Chapter 79

Tolerance to Lysergic Acid Diethylamide: Overview, Correlates, and Clinical Implications

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Abbreviations

5-HT$_{2A}$ Serotonin 2A receptor
im Intramuscular
ip Intraperitoneal
LSD Lysergic acid diethylamide
MDA Methylenedioxyamphetamine
mGlu$_{2/3}$ Metabotropic glutamate 2/3 receptor

INTRODUCTION

Lysergic acid diethylamide (LSD) is a serotonergic hallucinogen and, as such, an agonist at serotonin 2A (5-HT$_{2A}$) receptors that induces profound alterations of human consciousness and stereotypic (gross) motor outputs in animals. LSD, internationally, is very popular among recreational drug users (Barratt, Ferris, & Winstock, 2014), and human research, after a long halt, has recently been resumed (Carhart-Harris et al., 2014; Schmid et al., 2015) with efforts to reimplement the drug into psychotherapy (Gasser et al., 2014). Given that certain psychopathologies, as implicated by animal research, might draw more benefit from repeated (rather than one-time) administration of LSD (Buchborn, Schröder, Höllt, & Grecksch, 2014; Gorka, Wojtasik, Kwiatek, & Maj, 1979), it—in light of the current developments—seems important to understand LSD's basic neuropsychopharmacology, not only as to its acuteness, but also as to its chronicity. Repeated administration of LSD, as with other substances of abuse, leads to a decline in the organism's responsiveness to various effects of the drug. This decline, commonly referred to as *tolerance*, might be acquired within the first hours of a single exposure (tachyphylaxis) or instead build up with multiple exposures over a few days. Tolerance to LSD was first described systematically in the mid-1950s (e.g., Cholden, Kurland, & Savage, 1955), yet, apart from a subsection in Hintzen and Passie (2010)'s comprehensive textbook on LSD's pharmacology, there are hitherto virtually no reviews specifically dedicated to this topic. Bridging the gap, we here review the most important findings about tolerance to LSD in humans and animals, discuss possible mechanisms, and outline clinical implications of repeated LSD administration.

TOLERANCE TO LSD IN HUMANS

Tolerance to LSD's Psychedelic Effect

Tolerance to LSD's psychedelic effect has been investigated most comprehensively by Isbell et al. They administered LSD to patients formerly addicted to opioids (n=4–11) and across multiple publications tested 11 different administration regimens (Table 1, Exps 1–11) (e.g., Isbell, Belleville, Fraser, Wikler, & Logan, 1956). LSD's psychedelic effect is characterized by (visual) illusions and pseudo-hallucinations, formal thought disorders, ambivalence, and exaltation of affection, as well as distorted perceptions of time, space, and body-self (e.g., Stoll, 1947). Isbell et al. quantified these by means of Abramson et al.'s 47-item questionnaire, which asked the patients to self-rate their psychophysiological state (e.g., "Are shapes and colors altered?" "Do you feel as if in a dream?" or "Do you tremble inside?" Abramson et al., 1955, p. 34), as well as of a four-level rating system used by a physician to externally estimate the severity of the patient's perceptual distortions. Except for one regimen, in which LSD was given twice a day (Table 1, Exp. 2), Isbell et al. usually administered LSD once per day, by mouth or intramuscularly. In most regimens, they started with a low dose of around 0.3 µg/kg and gradually increased it over 4 to 10 days to a final dose of around 1.4 µg/kg, which then was maintained (Table 1, Exps 1, 2, 5–11). Comparing the patients' reactions to the final dose before and at the end of a given regimen, Isbell et al. demonstrated that significant tolerance to LSD was evident after 4, 7 or 8, 11, 13–15, and 22 days of daily administration (Table 1, Exps 1, 2, 5–11) (see Table 1 for references, e.g., Isbell & Jasinski, 1969). On average (referring to the results of both the questionnaire and the physician's rating), the patients' mental responsiveness to LSD across the various regimens was reduced by around 78%.[1] Figure 1 depicts the rigorousness of this reduction. A 1.5 µg/kg dose of LSD, administered in a pretest, induced a strong mental reaction; after 2 weeks of daily

1. Percentage values in this review, if not directly extractable, were calculated on the basis of the mean values numerically or graphically reported in the original papers.

TABLE 1 Human Studies on Tolerance to LSD

	LSD Regimen	Tolerance		Reference and Sample Size
		Challenge	Noted for	
1	7 days: 20 µg daily increasing to 75 µg po (by 7th day)	8th day: 75 µg po	Mental (somatic effects nd)	Isbell et al. (1956) *n* = 8
2	1st day: 2× 10 µg 2nd day: 2× 20 µg 3rd day: 2× 30 µg po	4th day: 75 µg po	Mental (somatic effects nd)	*n* = 11
3	7–8 days: 90–130 µg → 3 days: 150 µg → 3 days: 180 µg po	Daily for mental effects; days 3, 6, and 10 for somatic effects	Mental (Ø - 87.79% for R, Ø - 78.98% for Q), mydriasis (Ø - 58.62%), HTN (Ø - 68.0%), and PTR (Ø - 117.07%)[a]	*n* = 4 or 5
4	7 days: Ø 1.28 µg/kg→ 77 days: Ø 1.55 µg/kg po	7th day: Ø 1.28 µg/kg 14th day: Ø 1.55 µg/kg 21st day: Ø 1.55 µg/kg 35th day: 3 µg/kg 49th day: 4.5 µg/kg 63rd day: 6 µg/kg po	Mental (Ø - 75.0% for R, Ø - 48.07% for Q) and mydriasis (Ø - 56.25%); inconsistent for HTN (Ø - 30.17%) and PTR (Ø - 5.2%)[a]	*n* = 7 FOA
5	6 or 7 days: 0.25 µg/kg daily increasing to 1.5 µg/kg po (by 6th day)	7th or 8th day: 1.5 µg/kg po	Mental, mydriasis, hyperthermia, HTN, and TACH; not for PTR	Isbell et al. (1961) *n* = 10
6	12 days: 0.15 µg/kg daily increasing to 1.5 µg/kg po (by 10th day)	13th day: 1.5 µg/kg po	Mental, mydriasis, hyperthermia, HTN, and TACH; not for PTR	*n* = 9 FOA
7	14 days: 0.3 µg/kg daily increasing to 1.5 µg/kg im (by 5th day)	15th day: 1.5 µg/kg im	Mental, mydriasis, HTN, and PTR; not for hyperthermia or TACH	Wolbach et al. (1962) *n* = 10 FOA
8	13 days: 0.3 µg/kg daily increasing to 1.5 µg/kg im (by 5th day)	14th day: 1.5 µg/kg im	Mental, mydriasis; trend for TACH and PTR; not for HTN or hyperthermia	Rosenberg et al. (1963) *n* = 10 FOA
9	21 days: increasing to 1.5 µg/kg im once daily[b]	22nd day: 1.5 µg/kg im	Mental, mydriasis, HTN, and TACH (hyperthermia and PTR nd)	Isbell et al. (1964) *n* = 6 FOA
10	13 days: daily increasing to 1.5 µg/kg im (by 6th day)	14th day: 1.5 µg/kg im	Mental and mydriasis; not for TACH, HTN, or PTR (hyperthermia nd)	Rosenberg et al. (1964) *n* = 6 FOA
11	10 days: 0.5 µg/kg daily increasing to 1.5 µg/kg im (by 5th day)	11th day: 1.5 µg/kg im	Mental, mydriasis, and TACH (HTN, PTR, and hyperthermia nd)	Isbell and Jasinski (1969) *n* = 10 FOA
12	5 days: 100 µg daily increasing to 500 µg im (by 5th day)	Daily	Mental (estimated by outward gross behavioral change)	Cholden et al. (1955) *n* = 4
13	2 weeks: 100 µg im	Daily		*n* = 4 schizophrenics
14	3–6 days: 100 µg po	Daily	Mental (somatic effects nd)	Abramson et al. (1956) *n* = 2
15	5 days: 10 µg (1st day) daily increasing to 75 or 100 µg (by 5th day) po	Daily	Mental (somatic effects nd)	*n* = 2 college graduates
16	4–7 days: 25–50 µg (1st day) daily increasing to 200 µg po[c]	Daily	Mental; partially for (undefined) autonomic effects	Balestrieri and Fontanari (1959) *n* = 5 PNP

Continued

TABLE 1 Human Studies on Tolerance to LSD—cont'd

	LSD Regimen	Tolerance		Reference and Sample Size
		Challenge	Noted for	
17	6 days: 0.25 μg/kg (1st day) daily increasing to 1.25 μg/kg (by 6th day) po	7th day: 1.5 μg/kg po	Mydriasis, PTR (mental effects nd)	Chessick et al. (1964) $n=9$ schizophrenics
18	1st day: 300 μg→ 6 days: 100 μg→ Months: 100 μg[d]	Daily (?)[d]	Mental	Hoffer and Osmond (1967)[d]

2×, twice; →, followed by; Ø, mean; HTN, hypertension; FOA, former opioid addicts; im, intramuscular; nd, not determined; PNP, psychiatric and neurological patients; PTR, patellar hyperreflexia; po, per os (by mouth); Q, 47-item self-rating questionnaire; R, rating by physician; TACH, tachycardia. Each row (1–18) contains the LSD regimen employed, the day(s) when tolerance was challenged, the results of challenge, samples, and the corresponding reference.
[a]*Percentage values (averaged across the different challenge days) were calculated on the basis of the mean values graphically presented in the original paper.*
[b]*Exact regimen details not stated.*
[c]*Regimens varied between subjects, exact details not stated.*
[d]*Exact details, administration route, and sample (size) not stated.*

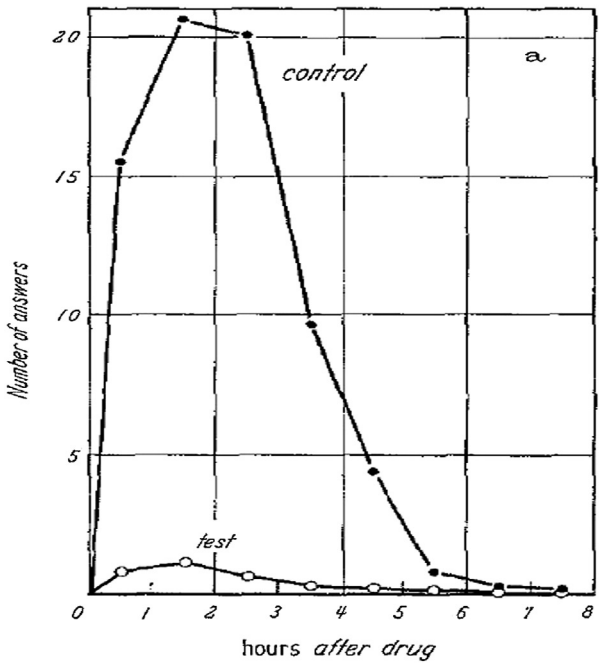

FIGURE 1 **Tolerance to the psychedelic effect of LSD in humans.** Mean time course of the psychedelic effect of a 1.5 μg/kg intramuscular dose of LSD (as determined by a self-rating questionnaire) before (control) and after (test) 2 weeks of daily LSD treatment ($n=10$). *Reprinted from Rosenberg et al. (1963, p. 11), Figure 2(A), with kind permission from Springer Science + Business Media.*

LSD treatment, however, the same dose was virtually inactive (Table 1, Exp. 8) (Rosenberg, Wolbach, Miner, & Isbell, 1963). In two further experiments, which Isbell et al. (1956) performed to outline the course of tolerance development, LSD's effects were quantified not only before and after, but also at various time points during the regimens (Table 1, Exps 3 and 4). In the first of these experiments, they administered an average dose of 138 μg to their patients for 2 weeks. Quantifying LSD's psychoactivity on each day, they demonstrated that a 52% decrease in the questionnaire responses occurred already by day 2. Tolerance as to both parameters, the questionnaire responses and the physician's rating, became near maximal by day 4 and thereafter remained stable on any of the 10 days that followed (Table 1, Exp. 3). In the second of their repeated-quantification experiments, Isbell et al. (1956) administered LSD in daily doses of 1.28–1.55 μg/kg for 84 days and challenged tolerance with increasing doses at weekly, and later biweekly, intervals. The patients' mental reactions to LSD were significantly reduced by days 7, 14, and 21. Although complete tolerance (especially in terms of the questionnaire responses) did not manifest in this experiment (Table 1, Exp. 4), LSD's initial activity in the weeks to follow failed to reignite even when the challenge doses were doubled, tripled, and quadrupled.

Apart from Isbell et al., there are four further groups that published research on mental tolerance to LSD in humans (Table 1, Exps 12–16, 18). Unfortunately, this research was restricted to single-case or anecdotal-like reports and, accordingly, lacks proper statistical analysis. In normal volunteers ($n=2$) and psychiatric/neurological patients ($n=5$), LSD's psychedelic effect during a 4- to 7-day treatment with increasing doses was strongly undermined by tolerance and barely detectable (Table 1, Exps 15 and 16) (Abramson, Jarvik, Gorin, & Hirsch, 1956; Balestrieri & Fontanari, 1959). In schizophrenics ($n=4$) who were administered LSD in increasing doses for 5 days, mental tolerance—as judged by the patients' outward behavior—manifested by day 2, became maximal by days 3 and 4, and slightly (if at all) reversed with the highest dose on day 5 (Table 1, Exp. 12) (Cholden et al., 1955). Similarly, in normal volunteers ($n=2$), schizophrenics ($n=4$), and an undefined group of subjects, tolerance to a 100-μg dose of LSD was (near) complete by day 3, varied slightly (if at all) on days 5 and 6, and thereafter (with continuous treatment) remained stable for up to weeks or months (Table 1, Exps 13, 14, 18) (Abramson et al., 1956; Cholden et al., 1955; Hoffer & Osmond, 1967).

Tachyphylaxis to LSD's Psychedelic Effect

Tolerance to the mental effects of LSD, as described above, substantially manifests 24 h after a one-time administration and can, therefore, be regarded as tachyphylaxis (see definition of terms).

Whether tachyphylaxis to LSD occurs at intervals shorter than 24 h, on the other hand, is largely unknown and can be discussed only with reference to anecdotal reports. Balestrieri and Fontanari (1959) injected two 200-μg doses of LSD at an interval of 6 h to two of their patients. The interval was chosen so that the second dose would challenge tachyphylaxis right after the (main) effects of the first dose had worn off. As the responses evoked by either dose were almost identical, though, tachyphylaxis at the given interval did not seem to occur. In two other reports, the administration of a second dose of LSD 3 h after the first dose (around the peak of the first dose's effects) led to a prolongation and/or intensification and reignited (perceptual) changes characteristic of the earlier phases of the first dose (Freedman, 1984; Hoffer, 1965). The acuteness of the second dose was briefer, however, and the prolongation it brought fell short of additiveness (Freedman, 1984). Thus, referring to the last report, tachyphylaxis to LSD might not occur only at a 24-h, but, to a certain degree, also at a 3-h interval.

Tolerance to LSD's Somatic Effects

Apart from alterations of human consciousness, LSD is known to stimulate and/or facilitate certain autonomic and spinal functions. Typically, LSD's somatic effects comprise a strong dilatation of pupils (mydriasis), patellar hyperreflexia, and slight increases in pulse (tachycardia), blood pressure (hypertension), and body core temperature (hyperthermia). As with mental tolerance, somatic tolerance to LSD has been most comprehensively investigated by Isbell et al. (Table 1, Exps 3–11) (see Table 1 for references, e.g., Isbell, Wolbach, Wikler, & Miner, 1961). LSD-induced mydriasis, in these investigations, showed a pattern of tolerance development similar to that of the psychedelic effect. With a mean decrease of 57.97%, tolerance gained significance after 3, 6, and 10 days (Table 1, Exp. 3); could be demonstrated when challenged on days 7 or 8, 11, 13–15, 21, and 22 (Table 1, Exps 4–11); and failed to reverse even when challenge doses were doubled, tripled, or quadrupled (Table 1, Exp. 4) (e.g., Isbell et al., 1956). Tolerance to LSD-induced patellar hyperreflexia and hypertension manifested by days 3, 6, and 10 as well (Table 1, Exp. 3); as to the other regimens, however, results were more inconsistent (Table 1, Exps 4–10) (e.g., Rosenberg, Isbell, Miner, & Logan, 1964). Tolerance to LSD-induced tachycardia and hyperthermia was not characterized as to its development over 3, 6, and 10 days; as to the other regimens, however, results again vary (Table 1, Exps 5–11) (e.g., Wolbach, Isbell, & Miner, 1962). Chessick, Haertzen, and Wikler (1964)—the only group that, apart from Isbell et al., employed a large enough sample to perform proper statistical analysis ($n=9$)—demonstrated that schizophrenic patients, at the end of a 1-week treatment, largely were tolerant to LSD-induced mydriasis and hyperreflexia. Their data partially conflict with those of Isbell et al., who, engaging in an almost identical regimen, showed tolerance to only mydriasis and not hyperreflexia (Table 1, Exp. 5 vs 17). Balestrieri and Fontanari (1959), who for 4–7 days administered LSD in increasing doses to a group of psychiatric and neurologic patients ($n=5$) (Table 1, Exp. 16), found that, although a high degree of mental tolerance was established, autonomic (not further defined) symptoms often remained. Thus, given this report and the above-mentioned inconsistencies regarding hyperreflexia, hypertension, tachycardia, and hyperthermia, tolerance to LSD's somatic effects is less clear-cut and (except from mydriasis) not necessarily coupled to mental tolerance.

Withdrawal and Recovery from Tolerance to LSD

Isbell et al., after their 14- and 84-day regimens (Table 1, Exps 3 and 4), withdrew LSD without the patients' knowledge and exchanged it with a placebo. The exchange was not recognized by the patients and symptoms of abstinence did not occur. Once withdrawn, 3 days off of LSD was sufficient for the patients to fully recover from somatic and mental tolerance (Isbell et al., 1956). Anecdotal reports from the other groups confirm that partial (Abramson et al., 1956) to full recovery from tolerance to LSD manifests within 3–6 days after discontinuation (Cholden et al., 1955; Hoffer & Osmond, 1967) and that no symptoms of withdrawal are encountered (Balestrieri & Fontanari, 1959).

Concluding Remarks on Tolerance to LSD in Humans

Human research on tolerance to LSD was performed exclusively in the 1950s and 1960s and is weakened by experimental drawbacks, including small sample sizes (of mostly psychiatric patients), incomplete documentation, and the usage of unvalidated psychometrics. Notwithstanding this, the given results convergently indicate that tolerance to LSD's overall psychedelic effect is rigorous. It requires 3–4 days of daily administration to reach near-maximum levels and 5 days of abstinence to completely reverse. As to long-term administration, although results and documentation are less dense, tolerance likewise appears to persist and not to reverse even if challenged with doses as high as 500 μg. Mental tolerance to LSD, most reliably, is accompanied by tolerance to mydriasis; across the various somatic effects of LSD, however, tolerance only inconsistently manifests. Future research, in addition to overcoming the above-named drawbacks, might benefit from differentiating LSD's overall psychedelic effect as to the individual dimensions of psyche (e.g., perception, affection, cognition, and ego-functioning), and investigate whether these equally adapt, or whether differential tolerance development occurs.

TOLERANCE TO LSD IN ANIMALS

Tolerance to LSD in animals varies critically with the strain and species used, the regimen of administration, and the behavior in question. Given the general overview provided by Hintzen and Passie (2010), we restrict our discussion here to three selected behaviors (i.e., shaking behavior, limb flicking, and hallucinogenic pausing), which have been investigated most elaborately in terms of tolerance and, like the human psychedelic effect, are thought to primarily arise from LSD's interaction with 5-HT receptors (see section: Pharmacodynamic Adaptations under Possible Mechanisms of Tolerance to LSD).

Tolerance to LSD-Induced Shaking Behavior in Mammals

Tolerance to LSD-induced shaking behavior, a repetitive movement of the mammal's head (and trunk) around the long axis of its body (Buchborn, Schröder, Dieterich, Grecksch, & Höllt, 2015), has been investigated in rats, cats, and monkeys. In an

TABLE 2 Studies on Tolerance to LSD-Induced Shaking Behavior in Animals

	LSD Regimen	Species/Strain and Shaking Behavior	Tolerance	References
1	1× 10 µg/kg ip → 50 µg/kg challenge after 2, 6, or 24 h	Cat: head and body shakes	Tachyphylaxis at 24 h (−85.6%); ns at 2 h (−57.2%) and 6 h (−67.6%)[a]	Trulson and Jacobs (1977)
2	1× 10 or 50 µg/kg ip → 50 µg/kg challenge after 1, 3, 5, or 7 days		Tachyphylaxis only at 24 h	
3	1st day: 50 µg/kg 2nd day: 50 µg/kg ip	Cat: head and body shakes	Tachyphylaxis (−90.5%)	Trulson et al. (1981)
4	5 days: 10 µg/kg im	Macaque: body shakes	Tolerance on 3rd day (−41.4%)[a] (other days nd)	Schlemmer et al. (1986)
5	5 days: 10 µg/kg im	Macaque: body shakes	Tachyphylaxis on 2nd day (−51.3%)[a] (other days nd)	Schlemmer and Davis (1986)
6	2 days: 10 µg/kg im		No tachyphylaxis (?) (−11.9%)[a] (significance nd)	
7	8 days: 14.2 µg/kg iv	Rabbit: open-field (endogenous 5-HT)-related head bobs	Cross-tolerance on 10th day (−40%) (other days nd)	Aloyo and Dave (2007)
8	8 days: 0.43 µg into each site of dHC	Rabbit: DOI-induced head bobs	No cross-tolerance on 9th day (other days nd)	Romano et al. (2010)
9	8 days: 1.3 µg into each site of dHC		Cross-tolerance on 9th day (−43.5%) (other days nd)	
10	8 days: 4.3 µg into each site of dHC		Cross-tolerance on 9th day (−44.4%) (other days nd)	
11	8 days: 13 µg into each site of dHC		No cross-tolerance on 9th day (other days nd)	
12	1× 25 µg/kg ip → 25 µg/kg challenge after 4, 8, or 24 h	Sprague–Dawley rat: head twitches and wet dog shakes	Tachyphylaxis at 4 h (−46.6%) and 8 h (−32.3%)	Buchborn, Grecksch, Dieterich, and Höllt (unpublished) (Figure 2(A))
13	4 days: 25 µg/kg ip	Sprague–Dawley rat: head twitches and wet dog shakes	No tolerance	Buchborn et al. (unpublished)
14	4 days: 25 µg/kg (morning) + 25 µg/kg ip (evening)[b]		Tolerance on 2nd day (−27.8%), 3rd day (−40.5%), and 4th day (−28.6%)	
15	4 days: 25 µg/kg (morning) + 250 µg/kg ip (evening)[b]		Tolerance on 2nd day (−46.5%), 3rd day (−66.8%), and 4th day (−66.8%)	Buchborn et al. (2015)
16	4 days: 10 ml saline/kg → 4 days: 25 µg/kg (morning) + 250 µg/kg ip (evening)[b]		Tolerance on 2nd day (−55.4%), 3rd day (−50.4%), and 4th day (−59.5%)	

→, followed by; 1×, once; 5-HT, serotonin; dHC, dorsal hippocampus; DOI, dimethoxyiodoamphetamine; im, intramuscularly; ip, intraperitoneally; iv, intravenously; nd, not determined; ns, not significant.
Each row (1–16) contains the LSD regimen employed, species, and shaking-behavior component(s) investigated for tolerance, results of tolerance investigation, and corresponding reference.
[a]*Percentage values were calculated on the basis of the mean values presented in the original paper.*
[b]*Evening dose was administered only on days 1, 2, and 3 (shaking behavior was quantified each day after the morning dose).*

investigation in Sprague–Dawley rats, we administered a single 25 µg/kg dose of LSD (intraperitoneally (ip)) and challenged acute tolerance, that is, tachyphylaxis, by readministering the same dose after 4, 8, or 24 h (Table 2, Exp. 12). As depicted in Figure 2(A), tachyphylaxis to LSD, with a 46.6% decrease in shaking behavior, manifested at the early interval, decreased to 32.3% at the intermediate interval, and was totally absent when both doses were separated by 24 h. Tachyphylaxis did not seem to represent an artifact of LSD accumulation because a 50 µg/kg dose of the drug (as investigated in non-"tachyphylaxed" rats) evoked even more

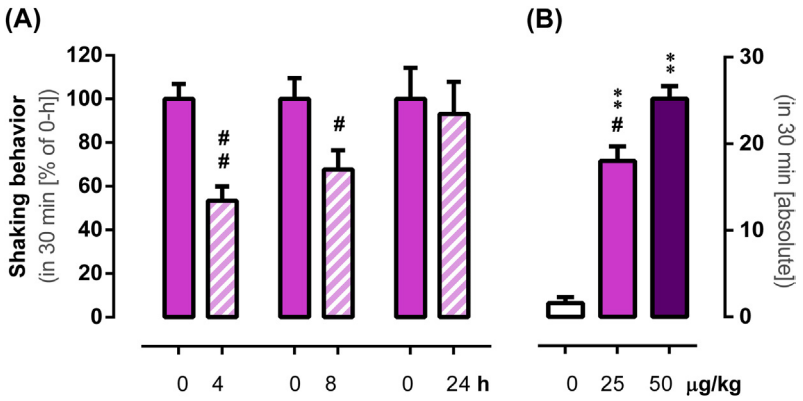

FIGURE 2 Tachyphylaxis to LSD-induced shaking behavior in rats. (A) Shaking behavior in Sprague–Dawley rats, as induced by two separate 25 µg/kg intraperitoneal (ip) doses of LSD at 4-, 8-, or 24-h interval. (B) Shaking behavior induced by a 25 or 50 µg/kg dose of LSD (ip). Each column shows the mean + SEM ($n = 5–7$ per group, two littermates per cage). Wilcoxon comparison to 0-h effect, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ (A). Mann–Whitney comparison to control, $^{**}p < 0.01$, and to 50 µg/kg effect, $^{\#}p < 0.05$ (B). For interpretation, see text. *For general methods see Buchborn et al. (2015).*

shaking behavior than a 25 µg/kg dose (Figure 2(B)) (Buchborn et al., unpublished). Having learned about the rapid onset and rapid reversal of tachyphylaxis, we focused in a next step on tolerance as it would develop over the course of 4 days. Administering LSD (25 µg/kg, ip) once or twice per day, we found tolerance to shaking behavior (with a maximal reduction by 40.5% on day 3) to arise only from the twice-per-day regimen (Table 2, Exps 13 and 14). The reduction was dose-dependent; when the second of each day's two doses was increased tenfold, the degree of tolerance likewise increased and by day 3 acquired a maximum of 66.8% (Table 2, Exp. 15) (Buchborn et al., 2015). In macaques, tolerance to LSD-induced shaking behavior manifested on day 3 as well, yet in contrast to Sprague–Dawley rats, a once-per-day regimen was sufficient to that end; results on tachyphylaxis are inconsistent (Table 2, Exps 4–6) (Schlemmer & Davis, 1986; Schlemmer, Nawara, Heinze, Davis, & Advokat, 1986). In cats, tachyphylaxis to LSD, compared to Sprague–Dawley rats, developed with a delay. Although a decrease in shaking behavior was already present 2 and 6 h after the first dose's administration, it became significant only at the 24-h interval and reversed when both doses were separated by 3 days (Table 2, Exps 1 and 2) (Trulson & Jacobs, 1977). Rabbits, after an 8-day treatment with LSD, showed significant (cross-)tolerance to head bobs (a variant of shaking behavior) challenged by dimethoxyiodoamphetamine or endogenous serotonin (Table 2, Exps 7, 9, 10) (Aloyo & Dave, 2007; Romano et al., 2010).

Tolerance to LSD-Induced Limb Flicking in Cats

Tolerance to LSD-induced limb flicking, a paw movement cats repeatedly exhibit as if to remove a foreign substance, has been investigated by Trulson et al. They injected a single 10 µg/kg dose of LSD (ip) and challenged tolerance, or rather tachyphylaxis,[2] by injecting a second, slightly higher dose of the hallucinogen (50 µg/kg, ip) at varying intervals. Tachyphylaxis to LSD (with a 23.7% decrease in limb flicking) could be detected as early as half an hour after the first dose's administration; it increased with longer intervals (−48.1% at 1 h, −51.3% at 2 h, and −74.2% at 6 h) and became near complete (−91.5%) when the second dose was administered 24 h after the first dose. Tachyphylaxis, similar to shaking behavior in rats (see previous section), did not seem to relate to an accumulation of LSD. If there had been such a relation, a 60 µg/kg dose of LSD (in non-tachyphylaxed cats) would have had to induce significantly less limb flicking than a 50 µg/kg dose; this, however, was not the case (Trulson & Crisp, 1983). Mirroring results for LSD's human psychedelic effect and shaking behavior in cats (see sections: Withdrawal and Recovery from Tolerance to LSD and Tolerance to LSD-Induced Shaking Behavior in Mammals), 3–5 days of abstinence was needed for limb flicking to recover from tachyphylaxis (Trulson & Jacobs, 1977).

Tolerance to LSD-Induced Hallucinogenic Pausing in Rats

In rats operantly conditioned to press a lever for food or water reinforcement, LSD interrupts the constancy of lever pressing and induces periods of nonresponding, that is, *hallucinogenic pausing* (Rech, Tilson, & Marquis, 1975). Tolerance to LSD-induced hallucinogenic pausing has been investigated in various rat strains. Sprague–Dawley rats treated daily with a 100 or 130 µg/kg dose of LSD (ip) became near-maximally tolerant to the pause-inducing effect of the drug within 3–6 days (Commissaris, Lyness, Cordon, Moore, & Rech, 1980; Freedman, Appel, Hartman, & Molliver, 1964; Rech et al., 1975); tachyphylaxis, when LSD was administered three times at 1-h intervals, occurred only as a trend (Freedman et al., 1964). When higher doses of LSD were used, tolerance was protracted. Thus, with 150 µg/kg as a daily dose, tolerance did not manifest before 6–10 days; with a 195 µg/kg dose, a 10-day regimen failed, and up to 2 weeks was needed (Freedman et al., 1964; Rech et al., 1975). The protraction of tolerance, as demonstrated for the 195 µg/kg dose, depended on the schedule of reinforcement; when a variable-interval (instead

2. Trulson and Crisp (1983) rejected the term tachyphylaxis and instead spoke of rapidly developing tolerance. Regarding both terms as synonymous, however (see definition of terms), we discuss their results in terms of tachyphylaxis.

of a fixed-ratio) schedule was employed, the onset of tolerance was accelerated to 1 week (Freedman et al., 1964). As to other rat strains, although the literature is less dense, tolerance had time and dose requirements similar to those in Sprague–Dawley rats. In CFN, hooded, and Wistar rats, with daily injections of 96, 100, and 130 μg/kg (ip), respectively, (near-complete) tolerance to LSD manifested within 3 days (Murray, Craigmill, & Fischer, 1977; Silva, Carlini, Claussen, & Korte, 1968; Winter, 1971). Again, however, no such manifestation could be observed when a high-dose regimen (250 μg/kg/day, ip, hooded rats) was employed at a fixed-ratio schedule (Murray et al., 1977). Holtzman rats, the only strain that markedly fell out of the alignment, even after 3 weeks of daily LSD administration (100 μg/kg, ip), exhibited undiminished hallucinogenic pausing. Only with a three-times-a-day regimen thereafter was tolerance finally manifested at the end of the fourth week (Kovacic & Domino, 1976).

Concluding Remarks on Tolerance to LSD in Animals

A generalized conclusion about tolerance to LSD in animals, given the variability of regimens engaged across the studies, is difficult. All three behavioral effects of LSD discussed are subject to tolerance, yet the temporal patterns of development vary. In cats and Sprague–Dawley rats, tolerance to limb flicking and/or shaking behavior manifests within a few hours after a single administration of LSD. Cats require 3 days of abstinence to recover; for rats, 1 day is enough. Tolerance to hallucinogenic pausing in rats is not as rapid; it varies with the dose, strain, and schedule of reinforcement and may need up to weeks to manifest.

POSSIBLE MECHANISMS OF TOLERANCE TO LSD

General pharmacology differentiates three basic mechanisms of tolerance—pharmacokinetic, pharmacodynamic, or learning-related in nature—that engage adaptations of the metabolism of the drug, the (molecular) targets of the drug, or the organism's capacity to expect and compensate for the effects of the drug.

Pharmacokinetic Adaptations

Trulson and Jacobs (1977) addressed the possibility that tolerance to LSD arises from adaptations of the drug's metabolism. When two doses of LSD were administered at a 2- or a 24-h interval to cats, they showed tachyphylaxis to limb flicking and shaking behavior at the early and the late interval, respectively (see section: Tolerance to LSD in Animals). Because the plasma and brain concentrations of LSD in the tachyphylaxed cats, at either interval, were virtually the same as they were in non-tachyphylaxed animals, however, the decrease in behavior did not seem to be accounted for by an upregulation of its degradation. Similarly, when CFN rats were treated for 3 days with a 96 μg/kg dose of LSD, the hallucinogenic pausing it induced was undermined by tolerance (see above), yet the degradation of LSD, as indicated by its liver and plasma levels, remained unaffected (Winter, 1971).

Pharmacodynamic Adaptations

LSD interacts with a variety of monoamine receptors (Ray, 2010) and tolerance, if pharmacodynamic, theoretically could arise from adaptations of any of these receptors. Despite LSD's promiscuity in receptor binding, however, shaking behavior in rodents (Buchborn et al., 2015), limb flicking in cats (Heym, Rasmussen, & Jacobs, 1984), and LSD's psychedelic effects in humans (Nichols, 2004) are thought to be primarily mediated by activation of (cortical) 5-$HT_{2(A)}$ receptors. For hallucinogenic pausing and shaking behavior, LSD's activity at 5-$HT_{1(A)}$ receptors (Rech, Commissaris, & Mokler, 1988) and heterocomplexation between 5-HT_{2A} and metabotropic glutamate 2 ($mGlu_2$) receptors, respectively, might additionally play a role (Moreno, Holloway, Albizu, Sealfon, & Gonzalez-Maeso, 2011). Repeated administration of LSD (130 or 260 μg/kg, ip) for 5 or 10 days has been shown to downregulate 5-$HT_{2(A)}$ binding sites in various brain areas of Sprague–Dawley rats, including brainstem, mesencephalon, hippocampus, and cortex. Other receptors, such as cortical 5-HT_{1A}, 5-HT_{1B}, and α_1-, α_2-, and β-adrenergic receptors; cortical serotonin transporters; or striatal dopamine D_2 receptors were not affected (Table 3: Exps 4, 13) (Buckholtz, Freedman, & Middaugh, 1985; Buckholtz, Zhou, Freedman, & Potter, 1990). In rabbits, repeated LSD administration downregulated 5-HT_{2A} (but not 5-HT_{2C}) receptors in the frontal cortex (Aloyo, Dave, Rahman, & Harvey, 2001), which co-occurred with tolerance to shaking behavior induced by endogenous serotonin (Table 3, Exps 14, 16) (Aloyo & Dave, 2007). In Wistar and Sprague–Dawley rats, frontocortical 5-$HT_{2(A)}$ downregulation and desensitization, respectively, were similarly paralleled by tolerance to the discriminative cue of LSD (Table 3, Exp. 15) (Gresch, Smith, Barrett, & Sanders-Bush, 2005) and shaking behavior induced by the serotonergic hallucinogens dimethoxymethyl- and dimethoxybromoamphetamine (Buchborn et al., 2015; Leysen, Janssen, & Niemegeers, 1989). Given these results in rodents and the finding that hallucinogen/entactogen-experienced humans, in a first positron-emission tomography study, exhibited (a trend for) reduced cortical 5-HT_{2A} binding sites, too (Erritzoe et al., 2011), it is overall very likely that (fronto-)cortical 5-$HT_{2(A)}$ downregulation indeed is one of the pharmacodynamic key adaptations from which tolerance to serotonergic hallucinogens, and so LSD, arises. In Sprague–Dawley rats, after a 3-day administration, on the other hand, LSD (130 μg/kg, ip) failed to reduce cortical 5-$HT_{2(A)}$ binding sites (Table 3, Exp. 11) (Buckholtz et al., 1990). Thus, tolerance to LSD (especially with administration regimens shorter than 5 days) might not be accounted for by mere 5-HT_{2A} downregulation. In a 2015 study, we administered LSD (25 + 250 μg/kg/day, ip) for 4 days to Sprague–Dawley rats and demonstrated that, although LSD-induced shaking behavior was increasingly undermined by tolerance (see section: Tolerance to LSD-Induced Shaking Behavior in Mammals), a reduction in frontocortical 5-$HT_{2(A)}$ signaling and binding sites did not occur or occurred only as a trend, respectively. In contrast to the lack of significant 5-$HT_{2(A)}$ regulation, however, LSD significantly reduced frontocortical glutamate binding sites and $mGlu_{2/3}$ signaling (Table 3, Exp. 18) (Buchborn et al., 2015). LSD has no affinity (Ray, 2010), but is thought to indirectly affect glutamate receptors via 5-HT_{2A}–$mGlu_2$ cross talk and 5-HT_{2A}-related glutamate release (see Figure 3) (Moreno et al., 2011; Muschamp, Regina, Hull, Winter, & Rabin, 2004). As the reduction in glutamate

TABLE 3 **Pharmacodynamics of Repeated LSD Administration in Animals**

	LSD Regimen	Behavioral Tolerance	Pharmacodynamic Correlate	References
1	1× 100 μg/kg ip	Sprague–Dawley rat: nd	FB, BS + SC: [^{3}H]5-HT binding UC	Trulson and Jacobs (1979)
2	4 days: 100 μg/kg/6 h ip		FB, BS + SC: [^{3}H]5-HT and [^{3}H]LSD binding↓	
			STR, LFB: D_2 binding UC	
3	1st day: 50 μg/kg →	Cat: shaking behavior, limb flicking	LSD-induced inhibition of dorsal raphe unit activity↑	Trulson et al. (1981)
	2nd day: 50 μg/kg ip			
4	10 days: 260 μg/kg ip	Sprague–Dawley rat: nd	Cortex, HC, STR, DE/ME, P/MO: [^{3}H]LSD binding to 5-HT_2↓ and to 5-$HT_{(1)}$ UC	Buckholtz et al. (1985)
5	1st day: 50 μg/kg ip	Cat: limb flicking	FB, BS + SC: [^{3}H]5-HT binding UC	Trulson (1985)
	(→ 2nd day: 50 μg/kg for challenge of tolerance)			
6	5 days: 50 μg/kg ip			
	(→ 6th day: 50 μg/kg for challenge of tolerance)			
7	5 days: 2× 50 μg/kg ip		FB, BS + SC: [^{3}H]5-HT binding↓	
	(→ 6th day: 50 μg/kg for challenge of tolerance)			
8	1× 130 μg/kg ip	Sprague–Dawley rat: nd	Cortex: 5-$HT_{2(A)}$ binding UC	Buckholtz et al. (1988)
9	1× 650 μg/kg ip		Cortex: 5-$HT_{2(A)}$ binding↓	
10	1× 130 μg/kg ip	Sprague–Dawley rat: nd	Cortex: 5-$HT_{2(A)}$ binding UC	Buckholtz et al. (1990)
11	3 days: 130 μg/kg ip		Cortex, STR, HT, BS: 5-$HT_{2(A)}$ and 5-HT_{1A} binding UC	
			ME, HC: 5-$HT_{2(A)}$ binding↓, 5-HT_{1A} binding UC	
12	5 days 16.25, 32.5, or 65 μg/kg ip		Cortex: 5-$HT_{2(A)}$ binding UC	
13	5 days: 130 μg/kg ip		Cortex, ME, HC, BS: 5-$HT_{2(A)}$ binding↓, 5-HT_{1A} binding UC	
			STR, HT: 5-$HT_{2(A)}$ and 5-HT_{1A} binding UC	
			Cortex: 5-HT_{1B}, $\alpha_{1/2}$, β, and SERT binding UC	
			STR: D_2 UC	
14	4 days: 0.03 μM/kg →	Rabbit: nd	FC: 5-HT_{2A} binding↓, 5-HT_{2C} binding UC	Aloyo et al. (2001)
	2 days: no injection →			
	4 days: 0.03 μM/kg iv			
15	5 days: 130 μg/kg sc (→ 6th day: 60 μg/kg for challenge of tolerance)	Sprague–Dawley rat: LSD vs saline discrimination	mPFC, ACC: LSD- and DOI-induced [^{35}S]GTPγS binding↓	Gresch et al. (2005)
			(m)PFC, ACC, FPC, CL, and EN: [^{125}I]LSD binding to 5-HT_{2A}↓	
16	8 days: 14.2 μg/kg iv	Rabbit: open-field (endogenous 5-HT)-related head bobs	FC: 5-HT_{2A} binding↓	Aloyo and Dave (2007)

Continued

TABLE 3 Pharmacodynamics of Repeated LSD Administration in Animals—cont'd

	LSD Regimen	Behavioral Tolerance	Pharmacodynamic Correlate	References
17	11 days: 130 µg/kg sc	Wistar rat (sham-operated): no tolerance to LSD-induced open-field hypolocomotion	FC: 5-HT_{2A} binding↑; α-MS, 8-OH-DPAT, 5-HT, DA, NA, and isoprenaline-induced [^{35}S]GTPγS binding↑	Buchborn et al. (2014)
			HC: 5-HT_{2A} binding UC; α-MS, DA, and isoprenaline-induced [^{35}S]GTPγS binding↓	
18	4 days: 25 µg/kg (morning) + 250 µg/kg ip (evening)[a]	Sprague–Dawley rat: shaking behavior	FC: 5-HT_{2A} binding(↓), [^{3}H]glutamate binding↓, DOB-induced [^{35}S]GTPγS binding UC, and LY35-induced [^{35}S]GTPγS binding↓	Buchborn et al. (2015)

1×, once; 5-HT, serotonin; 5-$HT_{1A/1B/2A/2C}$, serotonin 1A/1B/2A/2C receptor(s); 8-OH-DPAT, 8-hydroxy-2-[di-*n*-propylamino]tetralin (5-HT_{1A}); ↑, increase; ↓, decrease; (↓), trend for decrease; ACC, anterior cingulate cortex; $\alpha_{1/2}$, α-adrenergic 1/2 receptor; α-MS, α-methylserotonin (5-HT_2); β, β-adrenergic receptor; BS, brainstem; CL, claustrum; D_2, dopamine$_2$ receptor; DA, dopamine; DE, diencephalon; DOB, dimethoxybromoamphetamine (5-HT_2); DOI, dimethoxyiodoamphetamine (5-HT_2); EN, endopiriform nucleus; FC, frontal cortex; FB, forebrain; FPC, frontal parietal cortex; GTPγS, guanosine 5′-(γ-thio) triphosphate; HC, hippocampus; HT, hypothalamus; ip, intraperitoneally; isoprenaline, β-adrenergic; iv, intravenously; LFB, limbic forebrain; LY35, LY354740 ($mGlu_{2/3}$); ME, mesencephalon; mPFC, medial prefrontal cortex; NA, noradrenaline; nd, not determined; P/MO, pons/medulla oblongata; sc, subcutaneously; SC, spinal cord; SERT, serotonin transporter; STR, striatum; UC, unchanged.
Each row (1–18) contains the LSD regimen employed, species, and behavior investigated for tolerance, pharmacodynamics investigated for adaptation, and corresponding reference.
[a]*Evening dose was administered only on days 1, 2, and 3.*

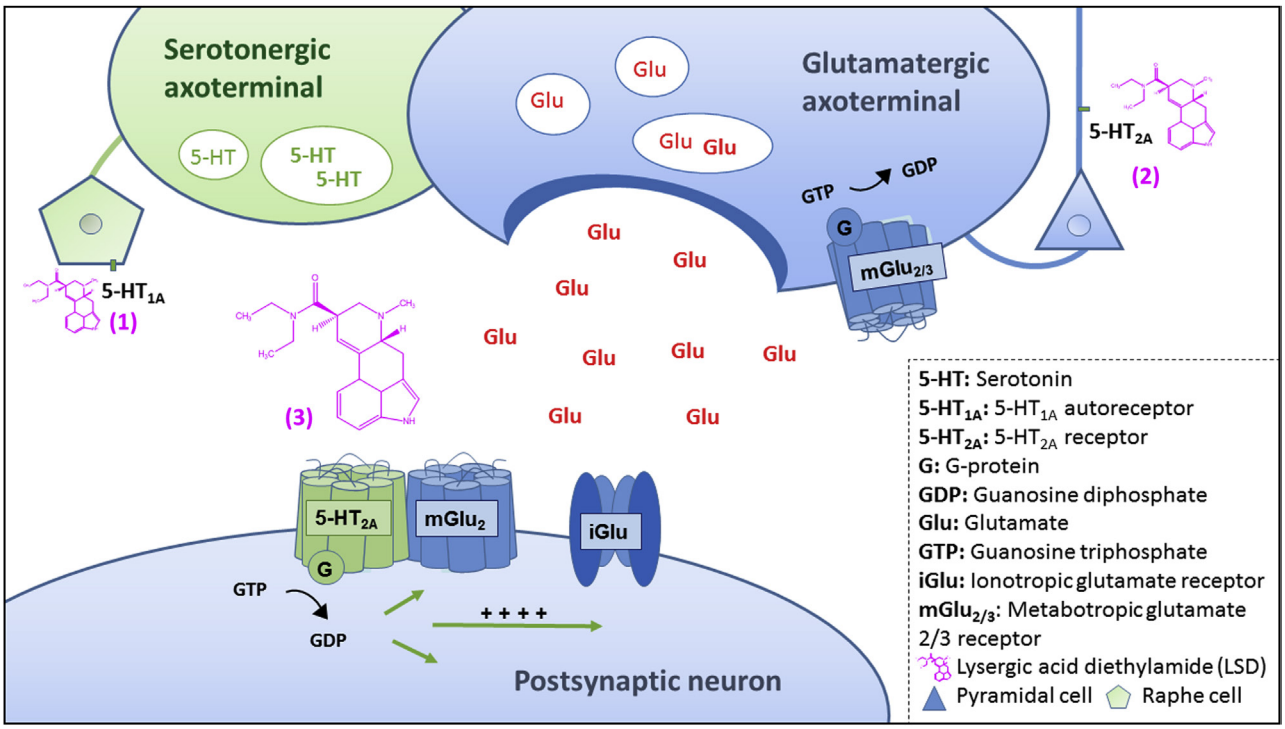

FIGURE 3 **Pharmacodynamics affected by repeated administration of LSD.** (1) LSD inhibits the dorsal raphe nucleus via activation of 5-HT_{1A} autoreceptors and (consequently) interferes with the release of serotonin. LSD via 5-HT_{2A} activation promotes glutamatergic transmission, which might involve (2) a facilitation of $mGlu_{2/3}$-sensitive glutamate release, as well as (3) postsynaptic amplification. Tolerance to LSD co-occurs with adaptations of 5-HT_{1A} autoreceptors, frontocortical 5-HT_{2A}, $mGlu_{2/3}$, and/or overall-glutamate receptors. Adaptations of 5-HT_{2A} and overall-glutamate receptors might be complementary to one another (for discussion, see text).

binding sites, in our study, was highly correlated with tolerance to LSD-induced shaking behavior ($r=0.86$), whereas unregulated 5-$HT_{2(A)}$ receptors were not (Buchborn et al., 2015), it appears that glutamatergic transmission stimulated downstream of LSD–5-HT_{2A} interaction (Figure 3) can adapt as a substitute for 5-HT_{2A} receptors and, thus, complement 5-HT_{2A} downregulation in certain phases of tolerance development.

The pharmacodynamics of tachyphylaxis to LSD are less well characterized. A one-time administration of LSD in Sprague–Dawley rats, only in an "unphysiological" dose (650 µg/kg, ip), induced cortical 5-$HT_{2(A)}$ downregulation (Table 3, Exps 8–10) (Buckholtz, Zhou, & Freedman, 1988). Furthermore, the mechanisms of tachyphylaxis to LSD-induced limb flicking, as suggested by an ontogeny study in cats, are different from the mechanisms of limb flicking itself (Trulson & Howell, 1983). LSD, by activation of somatodendritic 5-HT_{1A} receptors, inhibits the activity of serotonergic neurons of the dorsal raphe nucleus (Figure 3), and tachyphylaxis to limb flicking and shaking behavior co-occurred with a sensitization of this inhibition (Table 3, Exp. 3) (Trulson, Heym, & Jacobs, 1981). Whether the given 5-HT_{1A} sensitization, a depletion of glutamatergic vesicles, and/or any other adaptation beyond 5-HT_{2A}–glutamate interaction underlies tachyphylaxis to LSD, however, remains to be elucidated.

Learning-Related Adaptations

The role of behavioral accommodation for tolerance development has been investigated in terms of LSD-induced hallucinogenic pausing and shaking behavior. As discussed earlier, Sprague–Dawley and hooded rats became tolerant to LSD-induced hallucinogenic pausing within 3–6 days. Tolerance occurred only, though, when LSD was given on each of the administration days right before the lever-press session. When on the first days LSD was given after, and only on the last day before, the session, tolerance on the last day was completely absent. Thus, although both the pre- and the postsession rats received the same total amount of LSD, only the presession animals, which were able to anticipate and behaviorally compensate for the drug effect, became tolerant (Commissaris et al., 1980; Murray et al., 1977). Addressing a simpler form of learning, we challenged tolerance to LSD-induced shaking behavior with regard to habituation (Buchborn et al., 2015). Over the course of a multiple-day experiment, rats usually habituate and become less excited about the experimental procedure. To make sure that this decrease in excitation would not confound with tolerance, we habituated a group of animals for 4 days (before the actual LSD experiment) to daily saline injections and the experimental nonhome cages. As the overall decline in shaking behavior did not significantly differ between the so-habituated and the nonhabituated animals, however, (Table 2, Exps 15 and 16), tolerance did not seem to represent an artifact of contextual habituation.

Concluding Remarks on Mechanisms of Tolerance to LSD

Tolerance to LSD, as indicated by the given animal literature, is of the pharmacodynamic rather than the pharmacokinetic type and, in cases in which the drug interferes with the organism's need for reinforcement, can also be precipitated by behavioral accommodation. Regarding effects of LSD that originate in 5-HT_{2A}-related glutamate release in the cortex, cortical 5-HT_{2A} and/or (downstream) glutamate receptor downregulation is likely to constitute the key adaptation from which tolerance arises. As LSD's regulatory activity across the monoaminergic systems appears to be very complex, however (Table 3, Exp. 13 vs 17) (Buchborn et al., 2014; Buckholtz et al., 1990), further correlative studies are needed to more clearly establish the interrelation between tolerance and receptor regulation. Likewise, given the lack of human research into this field, imaging studies correlating mental tolerance to adaptations of receptor binding and/or brain metabolism, as well as pharmacokinetic studies, appear desirable.

PATHOLOGICAL AND THERAPEUTIC IMPLICATIONS OF REPEATED LSD ADMINISTRATION

It is generally assumed that LSD, compared to other substances of abuse, has a rather low addiction liability (e.g., Gable, 1993; Nutt, King, Saulsbury, & Blakemore, 2007) and consequently rarely is taken on a regular basis. That near-complete tolerance to the psychedelic effect of LSD manifests within 3–4 days (see section: Tolerance to LSD's Psychedelic Effect) might be one of the main reasons for recreational users to avoid its everyday administration. As tolerance to LSD reverses within 3–6 days of abstinence, however (see section: Withdrawal and Recovery from Tolerance to LSD), a weekend-based pattern of usage cannot be excluded (Barron, Lowinger, & Ebner, 1970; Ludwig & Levine, 1965). Likewise, as doses above 500 µg have not been challenged, yet, an overcoming of tolerance with even higher doses of LSD (and a subsequent abuse) cannot be ruled out.

Given its apparently low incidence, any putative sequelae and/or benefits of frequent LSD use are largely unknown, and only a few publications can be referred to. In two retrospective studies, in which subjects had a median of 75 lifetime exposures (at a mean age of 40; $n=16$) or an average of 29.3 exposures within 12.2 months ($n=20$), no (consistent) evidence of cognitive impairment and/or brain damage could be detected on the basis of a neuropsychological test battery (McGlothlin, Arnold, & Freedman, 1969; Wright & Hogan, 1972). In a third retrospective study, in which subjects (at a mean age of 20; $n=21$) had a mean of 65 LSD lifetime exposures, electroencephalogram measurements revealed an increased sensitivity to visual stimuli; the auditory two-tone evoked potential (which is sensitive to cognitive disorganization), on the other hand, was normal (Blacker, Jones, Stone, & Pfefferbaum, 1968). Bender (1970), who for weeks, months, and sometimes even years administered LSD in daily doses up to 150 µg to autistic and schizophrenic children, qualitatively concluded that the drug improved the well-being and the psychosocial adjustment of her patients. Although tolerance to LSD's perceptual effects in most children occurred by day 2, the clinical benefit they drew from the drug appeared to persist for months. Taking account of the fact that there is cross-tolerance between LSD and certain drugs of the antidepressant class (which is indicative of a mechanistic overlap), we, engaging the olfactory–bulbectomy rodent model of depression, evaluated the antidepressant-like property of repeated LSD treatment. Bulbectomized rats, reminiscent of

negatively biased cognitions of depressed patients, exhibit a deficiency in learning negative-stimulus avoidance. LSD (130 µg/kg, subcutaneous), given on 11 days in a row, ameliorated this avoidance learning deficiency, such as in former publications had been found only for antidepressant drugs, and additionally normalized the bulbectomy-related disruption of hippocampal 5-HT_2 signaling (Buchborn et al., 2014). In contrast to these salutogenic-like adaptations after short-term LSD treatment in bulbectomized Wistar rats, unimpaired Sprague–Dawley rats, after a 3-month every-other-day treatment with a similar dose of the drug (160 µg/kg, ip), exhibited pathological adaptations that in behavior and neurogenetics had a schizophrenia-like appeal (Martin, Marona-Lewicka, Nichols, & Nichols, 2014).

Concluding Remarks on Clinical Implications of Repeated LSD Administration

The cited literature indicates that repeated LSD administration at high frequency is uncommon among recreational drug users and, if performed at (weekly to) monthly intervals, does not seem to precipitate gross neuropsychological dysfunctions. Beyond once-in-a-while use, daily short-term administration of LSD, as implicated by experimental data in rats, might—if alternated with stimulus contexts that favor cognitive plasticity—entail therapeutic benefit for defined pathological conditions, such as depression; long-term use at an every-other-day rate (which probably impedes tolerance development), in contrast, might harbor pathology itself.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

- Tolerance to a drug can generalize to another drug, a phenomenon called cross-tolerance, and therefore influence the clinical course of polydrug abuse.
- Mental tolerance to LSD in humans generalizes to psilocybin and mescaline (and vice versa) (Isbell et al., 1961; Wolbach et al., 1962), moderately to dimethyltryptamine (Rosenberg et al., 1964), slightly (i.e., in terms of peak intensity) to scopolamine (Isbell, Rosenberg, Miner, & Logan, 1964), but not to amphetamine or tetrahydrocannabinol (Isbell & Jasinski, 1969; Rosenberg et al., 1963). LSD-tolerant dogs, moreover, exhibit cross-tolerance to several effects of MDA (methylenedioxyamphetamine) (Nozaki, Vaupel, & Martin, 1977).
- Given that psilocybin and methylenedioxymethamphetamine, which in the body is converted to MDA, like LSD, down-regulate cortical 5-$HT_{2(A)}$ receptors (Buckholtz et al., 1990; Reneman et al., 2002), an overlap in pharmacodynamic regulation is likely to account for cross-tolerance. Given that mescaline, on the other hand, fails to induce 5-$HT_{2(A)}$ down-regulation (Buckholtz et al., 1990), yet unknown (pharmacodynamic and/or pharmacokinetic) principles might play a complementary role.

DEFINITION OF TERMS

Serotonergic hallucinogen This is a psychedelic drug that by activation of serotonin 2(A) receptors provokes shaking behavior in (certain) mammals and alterations of consciousness in humans.

Tolerance This is a consequence of repeated or long-term exposure to a drug; the organism over days, weeks, and months becomes less responsive to the effects of the drug.

Tachyphylaxis This is acute tolerance to a drug. In consequence of a single exposure or multiple short-interval exposures to a drug, the organism within minutes and hours becomes less responsive to the effects of the drug.

Cross-tolerance Tolerance to a drug can diminish the effects of another drug if the enzymes that degrade both drugs and/or the (receptor) targets that mediate the drugs' effects overlap; this is called cross-tolerance.

5-HT_{2A} receptor This is a transmembrane protein highly enriched in the mammalian cortex cerebri that (upon occupancy by serotonin or serotonergic hallucinogens) regulates the cell's physiology through interaction with G proteins.

Shaking behavior This refers to head twitches and wet dog shakes. It is a behavior of (certain) mammals that is stereotyped by serotonergic hallucinogens. The mammal shows brisk rotational movements of head (and trunk) around the long axis of its body.

Limb flicking This is a behavior of cats that is stereotyped by serotonergic hallucinogens. The cat lifts its paw, rapidly shakes it, or flicks it away from the body as if to remove a foreign substance.

Hallucinogenic pausing This is also called hallucinatory pausing and refers to intermittent interruption of operant lever-press responding by rats, induced by serotonergic hallucinogens.

KEY FACTS OF LSD

- LSD is a semisynthetic derivative of the ergot alkaloid ergotamine; it was first synthesized in the year 1938 by the Swiss Sandoz chemist Albert Hofmann; the first systematic research on LSD was performed by Werner Stoll in Switzerland, and published in 1947.
- In the United States, manufacture and distribution of LSD were put under Federal control in 1966; other countries followed. After a long halt, human LSD research has been resumed in the 2010s by Robin Carhart-Harris and David Nutt in England as well as Peter Gasser and Matthias Liechti in Switzerland.
- LSD is a serotonergic hallucinogen; as such it is to be differentiated from anticholinergic deliriants, antiglutamatergic dissociatives, serotonin-releasing entactogens, and atypical hallucinogens (including the γ-aminobutyric acidergic muscimol, the cannabinoid tetrahydrocannabinol, and the κ-opioid salvinorin A).

SUMMARY POINTS

- In humans, mental tolerance to LSD manifests 24 h after its first administration, reaches a maximum by around the fourth day, remains relatively constant thereafter, and does not reverse unless a few days of abstinence is interspersed. Symptoms of abstinence, even after a 12-week treatment, do not occur.
- Recreational drug users, given the rapid onset of mental tolerance, generally do not apply LSD on an everyday basis; given the rapid reversal of tolerance, on the other hand, a once-per-week abuse may be encountered.
- In cats and rats, tolerance to LSD-induced limb flicking and/or shaking behavior manifests in a tachyphylaxis-like

manner; hallucinatory pausing in rats, as opposed, is more resistant to tolerance.

- The mechanisms of tolerance to LSD are of the pharmacodynamic rather than the pharmacokinetic type and (in terms of 5-HT_{2A}-related behaviors) appear to involve adaptations of (cortical) 5-HT_{2A} and/or (downstream) glutamate receptors.

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