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Harman-induced changes of extracellular concentrations of neurotransmitters in the nucleus accumbens of rats

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Abstract

Several β-carbolines, including harman, induce voluntary ethanol intake in rats. It is not clear yet which mechanisms cause these effects. One possibility is the stimulation of the mesolimbic reward system. In vivo microdialysis was used to investigate the effects of acute injections of harman (1-methyl-β-carboline) on extraneuronal concentrations of dopamine and 5-hydroxytryptamine in the nucleus accumbens, which is part of the mesolimbic reward system. Administration of harman (2.27 μmol/kg, intraperitoneal application) elicited an increase of the dopamine efflux by 72% which returned to basal levels after approximately 300 min. In contrast, administration of an intermediate dose of harman (13.65 μmol/kg, intraperitoneal application) caused a significant decrease in efflux, to 76% of basal levels. Still higher doses induced again an increased extracellular dopamine concentration. This change was statistically significant in only a subgroup of rats, possibly because individual animals reacted differently to the high doses. Extracellular 5-hydroxytryptamine in the nucleus accumbens was increased during the first 2 h after the administration of high doses (40.94 and 81.93 μmol/kg, intraperitoneal application). These findings indicate that harman affects the activity of mesolimbic dopaminergic neurons following a U-shaped dose-response relationship.

Keywords: β-Carboline; Dopamine; 5-HT (5-hydroxytryptamine, serotonin); Harman; Norharman; Microdialysis; Nucleus accumbens

1. Introduction

Harman (1-methyl-β-carboline) and norharman (β-carboline) are members of the family of mammalian alkaloids derived from neurotransmitters by a condensation reaction (Brossi, 1993). Chronic infusion of harman induces increased voluntary ethanol intake in rats (Rommelspacher et al., 1987; Adell and Myers, 1994). Norharman inhibits the withdrawal syndrome in morphine-dependent rats (Cappendijk et al., 1994). Blood levels of harman are elevated in alcoholics (Rommelspacher et al., 1996) and heroin addicts (Stohler et al., 1995). These and other findings suggest a role of at least some of the β-carbolines in alcoholism and drug dependence.

One possible mechanism to explain some of the addiction-relevant effects of harman is the activation of the mesolimbic reward system (Wise and Bozarth, 1987). Previous in vivo microdialysis experiments revealed a U-shaped dose-response relationship for the interaction of norharman with mesolimbic dopaminergic neurons (Sällström Baum et al., 1995). Low doses induced an increased extraneuronal level of dopamine in the nucleus accumbens whereas somewhat higher doses caused a reduction. Locally perfused harman excited nucleus accumbens neurons (extracellular single-unit recording, coupled with push-pull perfusion; 10^{-9}-10^{-11} M), while at higher concentrations (10^{-8}-10^{-6} M) depression was most pronounced (Ergene and Schoener, 1993). Furthermore, harman facilitated L-3,4-dihydroxyphenylalanine (L-DOPA)-induced stereotypy in mice, suggesting a pro-dopamine effect of the β-carboline (Pimpinella and Palmery, 1995).

Harman binds to several receptors in the brain, including those for 5-hydroxytryptamine (5-HT_2, IC_{50} 6.75 μM), dopamine (D_2, IC_{50} 163 μM) and the benzodiazepines (IC_{50} 7 μM), and to a distinct binding site for norharman (Müller et al., 1981; Pawlik and Rommelspacher, 1988; Strömbom et al., 1992). Furthermore, nanomolar concentrations of harman inhibit monoamine oxidase subtype A in vitro (May et al., 1991a,b) and in vivo (Rommelspacher et al., 1994). Harman evokes neuropsychopharmacological

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effects in mammals (Pletscher et al., 1959; Airaksinen and Kari, 1981). As shown with norharman (Sällström Baum et al., 1995), it is conceivable that harman also affects directly nucleus accumbens neurons. The nucleus accumbens is an important part of the mesolimbic reward system. Activation of the mesolimbocortical dopaminergic neurons leads to drug seeking behaviour in animals which can be regarded as equivalent to craving for alcohol and drugs by humans (Wise and Bozarth, 1987).

The present study investigates the effect of harman on the mesolimbic dopaminergic system in the rat brain by measuring the in vivo levels of dopamine and 5-hydroxytryptamine in the nucleus accumbens following intraperitoneal (i.p.) application of the compound. Furthermore, the levels of the following metabolites were determined: 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA).

2. Materials and methods

2.1. Animals

Male Wistar rats (Wist; Charles River, Germany; 220–300 g) were used. They were kept in groups of 4–6 in a controlled environment (12/12-h light/dark cycle; 22°C) for at least 7 days until surgery. Food and water were available ad libitum.

2.2. Surgery

Under ketamine (80 mg/kg i.p.; Sigma, USA) and xylazine (8 mg/kg i.p.; Sigma) anaesthesia, a guide cannula (CMA 12; Carnegie Medicine, Sweden) was implanted into the brain of rats mounted in a stereotaxic device (David Kopf Instruments, USA). The tip of the guide cannula was lowered into the nucleus accumbens. The coordinates were chosen according to the atlas of Paxinos and Watson (1985): anterior 1.2 mm, lateral 1.4 mm and ventral −6.5 mm (relative to bregma). The animals were allowed 72 h to recover from surgery in a controlled noise-insulated room (humidity 60%, temperature 22°C and 12/12-h light/dark cycle), during which time they were placed individually in a macrolon cage (size 34 × 20 × 25 cm).

2.3. Brain dialysis

The microdialysis probe (Carnegie Medicine; 2 mm membrane length) was inserted under light anaesthesia with diethylether through the guide cannula and connected to a microinjection pump (CMA 100; Carnegie Medicine). This probe was continuously perfused for 20 h with artificial cerebrospinal fluid (aCSF; 137 mM Na^+, 1.2 mM Ca^{2+}, 2.4 mM K^+, 144.2 mM Cl^-, 1.2 mM Mg^{2+}, 0.9 mM $NaH_2PO_4 \cdot H_2O$ and 1.4 mM $Na_2HPO_4 \cdot 2H_2O$; pH 7.0) before the experiment commenced. The flow rate was 2.0 μl/min. 20-min fractions containing 10 μl $HClO_4$ (0.5 M) were directly analysed by means of a high-performance liquid chromatography system connected with an electrochemical detector (Waters, USA, Coulochem II; ESA, USA, HPLC-ECD). After collection of 5 samples (basal level), harman-hydrochloride, norharman-hydrochloride (Sigma) or 0.9% sodium chloride (vehicle) was injected. All doses of the applied compounds were calculated as free base.

On completion of an experiment, rats were killed and histological analyses of the brain were performed to verify the position of the dialysis probe. Sections were cut using a cryostate microtome (M2700 Frigocut; Reichert-Jung, Germany) and stained with Cresyl violet.

2.4. Analysis of the dialysate

The catecholamines were separated by the HPLC-ECD system using a stainless steel column (Nova-Pak C_{18}, 4 μm, 150 × 3.9 mm i.d.; Waters). The reversed-phase ion pair mobile phase (pH 3.2) consisted of 25 mM NaH_2PO_4, 0.81 mM octylsulphate, 0.19 mM EDTA and 12.3% methanol (v/v; isocratic conditions). The flow rate was 0.9 ml/min and the temperature was kept at 22°C. The electrode was set at 350 mV. The detection limit for dopamine and 5-hydroxytryptamine was approximately 5 fmol per sample injected onto the column.

2.5. Statistics

The data are expressed as percentages of basal values (mean ± S.E.M., if not stated otherwise).

The mean of the basal level was defined as 100%. Data were analysed using one-way analysis of variance with Student-Newman-Keuls-test as well as Student's *t*-test for comparison between doses. The accepted level of significance for all tests was $P < 0.05$.

3. Results

3.1. Control conditions

The following mean basal levels were determined: dopamine 19.82 ± 0.56 fmol/50 μl, DOPAC 893.57 ± 4.84 fmol/50 μl and HVA 29.56 ± 0.47 pmol/50 μl (20-min samples containing in addition 10 μl perchloric acid; $n = 16$, mean ± S.E.M.). Intraperitoneal injection of 0.9% NaCl (vehicle) changed neither the mean level of dopamine nor that of its metabolites. The inter-individual and intra-individual changes (mean ± S.D.; $n = 5$ rats, 5 time points), 100 min before vehicle, were for dopamine 100 ± 11.7%, for DOPAC 100 ± 3.4% and for HVA 100 ± 9.1%. The mean level 100 min after i.p. injection was for dopamine 87.7 ± 16.5%, for DOPAC 99.9 ± 7.4% and for HVA 103.3 ± 13.6%.

Mean basal levels of extracellular 5-hydroxytryptamine were 8.62 ± 0.262 fmol/50 μl perfusate ($n = 12$; the levels were below the detection limit in 4 rats) and for 5-HIAA 4.31 ± 0.035 pmol/50 μl perfusate (mean ± S.E.M.). The mean level 100 min before vehicle was 100 ± 9.2% for 5-hydroxytryptamine and 100 ± 2.8% for 5-HIAA. The mean level after i.p. injection was 108.1 ± 14.9% for 5-hydroxytryptamine and 98.2 ± 4.4% for 5-HIAA (mean ± S.D.; $n = 5$ rats, 5 time points).

3.2. Effect of harman on extraneuronal dopamine levels in the nucleus accumbens

We used a similar dose range for the experiments with harman as in the earlier experiments with norharman (Sällström Baum et al., 1995). The lowest dose was 2.27 μmol/kg and then doses of 3.41, 6.83, 13.65, 27.31 and 40.96 μmol/kg were tested, the highest dose being 81.93 μmol/kg. For more extensive experiments, the doses 2.27, 13.65, 40.96 and 81.93 μmol/kg were selected. The lowest dose (2.27 μmol/kg) caused an increase in extracellular dopamine ($P = 0.0196$) and DOPAC ($P = 0.0459$) whereas HVA remained unchanged. At the intermediate dose (13.65 μmol/kg), a decrease of dopamine ($P = 0.0010$) was found whereas the DOPAC levels decreased slightly (not significant) and HVA decreased during the first 2 h ($P = 0.0093$). At higher doses (40.96 and 81.93 μmol/kg), an increase in dopamine was observed but it was not significant on the 5% level compared to basal levels. In contrast to the observations with dopamine,

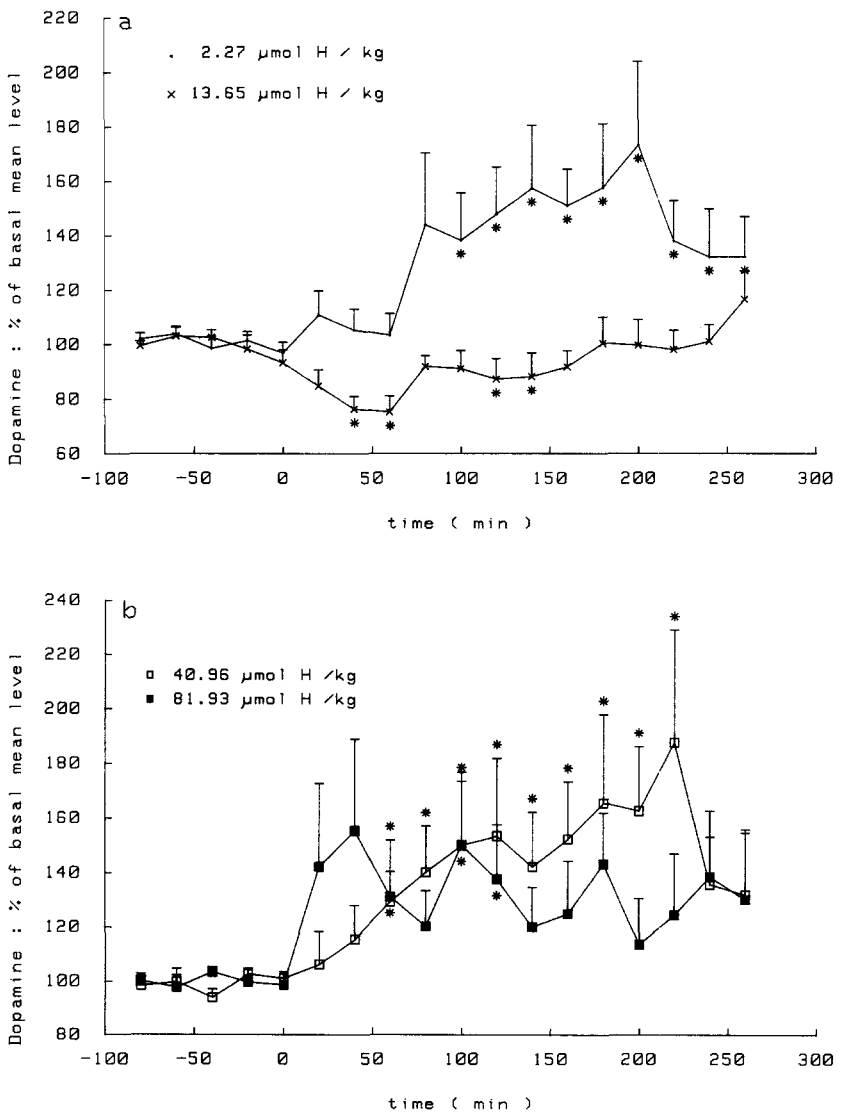

Fig. 1. (a,b) The effect of harman (H, i.p.) on extracellular dopamine (DA) concentration in the nucleus accumbens. Each point represents the mean ± S.E.M. from at least 8 rats. Abscissa: time before and after injection ($t = 0$). Significantly different values from the pre-injection value; * $P < 0.05$.

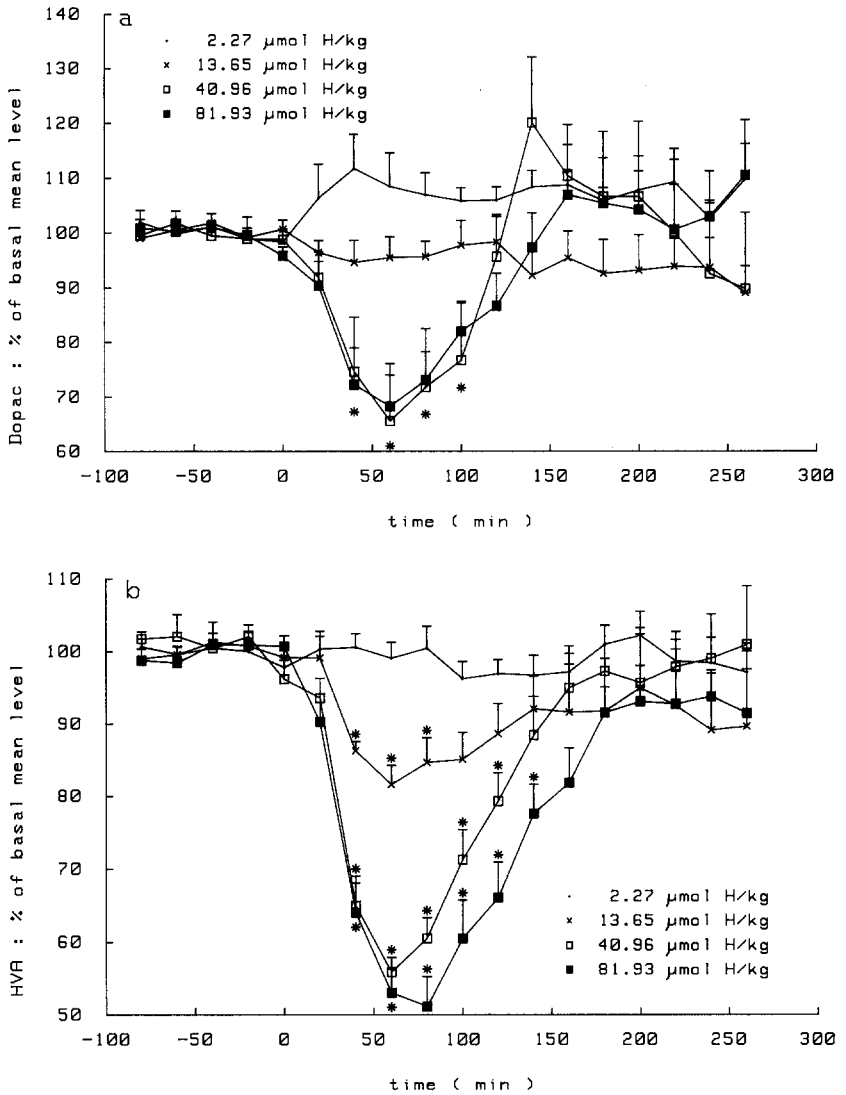

Fig. 2. (a,b) The effect of harman (H, i.p.) on extracellular 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) concentrations in the nucleus accumbens. Each point represents the mean ± S.E.M. from 8–15 rats. Abscissa: time before and after injection ($t = 0$). Significantly different values from the pre-injection value; * $P < 0.05$.

DOPAC decreased in the first 2 h ($P = 0.0006$ and 0.0000) as well as HVA ($P = 0.000$ and 0.0000) (Figs. 1a,b and 2a,b).

In the dose range of 3.41–27.31 μmol/kg, harman induced opposite reactions in the respective groups. Some rats showed increased dopamine levels whereas some rats showed decreased levels (Table 1).

Table 1
Number of rats with increased dopamine or decreased dopamine concentrations within 100 min following application of harman

μmol/kg	Increase	Decrease
2.27	9	1
3.41	3	1
6.83	2	2
13.65	0	5
27.31	2	2
40.96	6	3
81.93	9	2

3.3. Effect of harman on extraneuronal 5-hydroxytryptamine levels

The extraneuronal 5-hydroxytryptamine level in the nucleus accumbens did not change after the injection of the lower and intermediate doses. At higher doses (40.96 and 81.93 μmol/kg), an increase in the first 2 h ($P = 0.0235$ and 0.000) was detected. Analysis of data for single animals revealed that the higher the 5-hydroxytryptamine level, the weaker the increase of the dopamine level. The 5-HIAA level decreased following the highest dose (81.93 μmol harman/kg, $P = 0.0007$) (Fig. 3a,b).

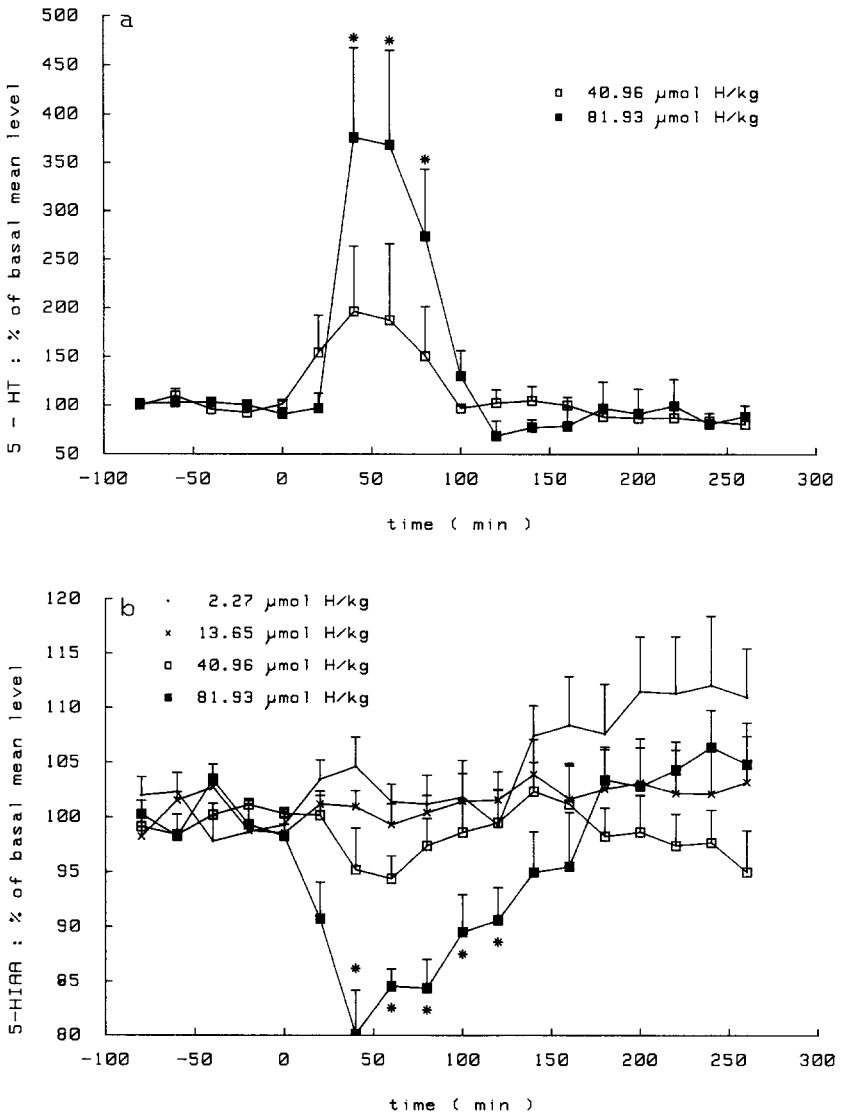

Fig. 3. (a,b) The effect of harman (H, i.p.) on extracellular 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations in the nucleus accumbens. Each point represents the mean ± S.E.M. from 8–15 rats. Abscissa: time before and after injection ($t = 0$). Significantly different values from the pre-injection value; * $P < 0.05$.

3.4. Comparison of the effects of norharman and harman

Harman caused a similar U-shaped dose-response relationship for dopamine levels in the nucleus accumbens as norharman did (Fig. 4; Sällström Baum et al., 1995). The lowest dose of norharman was more effective 40 and 60 min after i.p. injection than that of harman was. This was also found at a single time point (80 min after injection) with a high dose (norharman 43.97 μmol/kg, harman 40.96 μmol/kg).

The DOPAC concentrations were for some doses (2.27 harman/2.44 norharman and 13.65 harman/7.32 norharman μmol/kg) not significantly different between harman and norharman. For other doses (40.96 harman and 43.97 norharman μmol/kg), significantly lower levels were found 60–100 min after harman. Differences in HVA levels were not found for the lowest dose. For the intermediate dose, HVA was lower 60 and 80 min after i.p. injection of harman compared to norharman and 40–120 min after the highest dose (data are not shown in the case of norharman).

5-HIAA was not significantly different after harman and norharman with respect to the 3 doses investigated. 5-Hydroxytryptamine could not be compared, because no 5-hydroxytryptamine measurements were performed in the experiments with norharman.

4. Discussion

Application of harman caused a dose-dependent change in the levels of dopamine in the nucleus accumbens. The effect was triphasic. This mode of action has been observed in a previous study with norharman also (Sällström

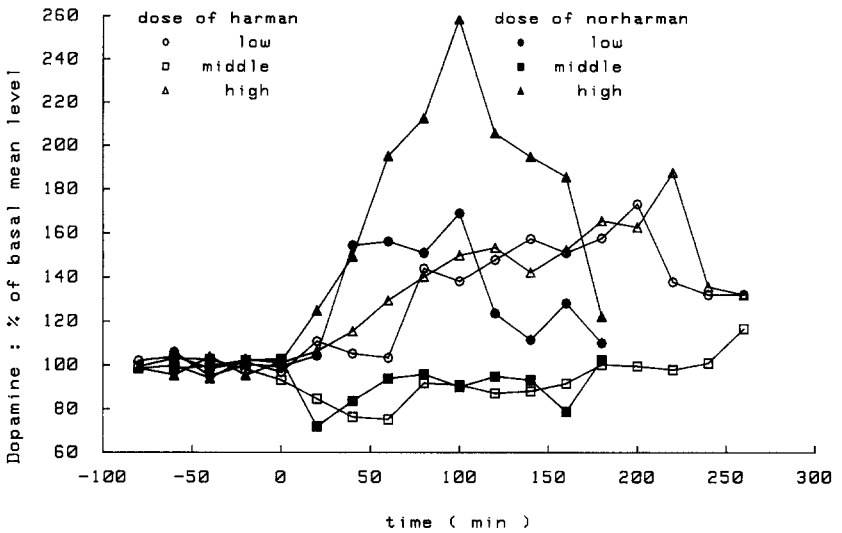

Fig. 4. Comparison of the effects of harman (H) and norharman (NH) on extracellular concentrations of dopamine (DA) in nucleus accumbens. Low dose in μmol/kg: 2.27 harman/2.44 norharman; middle dose in μmol/kg: 13.65 harman/7.32 norharman; high dose in μmol/kg: 40.96 harman/43.97 norharman. The norharman values are taken from Sällström Baum et al., 1995.

Baum et al., 1995). The latter β-carboline consists of the same heterotricyclic aromatic structure but lacks the methyl substituent in position 1. Activation of up to 80% of nucleus accumbens neurons by low concentrations of harman has been demonstrated in a study which used direct application to the neurons. For methodological reasons, the type of neurons activated could not be determined (Ergene and Schoener, 1993). The mechanism which causes the activation could be the interaction of harman and norharman with the distinct high-affinity binding site for [^{3}H]norharman (May et al., 1994). There is evidence that these sites are coupled to a second messenger mechanism (Rommelspacher et al., 1995). The harman concentration of 0.8 pmol/g brain tissue in whole brain (Rommelspacher et al., 1994) should be high enough to activate dopamine neurons, taking into consideration an uneven distribution, compartmentalization, and enriched concentration in monoaminergic synapses. An uneven distribution in human brain has been described for norharman, with concentrations of 16 μmol/kg measured in substantia nigra tissue (Matsubara et al., 1993).

The inhibiting actions of intermediate doses of harman were not unexpected. Similar effects have been observed with norharman in the nucleus accumbens in a previous study (Sällström Baum et al., 1995). Others have found that intermediate doses of harman inhibited up to 75% of the nucleus accumbens neurons (Ergene and Schoener, 1993). [^{3}H]Norharman is displaced from binding sites in rat forebrain by harman in a biphasic manner (May et al., 1994). Whether the observed in vivo findings can be explained by an interaction of harman with the low-affinity sites remains to be elucidated.

One of the most interesting findings was the different sensitivity of the rats to a certain dose of harman (Table 1). Although pharmacokinetic variation should be considered, this factor probably plays a role for only the high doses. The observation that the 3 low doses were effective in all animals and caused either a decrease or an increase in extraneuronal dopamine support the contention of a different sensitivity of individual rats. It can be speculated that rats with a different sensitivity differ also with respect to harman-induced behaviour, like, for example, ethanol preference. Furthermore, alcoholics with high depression and anxiety scores and a 'harm avoidance' personality have relatively high harman levels in the blood plasma (Rommelspacher et al., 1996). Whether the sensitivity of mesolimbic dopaminergic neurons towards harman indicates a propensity to consume ethanol (and other drugs) remains to be elucidated.

The high doses of harman activated several mechanisms. Both, dopamine and 5-hydroxytryptamine levels increased whereas those of HVA decreased. The highest dose caused a decrease in 5-HIAA. This pattern of effects suggests inhibition of monoamine oxidase A. Such a mode of action is supported by the observation that norharman does not change HVA levels. Norharman does not inhibit monoamine oxidase A (May et al., 1991a,b; Rommelspacher et al., 1994). In evaluating these findings, one should remember that there was a mismatch in the harman-induced changes in the extracellular levels of transmitters and metabolites. The basal levels of dopamine in the dialysate were approximately 45-times lower than those of DOPAC and the DOPAC levels were approximately 33-times lower than those of HVA. Similar differences have been reported by others as well (Zetterström and Fillenz, 1990; Juorio et al., 1994; Imperato and Di Chiara, 1984). Harman caused about a doubling of the dopamine levels (basal level approximately 20 fmol/50 μl dialysate) and a 50% decrease in HVA levels (basal level approximately 30 pmol/50 μl dialysate). The more pro-

nounced effect on HVA levels than on dopamine levels could be explained by the fact that after release, neurotransmitters and metabolites have to diffuse through the extracellular space before they enter the dialysis probe. Since most dopamine is taken up into the presynaptic compartment, only a small fraction diffuses into the extraneuronal space. HVA is formed by the extraneuronally located catecholamine-*O*-methyltransferase and distributes easily into the extraneuronal space (Dedek et al., 1979; Westerink, 1979). HVA is believed to be a good index of dopamine release.

A second action of harman could be stimulation of the benzodiazepine receptor in an inverse manner. Harman binds to the benzodiazepine receptor complex with a K_i value in the low micromolar range (Rommelspacher et al., 1980; Airaksinen and Mikkonen, 1980; Strömbom et al., 1992). Flurazepam and diazepam induce a decrease in dopamine efflux in the nucleus accumbens of freely moving rats (Finlay et al., 1992; Zetterström and Fillenz, 1990). Flumazenil, a benzodiazepine receptor antagonist, did not prevent the effects of high doses of harman on dopamine, homovanillic acid, 5-hydroxytryptamine and 5-hydroxyindoleacetic acid levels (data not shown). These findings suggest that inverse activation of benzodiazepine receptors by high doses of harman plays only a minor role if at all.

A further observation was the weaker efficacy of harman compared to norharman on extracellular dopamine levels. It is interesting to note that 40.96 μmol harman/kg was more effective in increasing dopamine levels than 81.93 μmol harman/kg, which seems to be in contrast to observations that dopamine is metabolized by monoamineoxidase A in rats (Waldmeier, 1987). One explanation could be that 5-hydroxytryptamine neurons inhibit mesolimbic dopamine neurons. Harman causes an increase in 5-hydroxytryptamine levels in the nucleus accumbens, possibly via inhibition of monoamineoxidase A. Monoamineoxidase A inhibition elicits an increased efflux of both dopamine and 5-hydroxytryptamine. At least in the case of dopamine, the increased outflow observed after monoamineoxydase A inhibition is voltage dependent and occurs by an exocytotic process (Colzi et al., 1993). 5-Hydroxytryptamine nerve endings have been described in the nucleus accumbens which inhibit dopamine release via 5-hydroxytryptamine$_{1A}$ receptors (Nissbrandt et al., 1992). The dopamine nerve terminals of the nucleus accumbens are endowed with 5-hydroxytryptamine receptors which inhibit dopamine release (Göthert, 1990). A further mechanism which could explain some of the findings could be that 5-hydroxytryptamine enters dopamine terminals with a subsequent exchange of 5-hydroxytryptamine for intraneuronal dopamine (Nurse et al., 1988; Schmidt and Black, 1989; Yi et al., 1991). Such a mechanism might be responsible for the observation that the dopamine metabolites were equally lowered by 40 and 80 μmol harman/kg body weight. It is important to know whether pathologically increased levels of harman are high enough to affect the multiple mechanisms described.

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