LSD (lysergic acid diethylamide), death? and distraction

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LSD

A semisynthetic substance derived from lysergic acid found in the parasitic rye fungus C. purpurea. Only the d-LSD isomer has psychoactive properties.
LSD

- Clear or white, odourless, tasteless powder formulated as capsules, tiny tablets (microdots) or small gelatin squares

- Synthesised in 1938 by Albert Hoffman at Sandoz – its psychoactive (hallucinogenic effects) were first discovered in 1943

- Pharmacology is complex – mechanisms still not completely understood today (Passie et al, 2008). LSD has been used by tens of millions of people over the last 50 years and has been administered to tens of thousands of patients in psychotherapeutic settings
What are the pharmacological mechanisms of LSD?

• LSD is thought to preferentially inhibit serotonergic (5HT) cell firing in the CNS (Passie et al, 2008)

• So called “partial agonist activity” at 5HT2\textsubscript{A} receptors mediates the psychedelic effects of LSD. LSD also has full agonist activity at 5HT1\textsubscript{A} and 5HT1\textsubscript{C} receptors

• Since serotonergic systems appear to be intimately involved in the control of sedation, sleep and attention and mood, it is possible to explain the actions of LSD (agitation, paranoia, thought disorder and grandiose thinking) by disinhibition of these critical systems
LSD effects...

• Time to onset of acute effects after ingesting LSD is ½-1 hour later
• Psychological effects 4-12 hours duration
• A moderate dose (75-150 micrograms orally) will significantly alter the state of consciousness (Passie et al, 2008)
  – Stimulation of affect (mostly euphoria)
  – Enhanced introspection
  – Altered psychological functioning, including dreams and perceptual changes such as illusions, pseudo hallucinations and alterations of thinking and time experience (leading to overestimation of time intervals) occur
  – Psychomotor functions (co-ordination and reaction time) are frequently impaired
  – Impaired judgment and decreased performance on tests of attention and concentration
## Table 1

Typical sensory and psychological effects under the influence of a medium dose of LSD (100–200 μg p.o.)

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory alterations (visual, auditory, taste, olfactory, kinaesthetic)</td>
</tr>
<tr>
<td>Illusion</td>
</tr>
<tr>
<td>Pseudo-hallucination</td>
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<tr>
<td>Intensification of color perception</td>
</tr>
<tr>
<td>Metamorphosis-like change in objects and faces</td>
</tr>
<tr>
<td>Intense (kaleidoscopic or scenic) visual imagery with transforming</td>
</tr>
<tr>
<td>content</td>
</tr>
<tr>
<td>Alterations of affectivity</td>
</tr>
<tr>
<td>Intensification of emotional experience: euphoria, dysphoria, anxiety,</td>
</tr>
<tr>
<td>mood swing</td>
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<tr>
<td>Alterations of thinking</td>
</tr>
<tr>
<td>Less abstract and more imaginative thought</td>
</tr>
<tr>
<td>Broader and unusual association</td>
</tr>
<tr>
<td>Attention span shortened</td>
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<tr>
<td>Alterations of body perceptions</td>
</tr>
<tr>
<td>Change in body image</td>
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<tr>
<td>Unusual inner perception of bodily processes</td>
</tr>
<tr>
<td>Metamorphic alteration of body contours</td>
</tr>
<tr>
<td>Memory changes</td>
</tr>
<tr>
<td>Reexperiencing significant biographical memories</td>
</tr>
<tr>
<td>Hypermnesia</td>
</tr>
<tr>
<td>Age-regression</td>
</tr>
<tr>
<td>Mystical-type experiences</td>
</tr>
</tbody>
</table>
LSD

- Physical effects

  - Cardiovascular – mild increases in heart rate or blood pressure – may be secondary to anxiety or restlessness; require only supportive care

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sokoloff et al. [75], (n = 13, 120 µg i.v.)</th>
<th>DiMascio et al. [67], (n = 6, 1 µg/kg p.o.)</th>
<th>Kornetsky [35], (n = 10, 100 µg p.o.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood pressure (mmHg)</td>
<td>+5, SD 2.9</td>
<td>+12% (syst.)</td>
<td>+13 (SD unknown)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+10% (diast.)</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>+15 SD 7</td>
<td>+18%</td>
<td>+19 (SD unknown)</td>
</tr>
</tbody>
</table>

SD = standard deviation.

- ©acknowledged Passie et al, CNS Neuroscience and Therapeutics, 2008

- Neurological - dose-dependent hyper-reflexia (exaggerated reflexes) and mild ataxia (staggering gait)
Serotonin toxicity ??

• Hunter Serotonin Toxicity Criteria (84% sensitive and 97% specific)

• The only case reports of toxicity in the literature are not typical of ST, although one cases exhibited hyperthermia (Klock et al, 1974 and Friedman et al, 1971)

• LSD does not seem to be associated with serotonergic symptoms or features of ST, either in “usual” doses or in overdoses

• Interesting because it is the indolealkylamine with the greatest agonist potency at the 5HT2A receptor
Reported “dramatic reactions’ to LSD

- Hysterical behaviour, hyperactivity and hyperthermia were exhibited by a young man who took a large dose of LSD (Friedman and Hirsh, 1971)

- Two girls took a single dose of LSD and developed delayed psychotic reactions 2 weeks later requiring admission to hospital (Cooper, 1974)
Bad trips..

- Traumatic experiences can have long-lasting effects on LSD users
  - Mood swings
  - Rarely flashback phenomena
Tolerance

- Humans show a decrease in response to the autonomic and psychological effects of LSD after repeated administration (e.g. after a few daily doses)
Can LSD cause death?

• Put simply, LSD does not cause death by direct toxicity at recreational or therapeutic doses (less than 500 microgram). There have been no well documented human deaths directly from an LSD overdose, though LSD has been implicated in accidental deaths, suicides and homicides (Pattie et al, 2008).

• People who consumed very high doses of LSD intranasally had plasma concentrations 1000-7000 microgram/100mL plasma – had coma, hyperthermia, vomiting, light gastric bleeding and respiratory problems. All survived with hospital treatment, and with no residual effects (Klock et al, 1974).
Can LSD cause death?

- A case in which death was “directly attributed to LSD”
Fysh et al, 1985

• a 25 y old man who died 16 hours after hospital admission; ante-mortem serum and post-mortem blood contained 0.014 and 0.005mg/L LSD, respectively

• However, it reports solely the tox analysis and fails to explain any of the circumstances of the death, casting doubt that the only explanation for death was the LSD
Can LSD cause death?

- “In general, LSD is not reported to substantially increase the risk of suicide, and those who do commit suicide after taking LSD are likely to have suffered from pre-existing suicidal tendencies.
- Some deaths have been associated with inebriated or combative behaviour while under the influence of LSD, including falling or jumping from a height or dying after being beaten by police. Estimated less than one death per million LSD use sessions, with risk of death being higher amongst those predisposed to suicide.”

Erowid 2013
Famous US cases: Diane Linkletter

- October 1969

- This 20 y old woman jumped out of a window and fell to her death. No direct evidence connected LSD to her death – no drugs on post-mortem examination. However, her famous father Art Linkletter said that LSD had caused her death, that LSD flashbacks had led to her suicide.

Erowid, 2013
Famous US cases: Frank Olson

- "1953"
- Was thought to have thrown himself out of a hotel window
- Later revelation by the CIA indicate that he was dosed with LSD without his consent, and may have been bludgeoned and thrown out of his hotel room by CIA agents – no longer considered a clear case of LSD-related suicide"

Erowid 2013
Making the diagnosis of LSD intoxication

• A clinical diagnosis based on a positive history of exposure to LSD (with analytical confirmation) and suggestive physical findings
  – Mild to moderate sympathomimetic effects (increased HR or BP)
  – Ongoing perceptual and sensory illusions
  – Removal of clothes can result from LSD intoxication causing heat generation by CNS stimulation of the sympathetic system, increased muscle use and restlessness induced by LSD
Autonomic hyperarousal state ("excited delirium" and LSD (Gill, 2008))

LSD exposure
   Sudden onset of bizarre and violent behaviours
      Combativeness, confusion, hyperactivity, paranoid delusions, hallucinations, hyperthermia
         Sudden death ??
Detecting LSD in man

• Since LSD is ingested in quite small amounts, the LSD to be detected in biological samples is likewise quite small
• The metabolism of LSD has not been extensively studied in man
• On the basis of animal studies it is known to undergo extensive biotransformation via N-demethylation, N-de-ethylation and hydroxylation to inactive metabolites (Axelrod et al, 1956)
Detecting LSD in man

- Average time to peak concentration in serum after oral dosing is 3-5 hours
- Average serum elimination half-life from peak serum concentration is 3 hours (Wagner et al., 1968)
- Patients receiving treatment for LSD intoxication, manifested by agitation or unconsciousness, have had plasma and urine concentrations as high as 0.004 and 0.008 mg/L respectively (Baselt) (Taunton-Rigby et al., 1973)
Detecting LSD in man

• Average time for determination of LSD in urine is 2-4 days
• in most LSD positive urine samples the metabolite, 2-oxo-3-hydroxy-LSD is present at higher concentrations than LSD, and can be detected after LSD ingestion for a longer time than the LSD itself (Reuschel et al, 1999)
• urine concentrations of unchanged LSD ranged from 0.001-0.055mg/L in the 24 hours after ingestion of 200-400 micrograms of the drug by humans
Conclusions

- LSD is a potent psychotropic agent with few physiological effects
- Death due to *direct toxicity* of LSD is not recognised
- Death can occur as a result of poor judgment/behavioural effects with either trauma or inappropriate restraint
- As with every drug of abuse, it is important to actively seek analytical confirmation of the drug exposure
Thank you!

• Any questions ??
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