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Tolerance to LSD – How the brain bolts the doors of perception

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LSD had always been a *once-in-a-while* drug. Compared to other recreationally used drugs, the serotonergic psychedelic *lysergic acid diethylamide* (LSD) is thought to have a rather low addiction liability1 and its consumption at high frequency has therefore never really been a topic, neither to the public nor to science. Things have changed.

Ushered in by press articles on LSD use in Silicon Valley,2,3 as well as James Fadiman's *Psychedelic Explorer's Guide*,4 a new way of taking LSD has gained public attention. Within the so-called *psychedelic microdosing regimen*, which is believed to enhance mood and creative thinking, people consume LSD and other psychedelic drugs in low (non-psychedelic) doses, but on a regular basis.5 Although the 21st century is said to mark a psychedelic renaissance with reawakened scientific interest in the acute effects of psychedelics, surprisingly little science can yet tell us what happens when LSD is consumed regularly, again and again.

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Drugs change their face over time – or do we?

A variety of recreationally used psychoactive drugs are notorious for their potential to lure consumers into frequent and/or long-term consumption. Although LSD does not share comparable qualities, the clinical

experience with addictive substances teaches us an important lesson: the effects of consuming a drug only once in a while do not necessarily equal the effects of frequent or long-term consumption of that drug.

Addictive drugs, when taken once in a while, induce their acute effects: euphoria, excitement, or a sense of calm, to name a few of the sought-after drug rewards. When repeatedly consumed at short intervals, however, the desired effects often fade, leaving a state of *pharmacological tolerance*. The disappointed user might seek to overcome tolerance by consumption of higher drug amounts, which increases the burden on the body. New, usually more unpleasant effects might manifest over time, and quitting the drug may cause a withdrawal syndrome; where there used to be a burst of energy, for instance, there is now depletion.6

If the drug is properly stored and its purity remains the same, however, it is unlikely that the drug changes its properties towards the body over time. It must be the other way around instead: The body changes its properties towards the drug.

LSD's unusual infatuation with tolerance

LSD is unusual. Tolerance with respect to LSD's psychedelic effects comes in a rush, yet published reports on addiction-like patterns and/or withdrawal symptoms surrounding the use of classic serotonergic psychedelics are almost unheard of. Published anecdotes and experimental research in humans are generally consistent and indicate that the psychedelic experience almost completely subsides when psychedelic doses of LSD are taken around four days in a row.

And yet, tolerance seems to go as quickly as it comes. Within less than a week of discontinuation, the original intensity of the psychedelic experience can be reignited.7 In an early human study from the mid-1950s, psychedelic doses of LSD were given daily for two to three weeks, or even up to three months. By the end of the repeated LSD dosings, tolerance was so profound that when researchers replaced the drug with mere water, subjects did not even recognise that it was not LSD they had received. Nor were there any signs of withdrawal.8

Most of the research on human tolerance to LSD was done back in the 1950s and '60s. While there is large agreement on the quick rise and fall of psychedelic tolerance, there are still a lot of questions that have remained unanswered ever since. In most of the performed experiments, LSD was given for a few days only, usually in daily increasing doses or in repeated, full psychedelic doses.7 Microdosing, as it is done today, was not common back then. Therefore, we do not know if and how tolerance develops when LSD is given in microdoses every other day for months and years. Importantly, the mechanisms whereby psychedelic tolerance arises in humans remains largely undiscovered: If it is not the drug that changes, what is it within the body that renders LSD inactive? What is it that the brain does to bolt the doors of perception seemingly at a moment's notice, then go on and re-open some days later?

Bolted doors – when LSD cannot find its interaction partner in the brain

In order for LSD to alter consciousness, it needs to be carried to the brain via blood flow and bind to receptors embedded within the membranes of brain cells. A singular cell can be thought of as a tiny room in the brain. Its membrane, in this analogy, is like a flexible wall or a fine net that separates the individual cell from other cells. A receptor can be thought of as an even tinier bead-chain crumpled together into the cell's membrane so that one part of the chain protrudes to the outside and the other part protrudes to the inside of the cell. There is a myriad of receptors within a given membrane, but the most important interaction partner for LSD is called the *serotonin (5-HT) 2A receptor*.

LSD approaches the cell from the outside, binds to 5-HT2A receptors, and allows for the receptors to relay LSD's unique message through the membrane and into the cell. One of the highest concentrations of 5-HT2A receptors in the body can be found within the membranes of so-called *pyramidal cells*, which populate the outermost layer of the brain (i.e., the cortex)9. Pyramidal cells have far-reaching branches that are well suited for integrating sensory, emotional, and cognitive information from all around the brain. It has been suggested that proper integration along the given branches and the "decision" of the pyramidal cells to pass information on or to keep it mum is key to whether it enters consciousness or gets denied.10 LSD has been shown to increase the responsiveness of cortical pyramidal cells to incoming information11 leading them to release more of their neurotransmitter glutamate12. Glutamate carries an excitatory message which invites other neurons to follow suit, become more responsive themselves, and thus help to spread the word sparked off by LSD. According to the current scientific understanding, it is this LSD-5-HT2A-glutamate triad that represents one of the cellular key principles of psychedelic activity.

So far, so good; but what does all of this have to do with tolerance? Suppose it is indeed the cortical LSD-5-HT2A-glutamate interaction that holds the key to the doors of perception. In that case, it might be a wise move for the brain to interfere with this interaction to become tolerant and regain its original balance. Given the lack of human research into this field, possible evidence for such interference can only be gathered from the animal kingdom. As in humans, LSD targets 5-HT2A receptors in animals to affect their behaviour. Rats, similarly to humans, also develop tolerance to LSD.7 When treated with LSD for five days, rats not only become tolerant to LSD's behavioural effects but also show *downregulation* of 5-HT2A receptors in the cortex of the brain.13,14 Downregulation means that the receptors are internalised (i.e., engulfed by the cell) and then decomposed within the cell15,21 so that they no longer provide a binding partner for LSD. The removed receptors are rapidly replenished when LSD is withdrawn, though, so that upon re-application LSD can bind to them again. At first sight, the cortical 5-HT2A downregulation found in rats nicely mirrors the come-and-go character of tolerance in humans. However, whereas first signs of tolerance in rats and humans are already detected on the second day following ingestion, cortical 5-HT2A downregulation has been shown not to appear before the fifth day of repeated LSD treatment.13 Thus, although important, 5-HT2A downregulation might not be the only process involved in the development of psychedelic tolerance.

To identify what other processes might be involved, we performed a study on tolerance to LSD in rats at the Institute of Pharmacology and Toxicology of the Otto-von-Guericke University in Magdeburg. We found that repeated LSD treatments reduced the capacity of glutamate to bind to its receptors in the cortex of tolerant rats, and that certain subtypes of glutamate receptors, namely mGlu2/3 receptors, became less responsive when stimulated.16 Intriguingly, these changes in the cortical glutamate system were visible before there were any signs of 5-HT2A downregulation. This could perhaps help explain those phases of tolerance that can be detected before five days of treatment. If we were to think of LSD binding to cortical 5-HT2A receptors as a "spark", we could think of the downstream release of glutamate (or other such relay systems) as the "tinder" needed for the psychedelic message to spread. In this analogy, then, LSD tolerance can begin via thinning out the tinder well before the spark itself is quenched.

Differential tolerance – is it safe to chronically (micro-)dose LSD?

When consumed in psychedelic doses and only once in a while, LSD – relative to other drugs of recreational use – is generally thought to exert rather low toxicity on the body's organ system.17 And consumption of low doses of psychedelics leads to lower plasma levels18 and lower binding to receptors than consumption of normal or high doses.19 Therefore, if psychedelic doses of LSD are rather safe for the body, one might expect low doses to be even safer. Although there is nothing to be said against this for once-in-a-while or short-term use,18,20 one should still keep in mind that acute safety does not necessarily equal chronic safety.

In our research on tolerance to LSD in rats, we investigated *hyperthermia* and so-called "wet dog shakes", two bodily effects that, like psychedelia, are mediated by LSD activating 5-HT2A receptors. LSD-induced wet dog shakes continued to occur when small doses were repeatedly given once or twice per day but subsided as some of the small LSD doses were exchanged by medium doses, or were given at a four-hour interval. LSD's effect on body temperature was even more resistant than wet dog shakes: Hyperthermia subsided only when most of the small doses were exchanged by medium doses.21

These findings point to two crucial characteristics of LSD tolerance: Firstly, tolerance depends on the dose and interval of consumption. The higher the dose and the smaller the interval, the more likely it is that animals become tolerant. Secondly, tolerance to LSD arises with respect to different effects in different ways, a phenomenon known as *differential tolerance*. Differential tolerance has also been shown for some of the bodily effects of LSD in humans: Effects on body temperature and blood pressure, for instance, only inconsistently indicate tolerance development.7

Similarly, when recreational microdosers were asked about their experiences, they reported a variety of side-effects. These included psychological effects like emotional instability, distractibility, or insomnia, as well as bodily symptoms like headache or dysregulation of body temperature.22 Thus, despite the rapid vanishing of psychedelia upon repeated intake of full-dose LSD, it overall turns out to be quite difficult to predict how the body adapts to a chronic supply of LSD – which effects decrease, which increase, and which pop up perhaps after long-term consumption. Purity and concentrations in a typical LSD blotter may vary, users might not strictly stick to the exact same intervals of consumption, or even be tempted to increase doses over time. Concerns of differential tolerance should, therefore, not be dismissed lightly when thinking about the safety of chronic LSD (micro-)dosing.

All of this, of course, does not exclude the possibility that repeated (micro-)doses of LSD may safely be applied in a (clinically) supervised context and/or even have therapeutically beneficial effects.23,24 It highlights, however, that the scientific understanding of the consequences of frequent and long-term LSD intake is in its infancy. Short-term tolerance to LSD might result from more discrete adaptions, such as 5-HT2A and glutamate receptor downregulation; long-term adaptions of the body to LSD – depending on the dose, interval, and length of intake – might be much more elaborate, though.25 More research is needed to tease out possible benefits and/or detriments of frequent use of psychedelics. Future research should not be restricted to the brain and psychological read-outs but perhaps also look at other organs, which express receptors psychedelics have high preference for.

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For Further Information

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