens in man.

LSD and psilocybin are known to alter the meaning of percepts [1,4]. There is evidence of aberrant assignment of salience in patients with schizophrenia [16], so understanding the neurobiology of LSD-induced misattribution of personal relevance and meaning could potentially provide insight into the biological basis for schizophrenia. Hence, in addition to testing whether ketanserin can block the subjective effects of LSD, Preller *et al.* also used functional magnetic resonance imaging (fMRI) to investigate the neural substrates responsible for LSD effects on meaning. The study showed that LSD increased meaningfulness ratings for previously meaningless or neutral music. Importantly, the effect of LSD on the perception of meaningfulness was accompanied by elevated activity in frontal cortical areas involved in self-referential processing.

In addition to potentially addressing the neurobiological basis of schizophrenia, these results are potentially relevant to the putative therapeutic effects of hallucinogens. According to two recent double blind, placebo-controlled crossover studies [17,18], a single dose of psilocybin can provoke long-lasting (≥6 months) reductions of anxiety and depression in cancer patients. In both studies, the therapeutic responses were correlated with psilocybin-induced mystical experiences. Previous trials also indicated that psilocybin [19] and LSD [3] have therapeutic potential, but those studies had small sample sizes or open label designs. The mystical states induced by psilocybin are consistently rated by subjects as being among the most meaningful experiences of their lives [17,20], resulting in enduring psychological transformations. Similar to psilocybin, LSD can also provoke mystical experiences [2]. The ability of hallucinogens to increase perceived meaningfulness and personal relevance could be one factor contributing to mystical experiences as well as to the beneficial therapeutic outcome. Patients who believe that death has profundity and meaning are more likely to peacefully accept the prospect of their impending death. Hence, although not the stated goal, the fMRI study conducted by Preller *et al.* may help to identify the brain regions involved in the therapeutic response to LSD and other hallucinogens.

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Vascular Morphogenesis: An Integrin and Fibronectin Highway

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A new study shows that endothelial cells use synaptic-like machinery to control polarized secretion and deposition of newly synthesised fibronectin. This process is coupled to active integrin recycling to the same locations and is fundamental for vascular development in zebrafish.

The formation of new blood vessels and their subsequent maturation into a functional tubular network that supports blood circulation are the defining events for embryonic development. Unsurprisingly, the elements that control vascular morphogenesis are also implicated in multiple life-threatening human diseases (e.g. ischemic cardiovascular disease and neoplastic development) and, as such, vascular biology has become an intensely studied research topic. Vascular development is

highly dependent on the continued and extensive crosstalk between endothelial cells that line the vessel wall and the underlying basement membrane, a specialized proteinaceous extracellular matrix (ECM). In particular, endothelial cells secrete fibronectin, a key ECM protein, as a soluble dimer that is then reorganized into a fibrillar network outside of the cell. In this bioactive fibrillar form, fibronectin provides important mechanical and chemical cues necessary for endowing endothelial cells with a

sense of polarity during vascular tubulogenesis [1–3].

Endothelial cell interactions with the ECM are predominately mediated by integrins, a family of transmembrane heterodimeric adhesion proteins consisting of α and β subunits. Integrins bind directly to ECM ligands, trigger important signalling pathways and provide a physical anchor between the cell cytoskeleton and the ECM. The fundamental requirement for fibronectin and its receptor, fibronectin-binding