Chemistry and Pharmacology of Hallucinogens, Entactogens and Stimulants

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Amphetamines, tryptamines, phencyclidines, tetrahydrocannabinol and substances of the ecstasy group are characterized as stimulants, hallucinogens and entactogens. The various effects of each group and their mode of action in different transmitter systems are described. 28 new compounds of the amphetamine and tryptamine series has been calculated, which exceed the hallucinogenic effects of mescaline. The different pathways of the metabolism of MDMA (ecstasy) and MDE in humans may probably explain their individual effects.

Hallucinogens, stimulants and entactogens can be classified according to both their psychological effects and chemical/pharmacological criteria. The psychological effects of stimulants can easily be described. In contrast, the effects of hallucinogens are hard to define. According to the most widely accepted definition (*Hollister*, 1968) hallucinogen effects are characterized by five common features:

1. changes in mood and perception are more dominant than any other effects hallucinogens might exert,
2. there is minimal memory or intellectual impairment,
3. use is not associated with either stupor or excessive agitation,
4. there are minimal side-effects from autonomic nervous system stimulation,
5. craving and (physical) addiction do not occur.

According to their chemical structure, hallucinogens can be classified in:

- phenylalkane amines such as amphetamines (e.g. DOB, MDA, MBDB) and phenethylamines (e.g. BDMPEA, 2 CB, Nexus),
- indolalkane amines such as LSD, psilocybin, bufotenine, and tryptamines (e.g. N,N-dimethyltryptamine),
- phenylcyclohexane amines (e.g. PCP and its analogs),
- cannabinoids (e.g. tetrahydrocannabinol),
- β-carbolines (e.g. harmine),
- tropane alkaloids (e.g. atropine), and
- isoxazoles (e.g. ibotenic acid and muscimol).

The term "entactogen" was formulated by *Nichols* in 1986. It comes from the Latin root tact(us) (to be moved) and the Greek roots en (within or inside) and gen(ein) (to produce). The term is meant to communicate the connotation of "producing a touching within". The benzodioxolylbutanamines and the methylendioxyamphetamines (Fig. 1) comprise a group with mainly „entactogenic" psychological effects. Various observations suggest that entactogens are different from hallucinogenic drugs, because these agents usually do not produce major changes in perception and thought.

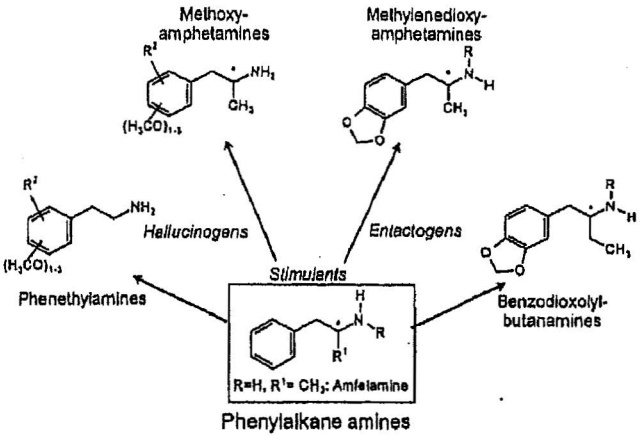

Fig. 1 Chemical structures of the phenylalkane amine group.

The phenylalkane amine group (Fig. 1) is a suitable psychotropic drug group for studying stimulant, hallucinogenic, and entactogenic properties (*Kovar* et al., 1996). More than 200 phenylalkane amines are known. Depending on their chemical structure, some of them possess stimulant effects, others hallucinogenic effects and others more entactogenic effects. Amfetamine and metamfetamine have a powerful centrally stimulating effect, can enhance physical performance to a considerable extent, and help overcome fatigue. Under the influence of stimulant amphetamines anxiety is mostly suppressed, formal thought might be accelerated, subjects mostly become talkative, and appetite is greatly reduced. Alteration of visual perception and hallucinations are the most characteristic effects of the methoxyamphetamines; aggression and agitation may be also observed occasionally. It has been reported that methylenedioxyamphetamines promote self-knowledge and the concept of self. Anxiety is clearly inhibited in an atmosphere of subjective relief from stress. The desire to communicate is an important characteristic of entactogenic drug effects. Alterations of visual perception may occur, and appetite is suppressed.

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Amfetamine interacts with the dopamine transporter to facilitate dopamine release from the cytoplasma through an exchange diffusion mechanism. At higher intracellular concentrations, amphetamine can also disrupt the vesicular storage of dopamine. In addition, amphetamines are inhibitors of the monoamine oxidase. Both actions will augment cytoplasmatic dopamine concentrations. Consequently, dopamine concentration in the synaptic cleft is also enhanced. Furthermore, amphetamines inhibit dopamine reuptake as a result of their binding to and transport by the dopamine carrier.

With the exception of phenethylamines, phenylalkane amines contain a chiral carbon atom at the alpha-position to the nitrogen in the side chain. Hence, two enantiomers exist. The two enantiomers differ in their affinity to receptors and their respective pharmacological effects: the (+)-S enantiomers of amphetamine and metamphetamine produce more pronounced CNS-stimulant effects than the (-)-R enantiomers. The CNS stimulant effect of amfetamine is attenuated by the following structural changes:

- loss of the α-methyl group or extension of the propylamine side chain, resulting phenethylamine and butylamine derivatives,
- alkylation of the nitrogen atom with the exception of monomethylation,
- substitution at the aromatic ring,
- oxygenation, hydroxylation, or methylation at the β-position of the nitrogen atom.

Modern investigations of quantitative structure-activity relationship (QSAR) aided by comparative molecular field analysis (CoMFA), have shown that the hallucinogenic effect is caused by steric as well as electrostatic aspects of the molecules (areas with partial positive or negative charges). The hallucinogenic effect is increased by the presence of a methyl group in the side chain of the methoxyphenethylamines and particularly, by a substituent of the aromatic ring at C-4 (Fig. 1). The substituent at this position probably takes up relatively little space. Forbidden steric areas are situated near position 3. In contrast, areas with positive partial charge near the aromatic ring at position 4 with possible extension towards position 3 and 5 enhance the hallucinogenic effect. This is also the case for areas with negative partial charge at positions 2 and 5. Hence, the 2,5-dimethoxy-amphetamines, which carry a relatively small substituent at position 4, such as a halogen atom, a halogen-methyl group, or a halogen-ethyl group, have the most pronounced hallucinogenic effects. Finally, the (-)-R enantiomers of the methoxyamphetamines are more potent than the (+)-S forms.

According to these QSAR and ComFA studies we calculated 28 new compounds of the amphetamine and tryptamine series, which exceed the hallucinogenic effects of mescaline by a factor of 7 to 820 (Table 1) (*Beuerle* et al., in press). By comparison, DOB, the most active amphetamine derivative yet known, has about 200 mescaline units (MU), which means that it is 200 times more potent than mescaline. For theoretical reasons, the possible error of the predicted values may be as high as a factor of three. It is now necessary to synthesize the postulated compounds and to test them biologically. Meanwhile, another research group under D. Nichols has synthesized the compound "new 5". According to Nichols the activity of „new 5" is slightly more potent than DOB (D. Nichols, personal communication).

Like the methoxyamphetamines, tryptamine and its analogs bind to the $5HT_{2A}$- and $5HT_{2C}$-receptors. Tryptamines are closely related to serotonin. Bufotenine and psilocin are tryptamines, which are hydroxylated at different positions (Fig. 2). Psilocin is the active form of psilocybin. The latter is much more stable than psilocin and can be administered per os. During absorption psilocybin is dephosphorylated. The two substances exhibit different isopotential lines. The isopotential lines of psilocin and DOB are also different; this indicates different affinities of the two latter substances to $5HT_{2A}$- and $5HT_{2C}$-receptors. In contrast, psilocin and LSD have similar isopotential lines; this indicates only minor differences in the attachments to the binding sites.

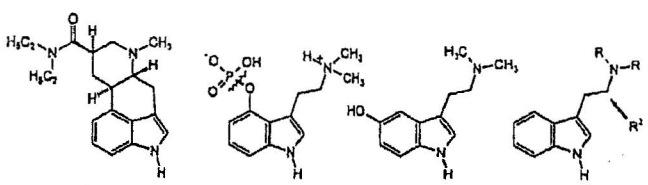

Fig. 2 Chemical structures of various indolalkane amines and tryptamines.

Table 1 Newly designed compounds and their activity in mescaline units

cpd	activity (mu)	cpd	activity (mu)	cpd	activity (mu)
new 1	83	new 11	140	new 21	44
new 2	82	new 12	61	new 22	820
new 3	210	new 13	79	new 23	170
new 4	70	new 14	110	new 24	95
new 5	180	new 15	39	new 25	220
new 6	210	new 16	230	new 26	160
new 7	320	new 17	22	new 27	13
new 8	63	new 18	54	new 28	7.7
new 9	10	new 19	85		
new 10	94	new 20	62		

Phencyclidines have a phenylcyclohexane amine structure (Fig. 3). The mother substance PCP has been known since 1926. In 1963 PCP was marketed under the trade name Sernyl®. In 1965 it was removed from the market because of its side-effects: agitation and hallucinations. During the 1970 s, PCP became widely abused. PCP can be synthesized easily from piperazine, cyclohexanol and potassium cyanide. For this reason the precursor piperidine was subject to legal restrictions. As a result, approximately 30 further new phencyclidines have been developed by clandestine laboratories, such as rolicyclidine, tenocyclidine, and eticyclidine. PCP produces its effects in the central nervous system by binding to high-affinity PCP sites (*Haerer* and *Kovar*, 1994). PCP binding sites are selective for substances that exhibit closely related physiologic and behavioral actions (*Zukin* and

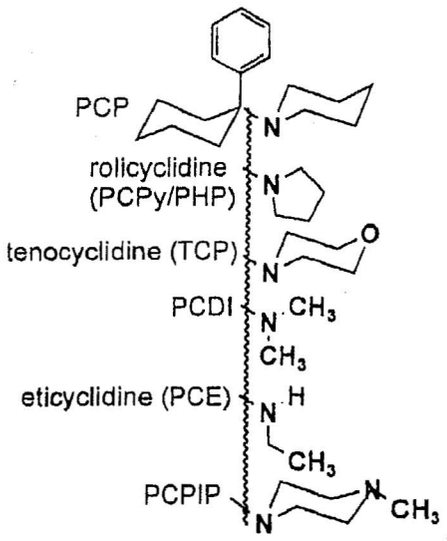

Fig. 3 Chemical structures of the most important phencyclidines.

Zukin, 1992). Sigma-opioids and cyclazocine are also active in the binding assay and exhibit PCP-like behavioral activity. A well-recognized consequence of ligand binding to the PCP sites is the blockade of the NMDA receptor. The PCP receptor is a site within the NMDA – activated channel. PCP derivatives stereospecifically and potently antagonize NMDA receptor-mediated excitation of spinal and cerebral neurons. Binding to the NMDA complex probably does not explain all behavioral effects of PCP, because PCP also binds to the sigma receptor.

Tetrahydrocannabinol (THC) – the active constituent of hashish and marihuana – is inactive in the PCP-binding assay and fails to elicit PCP-like behavior. The psychotropic effects of THC are mediated through the central cannabinoid receptor (CB 1), which was detected in 1988. In 1992 anandamide was found to be an endogenous ligand of the cannabinoid receptor (*Devane* et al., 1992). The essential structural prerequisites for ligand-receptor interaction of cannabinoids are the free phenolic hydroxyl group and the alkyl side chain at the aromatic ring. Extension and branching of the pentyl side chain yields the dimethylheptyl derivative with a greatly increased affinity for the cannabinoid receptors. A cannabinoid pseudoreceptor model for the CB1-receptor has been constructed by computer assisted drug design (*Schmetzer* et al., 1997).

The mode of action of the entactogens is complex and includes:
- enhancement of neuronal serotonin release from the cytoplasmatic stores,
- blocking of the serotonin reuptake site and thus prevention of serotonin reuptake,
- antagonistic effect at the alpha-2-heteroreceptor (producing further serotonin-release), and
- inhibition of the tryptophan hydroxylase.

The acute pharmacological effects of entactogens result in an excess of serotonin in the synaptic cleft. This may induce a serotonin syndrome. Furthermore, entactogens block not only serotonergic, but also noradrenergic and dopaminergic uptake-carriers. Thus, entactogens cause additional central

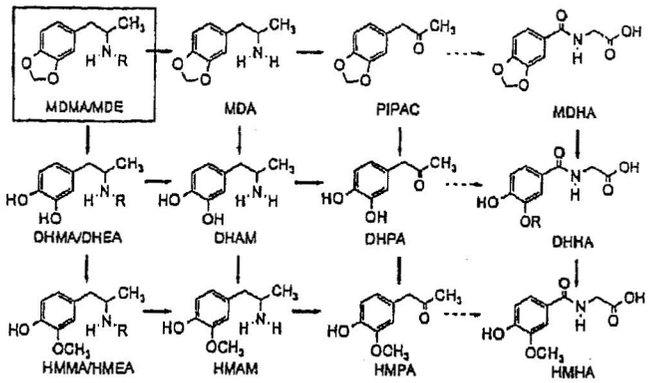

Fig. 4 Metabolism of methylenedioxy-N-methylamphetamine (MDMA) and methylenedioxy-N-ethylamphetamine (MDE).
DHMA/DHEA: 3,4-dihydroxy-N-methyl/ethyl-amphetamine
HMMA/HMEA: 4-hydroxy-3-methoxy-N-methyl/ethylamphetamine
MDA: Methylenedioxy-amphetamine
DHAM: 3,4-dihydroxy-amphetamine
HMAM: 4-hydroxy-3-methoxy-amphetamine
PIPAC: piperonylacetone
DHPA: 3,4-dihydroxyphenylacetone
HMPA: 4-hydroxy-3-methoxyphenylacetone
MDHA: methylenedioxy-hippuric acid
DHHA: 3,4-dihydroxy-hippuric acid
HMHA: 4-hydroxy-3-methoxy-hippuric acid

stimulating effects and interact with the central reward system (*Schmidt*, 1994).

The various effects and the neurotoxicity of MDMA and MDE may be related to their metabolism. Extensive studies of the metabolism and the potential toxicity of the metabolites have been done. In vivo and in vitro metabolism of methylenedioxyamphetamine in animals was first described by *Lim* and *Foltz* (1988). We investigated urine samples of healthy human subjects after ingestion of 140 mg MDE (*Ensslin* et al., 1996). Ten metabolites were found. Two overlapping metabolic pathways were postulated (Fig. 4). The first and predominant pathway leads – via ring degradation by O-dealkylation – to the corresponding 3,4-dihydroxymetabolites, which are subsequently methylated at the hydroxyl group at position 3 of the aromatic ring. The second pathway leads – via chain degradation by N-dealkylation – to MDA and the other corresponding primary amines, by O-dealkylation. Further oxidative N-deamination forms the substituted phenylacetone, which is degraded to the corresponding benzoic acid. This step is followed by conjugation with glycine to form substituted hippurates. Quantification of urinary excretion by high performance liquid chromatography (HPLC) revealed that, over a period of 32 hours, 19% of the MDE dosage was eliminated as MDE, 32% as hydroxymethoxyamphetamine, and 3% as MDA. In addition, we have to take into account that poor and extensive metabolizers will differ in their metabolism. This fact may probably explain the different effects of these drugs in different individuals.

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