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Pharmakopsych. 8 (1975) 176-184

ZUR DISKUSSION

Therapeutic Usefulness of Hallucinogenic Drugs as a Function of their Chemical Structure

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Summary

D-lysergic acid diethylamide (LSD) displays (1) the phenylethylamine pattern present in mescaline, cyclazocine and catecholamines and (2) the 4-substituted tryptamine structure of psilocybin which is a serotonin analog. Hence (a) Naloxone – a blocker of the LSD-like side effects of cyclazocine – should (and does) block effects of LSD, and (b) cross-tolerance may be present between LSD and cyclazocine but not between mescaline and psilocybin.

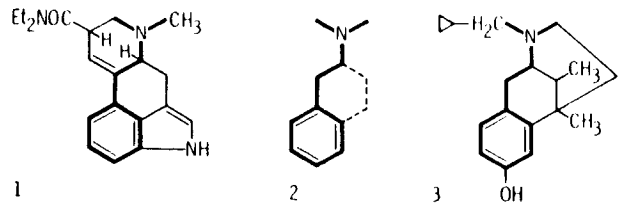
Even though *LSD* binds *subcortically*, its effect on regional perfusion of the brain and, presumably, function is primarily *cortical* and, since the perfusion shifts evoked by psilocybin are confined to *subcortical* regions, we assume that other compounds with the phenylethylamine structure such as *mescaline*, also may selectively affect cortical activity.

Zusammenfassung

Das D-Lysergsäurediäthylamid (LSD) enthält sowohl das Strukturelement des *Phenyläthylamin* – welches auch im Cyclazocine, im Meskalin und den Catecholaminen vorkommt – wie auch die 4-substituierte *Tryptamin*-Struktur des Serotonin-Analogs Psilocybin. Wir postulieren daher eine "cross tolerance" zwischen LSD, Cyclazocine und Meskalin, jedoch das Fehlen einer solchen zwischen Meskalin und Psilocybin. Überdies wird gezeigt, daß Naloxone die "LSD-Nebenwirkungen" des Cyclazocine wahrscheinlich darum zu blockieren vermag, weil Naloxone selbst ein LSD-Antagonist ist.

Obwohl LSD *subkortikal* gebunden wird, hat es einen vornehmlich *kortikalen* Angriffspunkt, was seine Wirkung auf die lokale Durchblutung und wahrscheinlich auch Funktion des Gehirnes betrifft. Da die durch Psilocybin hervorgerufenen Veränderungen der Gehirndurchblutung auf subkortikale Regionen beschränkt sind, nehmen wir an, daß andere Substanzen mit der Phenyläthylaminstruktur, wie z.B. Meskalin, auch selektiv die kortikale Aktivität beeinflussen können.

It was pointed out recently (1) that both 9,10-didehydro-N,N-diethyl-6-methyl-ergoline-8β-diethylcarboxamide (LSD) – Fig. 1, No. 1 – and the narcotic antagonist cyclazocine (Fig. 1, No. 3) share the phenylethylamine pattern (Fig. 1, No. 2) which is also displayed by mescaline (Fig. 2, No. 4) and related substances including the methoxy-substituted amphetamines (2). The cross-tolerance between mescaline and LSD (3) is in accord with this common structural element and can not be attributed to metabolic disposition (4). Cyclazocine, an N-cyclopropylmethyl benzomorphan, has been repeatedly reported to induce "psychotomimetic side effects" (5) an observation which – one of us (R.F.) was able to personally verify during the year 1973 at the Narcotic Clinic of Friends Med. Sci. Res. Ctr., Inc., Baltimore, Maryland 21227. These "side effects", however, subside on repeated administration of the drug. In other words, tolerance to the hallucinogenic effects of cyclazocine develops in the same manner as it does after repeated administration of either LSD or mescaline (6). Hence it may be not unreasonable to assume that cross-tolerance may be induced between LSD and cyclazocine since both hallucinogenic drugs display the phenylethylamine configuration.



1 2 3

Fig. 1 The 2-amino-tetralin which includes the phenylethylamine structure (No. 2) is a common feature of both LSD (No. 1) and cyclazocine (No. 3). Note, that mescaline (Fig. 2, No. 4) is also a phenylethylamine derivate.

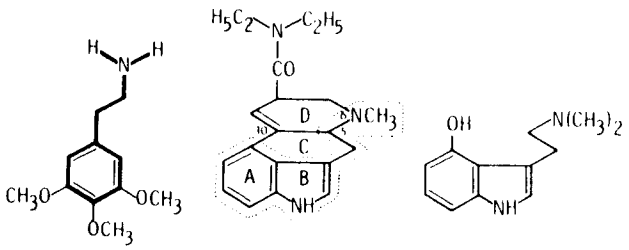


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Fig. 2 The 4-substituted tryptamine structure (follow dotted line in No. 5) is a common feature of both LSD (No. 5) and psilocin (No. 6). Note, that psilocin (No. 6) and mescaline (No. 4) do *not* share the same structural elements.

Moreover, since Naloxone can block the LSD-like side effects of cyclazocine (7) we hypothesized that it should be possible to block LSD effects with Naloxone. Indeed in double-blind pilot experiments 0.12 mg/kg Naloxone given i.m. to rats could restore mobility in general and exploratory behaviour in particular when administered 30 minutes *after* the i.p. administration of 375 μg/kg LSD, a dose which induces a catalepsy-like immobilization (8). We intend to follow up these experiments in our search for an effective and fast blocker of LSD-induced 'bummers' or bad trips in humans.

LSD, of course, displays *two* distinctive structural features: (a) the phenylethylamine structure, with its freely mobile side chain present in mescaline and the catecholamines – follow ring A, C and D in Fig. 2, No. 5 – and (b) the tryptamine structure substituted in position 4 of the indole nucleus (9) which is also a structural feature of psilocin (Fig. 2, No. 6), the active compound of psilocybin and resembles serotonin. Based on these structural considerations, one would expect cross-tolerance to prevail not only between LSD and mescaline (6) but LSD and psilocin and LSD and tryptamine, as well. This is indeed the case (10, 11). Pursuing the same logic, we would postulate a lack of cross-tolerance between mescaline and psilocin since these drugs do not share a common structural feature. A check of the literature, in fact, reveals no report of cross-tolerance between mescaline and psilocybin (or psilocin). Appel and Freedman assumed that "tolerance to appropriate doses of any one compound will induce cross-tolerance with any of the other drugs" (12) and come to this conclusion after having tested a variety of LSD, psilocybin and mescaline combinations, but *not* the mescaline-psilocybin one (12).

It is intriguing in this context to note that while the binding of LSD is primarily subcortical (13, 14), the effects of LSD, when assessed in terms of *blood flow*, appear to be exerted predominantly in cerebellar, frontal and parietal cortical areas (15). By contrast, preliminary studies with Δ^9-THC and psilocybin (16) suggest that these two drugs induce a rather different pattern of cerebral perfusion and function, one which is confined to subcortical regions of the rat brain.

Since tolerance and cross-tolerance relationships between man and rat are remarkably similar (12), we speculate about the possibility that (a) hallucinogenic drugs which display the phenylethylamine structure such as mescaline, – and some of its derivates (17) – affect cortical structures; (b) drugs with a tryptamine structure substituted in position 4 of the indole nucleus,

such as psilocybin, affect subcortical structures; and lastly (c) drugs such as LSD which contain both of the above structural features, affect both cortical as well as subcortical regions. Our subjective impressions from over 1,000 hallucinogenic drug experiences induced in healthy human volunteers over a period of 20 years imply easier control and practically no "bad trips" under psilocybin, and more and longer lasting 'flashbacks' from mescaline and particularly LSD.

The above considerations may be of practical relevance if and when hallucinogenic drugs are to be selected as tools to facilitate psychotherapy. These drugs in general and psilocybin in particular are meant to substitute for the charismatic psychotherapist. The drugs highten considerably the meaning of the therapeutic session and significantly shorten the therapeutic process. We suggest that the drugs to be considered should primarily affect subcortical structures.

The raised subcortical arousal in the patient intensifies the meaning and significance of the "set and setting" which become incorporated into the therapeutic experience. Since any and all experience may be considered as a cortical interpretation of subcortical activity (18, 19), the success of the therapist in organizing and directing the therapeutic experience, will depend on a shared set and setting, i.e. on the shared cortical interpretation of the patient's subcortical arousal.

Acknowledgment

Supported in part by NIH Grant NB-05526. We are grateful to Dr., Dr. h.c. *Albert Hofmann*, Burg, Switzerland for critically reading the manuscript.

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