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In-vitro and in-vivo metabolism of the presynaptic dopamine agonist 3-PPP to a catecholic analogue in rats*

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The dopamine agonist 3-PPP and its enantiomers are hydroxylated in-vitro by rat liver microsomes to the catecholamine 3-(3,4-dihydroxyphenyl)-*N*-n-propylpiperidine (4-OH-3-PPP) with K_m and V_{max} values of about 1 μM and 2 nmol (mg protein)$^{-1}$ min^{-1} respectively. As the catecholamine formed appears to be a good substrate for catechol-*O*-methyltransferase, in-vivo catecholamine formation in rats from 3-PPP was only detectable after inhibition of COMT by tropolone. The resulting brain levels of 4-OH-3-PPP, as measured by HPLC with electrochemical detection 45 min after administration, were about 350 pmol g^{-1} after i.p., and about 100 pmol g^{-1} after s.c. injection of 45 μmol kg^{-1} 3-PPP, with no significant difference between racemic, (+) or (−) 3-PPP. It was estimated that these catecholamine levels represent about 1–5% of the 3-PPP levels after i.p., and about 0·2–0·5% after s.c. administration of 3-PPP. The relevance of this metabolic conversion of 3-PPP for its pharmacological profile is discussed.

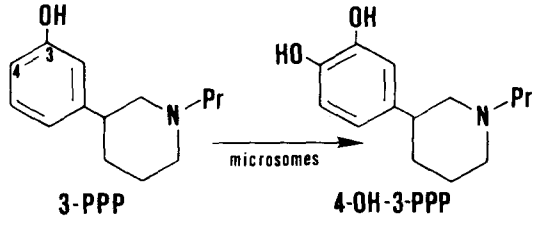
3-PPP (3-(3-hydroxyphenyl)-*N*-n-propylpiperidine) has been described as a dopaminergic agent of which the enantiomers have different pharmacological properties: at lower doses both enantiomers are presynaptic agonists, at higher doses *S*(−) 3-PPP shows postsynaptic antagonistic activity and *R*(+) 3-PPP postsynaptic agonistic activity (Hjorth et al 1983). In some recent studies the possibility of a metabolic activation of 3-PPP was suggested in order to explain discrepancies between in-vivo and in-vitro activities (Sminia & Mulder 1983; Markstein & Lahaye 1983), and to account for a difference in the time course of different effects (Arnt et al 1983). Theoretically one of the possible metabolic routes of 3-PPP is its conversion into a catecholamine (Scheme 1). The hydroxylation of phenolic compounds by a non-specific hydroxylating enzyme has been recognized for some time (Axelrod 1963) and catecholamine formation in-vivo is well documented for an appreciable number of drugs, e.g. morphine and derivatives (Daly et al 1965), oestrogens (Fishman 1983), alkylamphetamines (Coutts et al 1976), metaraminol (Fuller et al 1981), phenylephrine (Crowley et al (1983) and 'propranolols' (Nelson et al 1984). In addition, bioactivation of various classes of dopamine agonists by aromatic hydroxylation has been hypothesized or demonstrated several times, for instance for aminotetralins and aminoindanes (Fuller et al 1977; Rusterholz et al 1979; Cannon et al 1980), lergotrile (Parli et al 1978) and dipropylamino-ethylindole (Cannon et al 1984).

To investigate whether and to what extent hydroxylation of 3-PPP can take place and whether differences exist in this respect between the enantiomers of 3-PPP, we studied the catecholamine formation from racemic, (+) and (−) 3-PPP in-vitro and in-vivo.

MATERIALS AND METHODS

Drugs and chemicals

3-(3-Hydroxyphenyl)-*N*-n-propylpiperidine HBr (3-PPP) and its enantiomers *R*(+) 3-PPP HCl and *S*(−) 3-PPP HCl were gifts from Astra Läkemedel AB, Sweden. 3-(3,4-Dihydroxyphenyl)-*N*-n-propylpiperidine HBr (4-OH-3-PPP) was synthesized



SCHEME 1. Chemical structures of 3-PPP and its catecholamine analogue 4-OH-3-PPP.

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according to Hacksell et al (1981). Tropolone was obtained from Aldrich (Beerse, Belgium), *S*-adenosyl-L-methionine (SAM) and sodium adenosine diphosphate (NADPH) from Boehringer (Mannheim, FRG). All other chemicals were analytical grade from E. Merck (Darmstadt, FRG).

Enzyme preparations

Rat livers were homogenized in 4 volumes cold 0·15 M KCl, centrifuged at 10 000*g* for 20 min and the supernatant was centrifuged for 60 min at 105 000*g*. The supernatant was used as such as a crude catechol-*O*-methyltransferase (COMT) preparation and contained 15 mg protein ml^{-1}. The pellet was washed with 0·15 M KCl and again centrifuged at 105 000*g* for 60 min. The pellet was resuspended in 0·15 M KCl and the protein concentration adjusted to 5 mg ml^{-1}. This microsomal preparation was diluted 10-fold with 0·05 M phosphate buffer pH 7·4 before use.

In-vitro studies

3-PPP and enantiomers were incubated with liver microsomes in 10 ml glass tubes in a shaking water bath at 37 °C. Incubation constituents were (in final concentrations): 3-PPP (0·1–0·001 mM), NADPH (0·1 mM), $MgCl_2$ (2·5 mM), ascorbic acid (0·25 mM), EDTA (0·025 mM), phosphate buffer pH 7·4 (100 mM), microsomes (0·2 mg protein ml^{-1}) and H_2O to a final volume of 1·0 ml. After 10 min incubation, samples of 100–500 µl were taken, 20 µl perchloric acid (PCA) was added and after centrifugation for 15 min at 5000 rev min^{-1}, supernatants were transferred onto Sephadex G 10 columns and the amine fraction collected (see Assay). Two types of blank incubations were always included: one without microsomes and one without substrate. In addition, tubes with 4-OH-3-PPP instead of 3-PPP were included in each incubation experiment, for the determination of the recovery and stability of 4-OH-3-PPP. Incubations of 4-OH-3-PPP with COMT were also performed in 10 ml glass tubes in a shaking water bath at 37 °C. Incubation constituents were (in final concentrations): 4-OH-3-PPP (1–0·01 mM), SAM (150 mM), $MgCl_2$ (10 mM), phosphate buffer pH 7·4 (50 mM), COMT (1·5 mg protein ml^{-1}) and H_2O to a final volume of 1·0 ml. Samples of 20–100 µl were taken after 15 min and processed as described above.

In-vivo studies

Female Wistar rats (180–200 g, CDL Groningen, The Netherlands) were used and allowed free access to water and food. Drugs were dissolved in 0·9% NaCl (saline) and injected in volumes of 2 ml kg^{-1} (intraperitoneal, i.p.) or 1 ml kg^{-1} (subcutaneous, s.c.). 4-OH-3-PPP brain concentrations were determined 45 min after i.p. or s.c. injection of 3-PPP and enantiomers, with and without tropolone pretreatment (50 mg kg^{-1} i.p., 30 min before 3-PPP administration): rats were decapitated, cerebellum, cortex and striatum were dissected and immediately frozen on dry ice and kept at −80 °C until assay.

4-OH-3-PPP assay

For the determination of 4-OH-3-PPP brain levels, a HPLC method with electrochemical detection was used as described for the assay of endogenous catecholamines and metabolites and catecholic dopamine agonists (Westerink & Mulder 1981; Feenstra et al 1982). Briefly, tissue or incubation samples were homogenized in 1·0 ml PCA 0·1 M and centrifuged for 15 min at 5000 rev min^{-1}; supernatants were transferred to small Sephadex G10 columns and after washing with 2·5 ml formic acid 0·01 M, another 2·5 ml of formic acid fraction, containing the amines was collected. 20–500 µl of this eluate was injected with a Rheodyne injection valve onto a 150 × 4·6 mm Nucleosil 5 C18 column. 4-OH-3-PPP was eluted with a McIllvaine phosphate-citrate buffer pH 4·0 containing 15–24% methanol, using a flow rate of 1·0 ml min^{-1}. A rotating carbon-paste amperometric detector (Oosterhuis et al 1980) set at an electrode potential of 600 mV vs a Hg/Hg_2Cl_2 reference electrode was used for electrochemical detection. Routinely, 3–6 recovery samples were included in each run, by adding 5–50 ng to control brain tissue. Incubation and brain concentrations were calculated with the aid of calibration curves obtained with standard 4-OH-3-PPP solutions.

For the detection of *O*-methylated derivatives in incubation samples of 4-OH-3-PPP with COMT essentially the same method could be used, but the methanol concentration of the mobile phase was increased to 27% and the electrode potential was set at 750 mV.

RESULTS AND DISCUSSION

4-OH-3-PPP assay

For the measurement of catecholamine levels in biological samples we currently use a reversed phase HPLC method with amperometric detection, in combination with perchloric acid extraction and purification over Sephadex G10 columns. This method has been used for the assay of endogenous

catecholamines and metabolites (Westerink & Mulder 1981) as well as for the determination of brain levels of catecholic dopaminergic drugs (Feenstra et al 1982). The versatility and general applicability of this assay procedure is clearly shown by the simple modifications of the standard procedure required for the determination of catecholamines from a different chemical class like the phenylpiperidines. Determination of the recovery of extraction and purification step, assessment of the electrochemical behaviour of the catecholamine and selection of an appropriate mobile phase are only needed to choose the optimum assay conditions. The recovery of 5–50 ng 4-OH-3-PPP, added to brain tissue weighing 20–200 mg, was 86·8 ± 5·6% (mean ± s.d., n = 32). As the within-run coefficient of variation was 2–5%, the use of an internal standard appeared to be unnecessary; instead, with each run 3–6 recovery determinations were included.

A McIllvaine buffer of pH 4·0, with varying percentages of organic modifier (about 15% when a high sensitivity was required for the detection of low 4-OH-3-PPP concentrations, about 24% for high concentrations) was found suitable in order to obtain a reasonable retention time without interference of peaks from endogenous compounds (Fig. 1).

A current-voltage curve of 4-OH-3-PPP, recorded in McIllvaine buffer with 20% methanol (Fig. 3), showed that at 600 mV about 90% of the maximum response at 750 mV was reached and consequently 600 mV was chosen as the electrode potential. Using a 200 µl loop the minimal detectable quantity (peak height 3 times the amplitude of the noise) was about 10 pg, which means a detection limit in 50 mg brain tissue of about 2 ng g^{-1}. This minimal detectable concentration can be lowered if necessary, by increasing the loop volume to 2 ml and injecting 80% of the 2·5 ml Sephadex eluate, which can be done without a significant increase in peak width, as was also shown for the determination of low levels of aminotetralin derivatives (Feenstra et al 1983).

As methoxy-hydroxy derivatives elute from the Sephadex columns in the same formic acid fraction as the catecholamines, the above described assay procedure can be used for the detection of *O*-methyl metabolites in incubation samples of 4-OH-3-PPP with COMT (Rollema et al 1980). Only modifications of the mobile phase are needed, as a higher methanol concentration is required in view of the higher capacity factors, and of the electrode potential, as methoxy-hydroxy compounds are less easily oxidized. Fig. 2 shows that at 750 mV, using a mobile phase with 27% methanol, the two isomeric

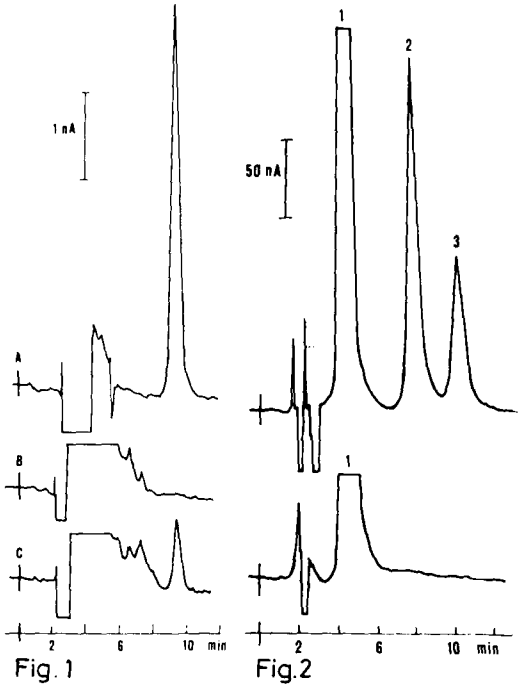

FIG. 1. Chromatograms of: A (Upper tracing)—authentic 4-OH-3-PPP (4 ng ml^{-1}); B (Middle tracing)—striatal extract from rat 45 min after i.p. administration of 45 µmol kg^{-1} (±)-3-PPP; C (Lower tracing)—striatal extract from rat pretreated with tropolone, 45 min after i.p. administration of 45 µmol kg^{-1} (±)-3-PPP. Nucleosil 5 C18 column; phosphate-citrate buffer pH 4/18% methanol; 200 µl loop; 1 ml min^{-1}; electrode potential 600 mV.

FIG. 2. Chromatograms of: A (Upper tracing)—15 min sample from incubation of 4-OH-3-PPP (1 mM) with COMT and methyldonor SAM. B (lower tracing)—15 min sample from incubation of 4-OH-3-PPP (1 mM) with COMT (no SAM) added). 1 = 4-OH-3-PPP, 2 and 3 = *O*-methylated 4-OH-3-PPP isomers. Nucleosil 5 C18 column; phosphate-citrate buffer pH 4/27% methanol; 20 µl loop; 1 ml min^{-1}; electrode potential 750 mV.

O-methyl derivatives of 4-OH-3-PPP are easily detected in an incubation sample.

In-vitro hydroxylation of 3-PPP

Catecholamine formation from phenolic drugs in-vitro is usually measured indirectly by adding, besides the microsomal enzymes, the enzyme COMT and cofactors to the incubation mixture and monitoring the amount of *O*-methylated catecholamine formed (Daly et al 1965; Paul et al 1977). A drawback of this method is that in the case of the formation of catecholamines which are poor substrates for COMT, a combination of hydroxylation and *O*-methylation rates is measured. We found that

the addition of ascorbic acid and EDTA sufficiently prevented the oxidative degradation of the catecholamines, without interfering with the enzymatic reaction, thus enabling a direct measurement of catecholamine formation by assaying the catecholamines with HPLC and electrochemical detection.

Formation of 4-OH-3-PPP from 3-PPP was unequivocally demonstrated by comparison of chromatograms of incubation samples with those of authentic 4-OH-3-PPP under various conditions and by the identical current-voltage curves of biological samples and 4-OH-3-PPP standards (Fig. 3). In the concentration range 0·1–0·001 mM Lineweaver-Burk plots were linear and from these the K_m and V_{max} were calculated (Table 1). K_m values were in the μM range, which is in agreement with reported K_m values for the aromatic hydroxylation of such different drugs as e.g. amphetamine (Jonsson 1974), ethinyloestradiol (Shiverick & Notelovitz 1983) and nortriptyline (Mellström et al 1983). V_{max} values varied from about 1·5 to 2·5 nmol (mg protein)$^{-1}$ min^{-1}. It is evident that, although the (−)-enantiomer of 3-PPP showed a tendency towards the highest V_{max} value with a *S/R* ratio of about 1·2, the apparent first-order rate constant V_{max}/K_m did not differ significantly for racemic, (+)- and (−)-3-PPP.

Table 1. K_m, V_{max} and apparent first-order rate constants (V_{max}/K_m) for the hydroxylation in-vitro by rat liver microsomes of racemic, (+)- and (−)-3-PPP. Values were calculated from Lineweaver-Burk plots (0·01–0·001 mM) and are the means ± s.e.m. of 3 separate experiments, each performed in triplicate.

	K_m (μM)	V_{max} (pmol (mg protein)$^{-1}$ min^{-1})	V_{max}/K_m
(±)3-PPP	1·1 ± 0·2	1754 ± 187	1595
(+)3-PPP	1·0 ± 0·1	1850 ± 52	1850
(−)3-PPP	1·4 ± 0·2	2332 ± 182	1666

In-vitro O-methylation of 4-OH-3-PPP

HPLC analysis of incubation samples of 4-OH-3-PPP with COMT and the methyldonor SAM showed that two isomeric *O*-methylated metabolites of 4-OH-3-PPP (the 4-methoxy-3-hydroxy and the 4-hydroxy-3-methoxy compound) are formed in-vitro in appreciable amounts (Fig. 2). Although exact kinetic data cannot be given, because the *O*-methyl derivatives were not available, the K_m was estimated from a Lineweaver-Burk plot from 1–0·01 mM to be about 80 μM, which is comparable with the K_m value of 6,7-dihydroxy-2-aminotetralin, an excellent substrate for COMT and known to be extensively *O*-methylated in-vivo (Rollema et al 1980; Youde et al 1984). Assuming similar electrochemical responses of methoxy-hydroxy derivatives, the V_{max} for *O*-methylation of 4-OH-3-PPP was estimated from a comparison with 6,7-dihydroxy-2-aminotetralin in the same incubation experiment to be about 5 times higher than the V_{max} of the aminotetralin.

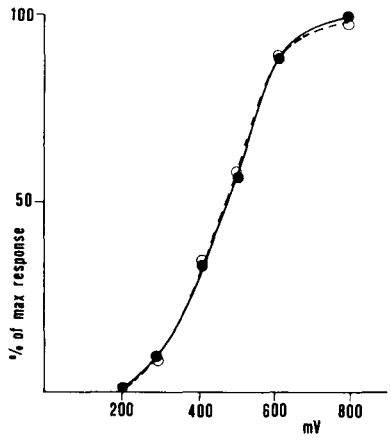

FIG. 3. Current-voltage curves of sample from authentic n-OH-3-PPP solution (○) and of a 10 min sample from incubation of (±)-3-PPP with rat liver microsomes (●). Nucleosil 5 C18 column; phosphate-citrate buffer pH 4/24% methanol; 20 μl loop; 1 ml min^{-1}.

In-vivo hydroxylation of 3-PPP

After injection of 3-PPP in doses up to 100 μmol kg^{-1}, 4-OH-3-PPP was not detectable in brain tissue. However, also after even high doses of 4-OH-3-PPP itself, only very low brain concentrations of the catecholamine were found, suggesting that 4-OH-3-PPP is a good COMT substrate and as such is rapidly metabolized by *O*-methylation. Evidence for this was obtained from in-vitro studies on the *O*-methylation of 4-OH-3-PPP (see above) and from the effect of COMT-inhibition on 4-OH-3-PPP levels. Pretreatment with the COMT inhibitor tropolone caused a more than 100-fold increase in catecholamine concentrations after injection of 4-OH-3-PPP, while after administration of 3-PPP to tropolone-pretreated rats 4-OH-3-PPP was indeed detectable in the brain (Table 2). When 3-PPP was given i.p., brain levels of 4-OH-3-PPP were about 60–100 pmol g^{-1}, 45 min after 20 μmol kg^{-1}, and about 300–450 pmol g^{-1}, 45 min after 45 μmol kg^{-1}. We did not find any indications for a regional distribution of the catecholamine in rat brain, although levels in the cortex were usually somewhat higher than in the other tissues studied, which may

Table 2. Rat brain concentrations of 4-OH-3-PPP (pmol g^{-1}) 45 min after i.p. administration of 20 μmol kg^{-1} 4-OH-3-PPP and 20 μmol kg^{-1} 3-PPP, with and without tropolone pretreatment (50 mg kg^{-1} i.p. 30′ before drugs). Values are means ± s.e.m. (n = 3).

	Concn 4-hydroxy-3-PPP (pmol g^{-1})		
	Striatum	Cerebellum	Cortex
4-OH-3-PPP (20 μmol kg^{-1})	14·5 ± 1·7	6·4 ± 2·0	7·7 ± 1·0
3-PPP ,,	ND	ND	ND
4-OH-3-PPP + tropolone ,,	1295 ± 35	1044 ± 14	1584 ± 32
3-PPP + tropolone ,,	85·7 ± 4·3	63·2 ± 1·9	109·8 ± 18·6

be due to the higher blood flow in the cortex compared with striatum and cerebellum (Rapoport et al 1979).

Subcutaneous injection of 3-PPP resulted in much lower catecholamine levels: 45 min after 45 μmol kg^{-1} s.c., 4-OH-3-PPP brain concentrations were about 100 pmol g^{-1} (Table 3). This decrease in catecholamine brain levels is undoubtedly due to a much less effective metabolism of 3-PPP when injected s.c., as it seems that brain levels of 3-PPP itself are about 2-fold higher when 3-PPP is given s.c. (see below).

In agreement with the results of in-vitro studies, no significant differences were found between 4-OH-3-PPP brain levels after racemic, (+)- or (−)-3-PPP administration, i.p. as well as s.c., although the (−)-enantiomer usually gave the higher catecholamine levels, showing approximately the same *S/R* ratio of 1·2 as we found for the *S/R* ratio for the V_{max} in the in-vitro studies (Table 3). Recently, *S/R* ratios for the aromatic hydroxylation of monohydroxypropranolol to catechols were also found to be about 1·15, i.e. only marginally stereoselective (Nelson et al 1984).

3-PPP vs 4-OH-3-PPP brain concentrations

Preliminary results from a pilot experiment on the determination of 3-PPP levels, also using a HPLC method with electrochemical detection (Rollema, in preparation) allow an estimation of 3-PPP brain concentrations after 45 μmol kg^{-1} 3-PPP. I.p. administration resulted in brain concentrations of about 10–12 nmol g^{-1} and s.c. injection in about 18–24 nmol g^{-1}. From these preliminary data it appears that the brain concentrations of 4-OH-3-PPP represent between 1–5% of 3-PPP brain concentrations after i.p. injection and between 0·2–0·5% after s.c. injection of 3-PPP in rats pretreated with tropolone. Also in this respect no differences were found between racemic, (+)- or (−)-3-PPP.

Table 3. Rat brain concentrations of 4-OH-3-PPP (pmol g^{-1}) 45 min after i.p. and s.c. administration of 45 μmol kg^{-1} (+)-3-PPP and 45 μmol kg^{-1} (−)-3-PPP, all with tropolone pretreatment (50 mg kg^{-1} i.p. 30 min before drugs). Values are means ± s.e.m. (n = 3).

		Concn 4-hydroxy-3-PPP (pmol g^{-1})		
		Striatum	Cerebellum	Cortex
(+) 3-PPP 45 μmol kg^{-1}	i.p.	368·4 ± 33·5	294·5 ± 48·1	350·9 ± 56·9
	s.c.	107·9 ± 5·2	111·1 ± 19·6	127·3 ± 9·2
(−) 3-PPP 45 μmol kg^{-1}	i.p.	427·3 ± 62·8	396·0 ± 28·6	470·8 ± 57·5
	s.c.	102·4 ± 15·5	112·1 ± 9·5	124·5 ± 14·7

CONCLUSIONS

Our results show that ring hydroxylation of the dopamine agonist 3-PPP to its catecholic analogue 4-OH-3-PPP is, in fact, a metabolic pathway for 3-PPP. Brain concentrations of the catecholamine 4-OH-3-PPP after i.p. and s.c. injection of 3-PPP are low and only detectable when tropolone is given to prevent the rapid *O*-methylation of the catecholamine. One might therefore conclude that catecholamine formation from 3-PPP does not play a significant role in the actions of 3-PPP. However, it is conceivable that the small amounts of 4-OH-3-PPP formed from 3-PPP may contribute to some of the dopaminergic effects of 3-PPP, because 4-OH-3-PPP brain concentrations resulting from administration of 4-OH-3-PPP itself, in doses causing dopaminergic effects, are also low. Like 3-PPP, 4-OH-3-PPP is a dopamine agonist, but it lacks the presynaptic selectivity of 3-PPP. In-vivo, 4-OH-3-PPP was found to act on presynaptic dopamine receptors, as shown by its inhibition of DOPA-accumulation in rat brain, and on postsynaptic dopamine receptors, demonstrated by its antagonism of reserpine-induced immobility in rats (Hacksell et al 1981). A comparison of the in-vivo potencies of 4-OH-3-PPP with those of the 3-PPP enantiomers shows that the catecholamine is about 5 times less potent than (+)- and (−)-3-PPP, which are equipotent, as a presynaptic agonist, while it is several times more potent than (+)-3-PPP as a postsynaptic agonist, (−)-3-PPP being virtually inactive at this site (Hjorth et al 1983). This difference in postsynaptic potency is actually much greater, when the difference between the concentrations at the site of action is taken into account: 4-OH-3-PPP brain concentrations are 10^3 fold lower than those of 3-PPP after equimolar doses of both compounds. In other words, on the basis of effective concentrations at the receptor site, 4-OH-3-PPP is at least 10^4 times more potent that 3-PPP. Hence it is tempting to suggest that in particular the postsynaptic agonistic effect of the (+)-enantiomer of 3-PPP may be due to in-vivo formation of its catecholic analogue. In this respect it is noteworthy

that (+)-3-PPP shows a much later onset of action as a postsynaptic agonist than as a presynaptic agonist (Hjorth et al 1983; Arnt et al 1983).

In-vitro, the absence of an inhibitory effect of 3-PPP on electrically- or K^+-stimulated [^{3}H]dopamine overflow from rat striatal slices has been reported by several authors (Sminia & Mulder 1983; Langer et al 1983; Starke et al 1983; Markstein & Lahaye 1983; Keller & Imhof 1983). In contrast, 4-OH-3-PPP was found to be an effective agonist in this model for presynaptic agonistic activity (Keller & Imhof 1983). The possibility that catecholamine formation in-vivo is also of some significance for the in-vivo presynaptic agonistic effects of the 3-PPP enantiomers can therefore not be ruled out.

From our results it is evident that the important role of *O*-methylation of the catecholamine should also be taken into account. It is known that COMT can exhibit stereoselectivity towards catecholamine enantiomers (Gordonsmith et al 1982; Rollema et al 1983) and it is possible that *R*- and *S*-4-OH-3-PPP, formed from the respective 3-PPP enantiomers are *O*-methylated at different rates, resulting in differing brain concentrations. It would be interesting to resolve 4-OH-3-PPP into its enantiomers in order to investigate whether *R*- and *S*-4-OH-3-PPP have different pharmacological profiles and whether they show different susceptibilities to *O*-methylation by COMT.

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