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MINIREVIEW

STRUCTURE-ACTIVITY-RELATIONSHIPS OF CERTAIN HALLUCINOGENIC SUBSTANCES BASED ON BRAIN LEVELS

W.H. Vogel and B.D. Evans

Department of Pharmacology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107

Certain methoxylated and/or N-methylated derivatives of phenylethylamine (e.g. mescaline) and tryptamine (e.g. dimethyltryptamine) are known to be hallucinogenic in man and to produce abnormal behavior in animals (e.g. 1-8). These compounds are of particular interest since they resemble structurally certain known putative neurotransmitters in the mammalian brain and since some of them occur naturally in mammalian and human tissues and fluids (e.g. 9-13). These compounds have been widely studied and various attempts have been made to discover the mechanism(s) of action of these "hallucinogenic" substances. Certain concepts have been evolved from structure-activity-relationship studies (SAR) as to their behavioral potency, the optimal chemical structure necessary for "hallucinogenic" activity and the possible architecture of the "hallucinogenic receptor" in the brain (e.g. 4-6,8,14-20). However, comparisons and conclusions in animal and human studies have been based primarily on the doses administered and not on the brain levels necessary to produce "abnormal" behavior. Although the dose administered is readily available, it is unfortunately no accurate measure of the actual level of a particular compound in the brain because the brain level is a function, in addition to other variables, of the specific fate of the compound in the organism including absorption, distribution, metabolism, penetration through the blood-brain-barrier (BBB) and excretion. For example, one compound might appear to be less potent than another based on administered doses simply because it is too quickly metabolized and cannot accumulate in the brain or a compound might appear to be extremely potent because it is preferentially concentrated in the central nervous system. To remove such uncertainties about the metabolic fate, we have tried to compare compounds on the basis of actual brain level.

Requirements for selection of compounds in this review were: availability of brain levels of the particular compound as well as their effects on behavior under relatively comparable conditions. The latter criterion is important because the potency of a compound does vary with the behavioral test used, e.g. 3 umoles/kg of LSD interfere with the conditioned avoidance response (CAR) in the shuttle box (5) whereas 0.2 umoles/kg of LSD affect a fixed ratio schedule of positive reinforcement (21). Upon review of the literature, most compound seem to have been tested in the rat using the simple CAR in a shuttle-box. For this reason, the rat as test subject and the CAR as test method were chosen. Thus, selection is based on the availability of comparable data and not

because we feel that the rat or the CAR are superior to other animals or tests. Also, certain estimates had to be made when obtaining data from different sources, e.g. brain levels at 20 mg/kg at 20 minutes were available but not at 10 mg/kg at 5 minutes; since the latter was needed, we had to extrapolate to obtain this particular brain level.

We are using in this paper, and would like to introduce, the concept and term of "minimal effective brain level" (MEBL). The MEBL is the brain level expressed as moles/g of brain at the time an animal first shows significant deviation from normal behavior in a particular behavioral situation, in this case a significant reduction in CAR. SAR studies using MEBLs will be referred to as SAR II in the table whereas studies using administered doses will be referred to as SAR I. Based on the particular selection criteria used in this paper, MEBL values given in this review might differ from those published earlier by this laboratory.

Phenylethylamine and Derivatives

The Table shows the behavioral activity of phenylethylamine and some of its derivatives. Based mainly on the work of Ernst (4,22,23) and Smythies and co-workers (7,8,24) using doses administered (SAR I), it had been postulated that a methoxy group in the para position of the benzene ring is necessary for behavioral activity and interference with the CAR and that potency increases with the number of methoxy groups as long as the 3,4,5-positions (2,4,5-trimethoxyphenylethylamine appears inactive) are occupied. It has been claimed that 4-methoxyphenylethylamine might be a paradigm hallucinogenic substance and the lack of behavioral activity at the lower doses is due to the rapid metabolism and to the inability of the compound to accumulate in the brain.

SAR II shows basically the same trend (25-27,30). Phenylethylamine is weak and potency increases with the number of methoxy-groups. However, the SAR II raises the question of the behavioral activity of 2,4,5-trimethoxyphenylethylamine and the importance of the 2,4,5-configuration since the compound does not cross the blood-brain-barrier. Thus, its activity and potency remain unknown until the behavioral activity is determined perhaps following the direct injection of the compound into the central nervous system. SAR II also rules out the possibility of 4-methoxyphenylethylamine as a particularly potent psychoactive substance since it can be found in relatively high concentrations in the brain before it affects the behavior of the animal.

Phenylethanolamine and Derivatives

Phenylethanolamine and a variety of its methoxylated and/or N-methylated derivatives were found to have only weak activity or no effect on the CAR (25,30-32). A study of the physiologic disposition of these compounds reveals that they do penetrate the CNS and can be found in the brain at substantial levels (25,32, 33). Thus, β-hydroxylation of psychoactive phenylethylamines seems to decrease or abolish behavioral activity. This seems also to be true for other compounds such as amphetamine, methamphetamine and 6-hydroxydopamine in which β-hydroxylation reduces

Table

Structure-Activity-Relationships of Certain "Hallucinogenic" and Inactive Compounds Based on Administered Doses (SAR I) or Minimal Effective Brain Levels or MEBL (SAR II)

Dose (SAR I) or brain (SAR II) level at which first significant deviation from normal behavior (CAR) occurs.

	SAR I umoles/kg		SAR II nmoles/g	
Phenylethylamine (PEA	300	(25)	25	(25)
4-Methoxy-PEA	> 100(t)	(8)	30	(26)
3,4-Dimethoxy-PEA	120	(8,28)	15	(27)
3,4,5-Trimethoxy-PEA	100	(8,28,29)	5	(30)
2,4,5-Trimethoxy-PEA	> 150	(8)	(n)	(25)
2,3,4,5,6-Pentamethoxy-PEA	10	(25)	1	(25)
Phenylethanolamine (PEOH)	500(f)	(31)	100	(33)
3,4-Dimethoxy-PEOH	> 450	(32)	> 30	(32)
3,4,5-Trimethoxy-PEOH	400	(25)	30	(25)
3,4-Dimethoxy-N,N-Dimethyl-PEOH	> 300	(32)	> 130	(32)
Phenylisopropylamine (PIA)	40	(8)	25	(38,39)
2,4,5-Trimethoxy-PIA	(a)	(40,41)	10(d)	(42)
2,3,4-Trimethoxy-PIA	(i)	(40,41)	30(d)	(42)
Tryptamine (T)	> 300	(43)	(n)	(43)
T (after MAO inhibition)	30	(43)	1	(43)
Dimethyl-T (DMT)	25	(5,6)	4	(44)
Diethyl-T	25	(5,6)	8	(44)
5-Hydroxy-T	100(p)	(5,6)	5	(45)
5-Methoxy-T	100	(5,6)	0.5	(46)
5-Hydroxy-DMT	100	(5,6)	2.5	(47)
5-Methoxy-DMT	10	(5,6)	7	(47)
Isolysergic Acid Amide	15	(51)	5	(51)
Lysergic Acid Diethylamide	3	(5)	0.5	(52)

Key

t = postulated as psychoactive but tremors at 100 uM/kg makes behavioral testing impossible
> = no activity up to this dose or brain level
n = not detectable
f = fleeting effects, interference with CAR lasted only 5 minutes
a = dose which affects CAR unavailable, affects underwater maze performance
i = dose which affects CAR unavailable, does not affect underwater maze performance
d = dose arbitrarily set at 100 uM/kg
p = peripheral effects may partly account for interference with CAR

or abolished CNS activity or toxicity (34-36). Dana ana, a cactus containing the alkaloid macromerine (N,N-dimethyl-3,4-dimethoxyphenylethanolamine), has been reported to be hallucinogenic in man and the pure alkaloid to be "potentially hallucino-

genic" in monkeys and cats (37). Based on our investigations, the alkaloid shows no effect on the CAR as would be expected from a psychoactive compound; thus it could be concluded that the cactus, if indeed active, probably contains some other psychoactive compound(s).

Phenylisopropylamine and Derivatives

Although these compounds have been extensively studied in a variety of behavioral tests, little information is available on their effect on the CAR and on the fate of these substances in rats with the exception of amphetamine. Amphetamine (phenylisopropylamine) interferes with the CAR in a "typical hallucinogenic pattern" at an approximate dose of 40 umoles/kg (8). Based on brain levels, however, amphetamine does not seem to be very potent at the "hallucinogenic" dose (38,39). Introduction of a methoxy group in the 2,4 and 5 positions enhances potency whereas methylation in the 2,3 and 4 positions inactivates the molecule (40,41). It is interesting to note that 2,4,5-trimethoxyphenylethylamine does not cross the BBB, yet 2,4,5-trimethoxyphenylisopropylamine does (42). Since the 2,4,5-configuration in the amphetamine series is active, it might be assumed that 2,4,5-trimethoxyphenylethylamine in the phenylethylamine series is also active if it could cross the BBB.

Tryptamine and Derivatives

Among the indoleamines, dimethyltryptamine, diethyltryptamine and 5-methoxydimethyltryptamine were found to be the most potent compounds based on doses administered (SAR I) leading to the conclusion that N-methylation or ethylation of tryptamine markedly enhances potency and that the introduction of a methoxy group in the 5 position of dimethyltryptamine enhances potency even further (5,6).

A comparison based on brain levels (SAR II) leads to very different conclusions (43-47). The most potent compound is actually 5-methoxytryptamine; brain levels are very low because the substance crosses the BBB only with great difficulty (46). Tryptamine alone is inactive because it is probably too rapidly metabolized (48); however, tryptamine after MAO-inhibition shows behavioral activity (43) and is close to 5-methoxytryptamine in potency. 5-Hydroxydimethyltryptamine also is rather potent since the compound has difficulty crossing the BBB and only small amounts reach the CNS (45). Dimethyltryptamine, diethyltryptamine and 5-methoxydimethyltryptamine are relatively weak and only appear potent because they are accumulated in the CNS against a concentration gradient (44,47). Apparently, N-methylation and ethylation do decrease potency. It is of interest to note that the two compounds with the highest potency, tryptamine and 5-methoxytryptamine, are naturally occurring in the mammalian brain (12,49,50).

Lysergic Acid Diethylamide and Derivatives

These compounds are considered here because of the potency of LSD and the fact that they contain the indole nucleus. LSD is most potent based on administered doses (5,51). The loss of the two ethyl groups from LSD decreases the potency by a factor

of 5 based on administered doses and by a factor of 10 based on brain levels (5,51,52).

Comparison

If one uses only the dose which interferes with the CAR, LSD would be considered the most potent compound. With reduced potency, pentamethoxyphenylethylamine, 5-methoxy-N,N-dimethyltryptamine and isolysergic acid amide would be the most potent compounds. Tryptamine, 5-methoxytryptamine and 5-hydroxy-N,N-dimethyltryptamine would rate as rather weak psychoactive compounds. However, if one uses the MEBL as the basis for comparison, different conclusions will be reached. LSD is still the most potent compound, but it must now share this role with 5-methoxytryptamine. Compounds slightly less potent would be tryptamine (after monoamine oxidase inhibition), pentamethoxyphenylethylamine and 5-hydroxy-N,N-dimethyltryptamine.

As a group, the indoleamines including LSD and isolysergic acid amide show highest potency. The phenylethylamines are next in potency and the phenylethanolamines are almost devoid of behavioral activity.

Summary

A structure-activity-relationship of a variety of behaviorally active and inactive compounds which are naturally occurring or closely related structurally to putative neurotransmitters has been assembled. For the first time comparisons of activity are based on actual brain levels instead of doses administered.

A different and new SAR is obtained if minimal effective brain levels (MEBL), instead of administered doses, are used. Differences are due to the fate of the substance in the body and its availability to the CNS. Predictions of brain levels based on in vitro data, blood levels and/or lipid solubility can be misleading.

It is suggested that the "minimal effective brain level (MEBL)" or that concentration of a substance in the brain in moles/g at which time the first significant behavioral effect in a particular test situation can be detected, be used as the basis of comparison in SAR studies of behaviorally active substances. This is, of course, not the ultimate parameter which might be the number of molecules of a substance at a particular receptor, but it would eliminate a great number of "artifacts" which can be controlled with the present state of the art.

The use of MEBLs will allow more valid correlations between behavioral activity and certain physico-chemical parameters of the compounds, and an attempt to use MEBLs was recently made by Houk and co-workers (53). Also, MEBLs in animals can serve as a better base for the interpretation of human studies and can make these behavioral studies in man more meaningful; for instance, the lack of behavioral activity in bufotenin in man observed recently (54) could perhaps be due to the fact that at the doses tested the compound did not reach the CNS in sufficient concentrations because of its extreme difficulty in crossing the BBB. Similarly, 3,4-dimethoxyphenylethylamine has been found to be

inactive in man after oral administration (55); based on our studies (27) the compound would actually not be expected to be active by this route since it is too quickly metabolized and cannot reach the MEBL, thus, the behavioral activity of this compound in man remains unknown.

Based on the criteria applied in this review, LSD and 5-methoxytryptamine are the most potent psychoactive substances followed by tryptamine (after MAO-inhibition) and pentamethoxyphenylethylamine. It is of interest to note that tryptamine and 5-methoxytryptamine are known to occur naturally in the mammalian brain. It remains to be determined what role, if any, these substances may play in the pathogenesis of abnormal behavior in man.

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