Kinetic profiles of incorporation of some psychedelics into brain tissue after subcutaneous application to rats

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Abstract

The psychedelics can appear as drugs of abuse and they have a potency to induce altered state of consciousness in individuals due to their action to serotonine, noradrenaline and dopamine receptor systems. However, the pharmacokinetic data of these agents are scarce or unknown. To verify the correlation with the reported psychedelic effects in humans, we aimed to get information on kinetics of incorporation of these drugs from blood into brain tissue in experiments with rats. Mescaline has been known as a classical hallucinogen with some structural relationships to other substances of our interest and can serve as the reference standard in our comparative study.

The single doses of mescaline, 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 4-bromo-2,5-dimethoxyamphetamine (DOB) or 4-methoxymethamphetamine (PMMA) were injected subcutaneously to male Wistar rats SPF and animals were sacrificed subsequently after defined time intervals . Collected samples of blood (serum or plasma) and whole brains were kept frozen at –20° C till analyses. Drugs were extracted, derivatized by acetylation and assayed by GC-MS.

The ratio of maximum brain to maximum serum or plasma concentrations differed significantly: from 0.32 for mescaline to 12.4 for DOB. The drug affinity to brain tissue in rats correlated well with their psychoactive potency reported. In all cases the delayed influx of drugs into brain related to blood could be observed in consensus with delayed onset of action and the detection window in the rat brains was in relation with the duration of euphoria reported in humans.

1. Introduction

The psychedelics can appear as drugs of abuse in various structural forms in illegal products of unknown composition with potential health risk to individuals or safety endangerment in specific circumstances. They have a potency to induce altered state of consciousness in individuals due to their action to serotonine, noradrenaline and dopamine receptor systems (1-8). Their kinetic properties may be important to interpret the temporal course of their psychedelic effects. However, the pharmacokinetic data from controlled studies are scarce or unknown.

With the attention focused to compounds structurally related to phenylalkylamines, we aimed to search for their response relation to the kinetics of incorporation into brain tissue. Mescaline has been known as the classical hallucinogen with some structural relationships to other substances of our interest and can serve as the reference standard in our comparative study. We have already confirmed that the temporal mescaline concentration profile in brain has been

directly related to its psychoactive or behavioral effects (9). The kinetic data summarized here were provided from several controlled independent animal experiments with rats after a single subcutaneous dose of the individual drug.

2. Experimental

2. 1. Animals, drug application, sampling

All experiments followed the guideliness and laws governing animal studies in the Czech Republic. The male Wistar rats SPF (Velaz Ltd. Prague) were administered single bolus doses of individual drugs in separated experiments as described in Table 1. After the drug administration, animals were sacrificed at specified time intervals and blood and whole brains were collected, and serum or plasma samples with brains were stored at –20°C till analyses by GC-MS. In experiments with DOB and PMMA plasma samples were used, while in experiments with mescaline and 2C-B serum samples were used.

Tab.1: Drug subcutaneous administration to rats. Description of experiments

Drug administered	**s. c. dose (mg/kg)**	**Number of animals per sampling time**	**Sampling intervals after dosing (hours)**
Mescaline.HCl	20	6	0.5 1 2 8
DOB.HBr	20	3	0.5 1 2 4 8 16 32
PMMA.HCl	40	3	0.5 1 2 4 8 16 32
2C-B.HCl	50	10	0.5 1 2 6

2. 2. Analytical methods

Drug isolation:

The brain tissue with appropriate internal standard was homogenized and deproteinated with methanol, the supernatant was used for drug extraction. SPE-DAU commercial discs (ANSYS Technologies) were used for drug extractions from biological samples, with the exception of DOB, where liquid extraction with ethylacetate was used. The provided extracts were acetylated before GC-MS analysis. The details of procedures were described elsewhere (9-10).

GC-MS analysis:

The Hewlet-Packard system HP6890-5973 with standard EI in SIM mode was used under operating conditions described elsewhere (9-10). The SIM mode was set up for particular analyses of specific drugs with appropriate internal standards.

3. Results and discussion

The summary of kinetic profiles of particular drugs in blood serum (plasma) vs. brain after a single bolus subcutaneous dose to experimental rats is presented in Figure 1.

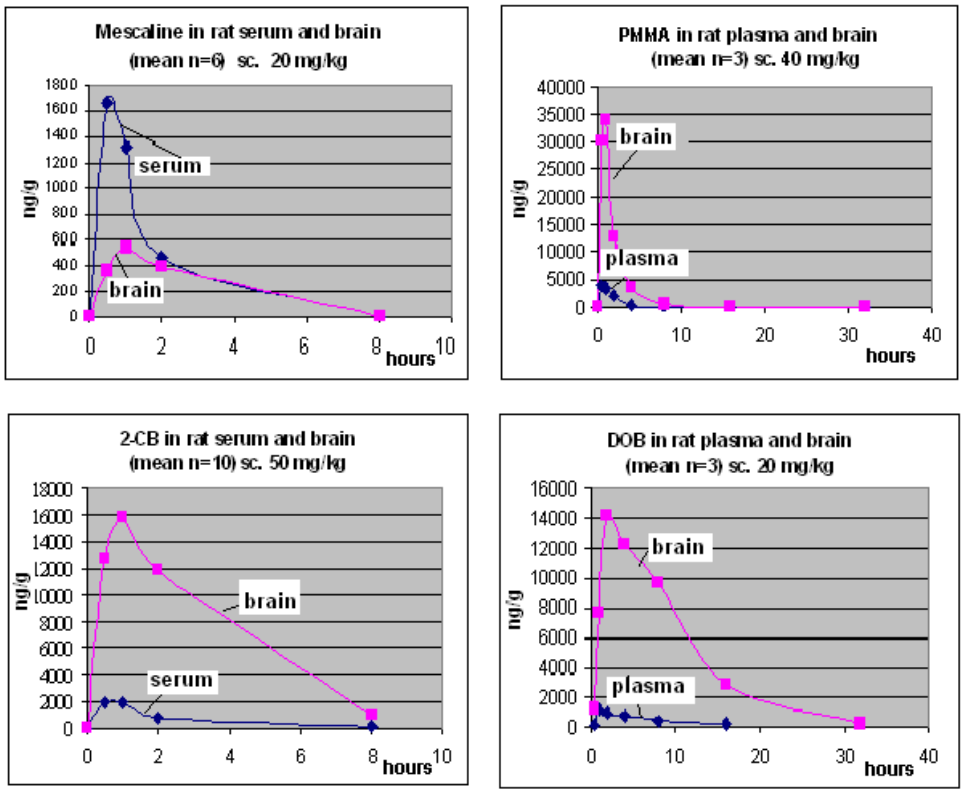

Fig. 1: Drug kinetic profiles in blood serum or plasma related to brain after subcutaneous administration to rats

Drug concentration ratios between rat brain and serum (plasma) are demonstrated in Table 2 and compared with the reported pharmacodymamic potency of the particular drug (1, 11). The mean interindividual concentration values of specific drugs in rat samples with appropriate SD in the whole experimental time interval are summarized in Table 3. The ratio of maximum brain concentration to maximum blood serum or plasma concentration of drugs involved into our comparative study differed significantly – from 0.32 for mescaline to 12.4 for DOB. In all cases the delayed influx of drugs into brain related to blood can be observed in our experimental rats. This phenomenon was in accordance with delayed onset of psychedelic action in humans (6,11). Drug detection window in brain tissue has been related to the duration of euphoria as it was ascertained in the behavioral study with mescaline (9) even though the dose response effect and the parameters of analytical method used were also important in this respect.

Tab. 2: Reported drug psychedelic potency in humans (1) and affinity to brain tissue after drug subcutaneous administration to experimental rats

DRUG	Potency[1] (M.U.)	Dose applied to rats (mg/kg)	Serum (plasma)		Brain		Ratio at t_{max}
			c_{max} (ng/ml)	t_{max} (min)	c_{max} (ng/ml)	t_{max} (min)	$c_{brain}/c_{serum\ or\ plasma}$
MESC	1	20 (n=6)	1657+/-314	30	538+/-67	60	0.32
PMMA	2	40 (n=3)	4014+/-1347	30	33870+/-5656	60	8.4
2C-B	16	50 (n=10)	2250+/-253	30	17102+/-4493	60	7.6
DOB	150	20 (n=3)	1144+/-148	60	14157+/-616	120	12.4

Mescaline unit (M. U.)

Tab. 3: The mean interindividual concentration values for specific drugs determined in the whole time interval in experiments with rats

DOB 20 mg/kg sc. (n=3)					
hours	*BRAIN (ng/g)*		*PLASMA (ng/ml)*		*BRAIN/PLASMA*
	C_{DOB}	*SD*	C_{DOB}	*SD*	
0.5	*3623*	*323*	*151*	*50*	*24*
1	*7649*	*690*	*1144*	*148*	*6.7*
2	*14157*	*616*	*919*	*156*	*15.4*
4	*12289*	*1157*	*704*	*84*	*13.4*
8	*9703*	*436*	*405*	*58*	*24*
16	*2872*	*307*	*156*	*56*	*18.4*
32	*219*	*132*	*nd*		
2C-B 50 mg/kg sc. (n=10)					
hours	*BRAIN (ng/g)*		*SERUM (ng/ml)*		*BRAIN/SERUM*
	C_{2C-B}	*SD*	C_{2C-B}	*SD*	
0.5	*14639*	*3042*	*2250*	*253*	*6.5*
1	*17102*	*4493*	*1892*	*523*	*9.0*
2	*12462*	*3786*	*900*	*279*	*13.8*
6	*982*	*187*	*773*	*311*	*1.3*
PMMA 40 mg/kg sc. (n=3)					
hours	*BRAIN (ng/g)*		*PLASMA (ng/ml)*		*BRAIN/PLASMA*
	C_{PMMA}	*SD*	C_{PMMA}	*SD*	
0.5	*30222*	*7039*	*4014*	*1122*	*7.5*
1	*33870*	*5656*	*3362*	*819*	*10.1*
2	*12898*	*3074*	*2073*	*428*	*6.2*
4	*3683*	*298*	*354*	*84*	*10.4*
8	*473*	*298*	*30*	*17*	*15.8*
16	*44*	*22*	*12*	*1.6*	*3.7*
32	*24*	*10*	*13*	*3.4*	*1.9*
MESCALINE 20 mg/kg sc. (n=6)					
hours	*BRAIN (ng/g)*		*SERUM (ng/ml)*		*BRAIN/SERUM*
	$C_{MESCALINE}$	*SD*	$C_{MESCALINE}$	*SD*	
0.5	*370*	*68*	*1657*	*314*	*0.22*
1	*538*	*67*	*1330*	*287*	*0.40*
2	*409*	*65*	*476*	*251*	*0.86*
6	*4*	*4*	*3*	*7*	*1.3*

The temporal delay to achieve the peak brain concentration was most apparent in the case of DOB and this experimental finding has been in accord with the dynamic response delay reported (6, 11).

The individual drug affinity to the lipophillic brain tissue in rats expressed as brain to serum (plasma) ratio values corresponded to their psychoactive potency in humans and can be expressed relative to mescaline in this sequence: MESCALINE < PMMA < 2C-B < DOB. The results from structure activity studies confirmed that psychedelic activity of phenylalkylamines depends on the presence of methoxygroups in position 2 and 5 of the aromatic ring and a hydrophobic 4-substituent (halogen, alkyl) (3, 8). The relative polarity of mescaline is high , therefore the higher dose of mescaline is necessary to cross the blood-brain barrier and to induce significant psychedelic effects (9), whereas lower doses of less polar hallucinogens are sufficient to achieve similar response.

The peak blood serum (plasma) concentrations accomplished in rats have not corresponded to particular doses applied tightly in quantitative sense. The possible saturation effect and the tissue accumulation after high doses might occur. The lung buffer capacity has been reported by Shulgin et al.(6, 11) and the lung ability to accumulate drugs was confirmed in our previous experiments with rats (10). This drug retention in lungs could impact to the temporal delay in accomplishing the maximum brain concentration and psychotropic response and the subsequent accumulation in brain may prolong the psychoactive effects.

4. Conclusions

Our experimental findings indicate the importance of the polarity of drugs under our study to the ability and efficiency to cross the blood/brain barrier and incorporate and persist in lipophillic brain tissue. The temporal drug brain profiles are in significant relation to the course of behavioral or psychotropic effects. This is the confirmation that the maximum psychoactive effects directly correlate with the pharmacokinetics of a particular drug.

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