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Structure–Activity Studies Leading to (−)1-(Benzofuran-2-yl)-2-propylaminopentane, ((−)BPAP), a Highly Potent, Selective Enhancer of the Impulse Propagation Mediated Release of Catecholamines and Serotonin in the Brain

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Abstract—The catecholaminergic and serotoninergic neurons in the brain change their performance according to the physiological need via a catecholaminergic/serotoninergic activity enhancer (CAE/SAE) mechanism. Phenylethylamine (PEA), tyramine and tryptamine are the presently known endogenous CAE/SAE substances which enhance the impulse propagation mediated release of catecholamines and serotonin in the brain. A PEA derivative, (−)deprenyl (selegiline), known as a selective inhibitor of MAO-B, is for the time being the only CAE/SAE substance in clinical use. Aiming to develop a selective CAE/SAE substance much more potent than (−)deprenyl, a series of new 1-aryl-2-alkylaminoalkanes, structurally unrelated to PEA and the amphetamines, was designed and prepared. Among them, (−)1-(benzofuran-2-yl)-2-propylaminopentane ((−)BPAP) was selected as a promising candidate substance for further studies. (−)BPAP significantly enhanced in rats the impulse propagation mediated release of catecholamines and serotonin in the brain 30 min after acute injection of 0.36 nmol/kg sc. In the shuttle box, (−)BPAP was in rats about 130 times more potent than (−)deprenyl in antagonizing tetrabenazine induced inhibition of performance. (±)BPAP protected cultured hippocampal neurons from the neurotoxic effect of β-amyloid in 10^{-14}–10^{-15} M concentration.

Introduction

Some neurons in the brain possess the previously unknown ability to change their performance, according to the physiological need, via endogenous activity enhancer substances. The noradrenergic, dopaminergic and serotoninergic neurons, the performance of which is controlled via a catecholaminergic/serotoninergic activity enhancer (CAE/SAE) mechanism, are the most suitable neurons in the mammalian brain for studying this peculiar regulation. Phenylethylamine (PEA), tyramine and tryptamine are the presently known endogenous CAE/SAE substances in the brain. A PEA derivative, (−)deprenyl (selegiline), which is the peculiar neuroprotective agent used to slow the progress of Parkinson's disease and Alzheimer's disease, is for the time being the only drug which acts primarily as a CAE substance.[1]

PEA and tyramine, the endogenous indirectly acting sympathomimetic amines, are on the one hand, enhancers of the impulse propagation mediated transmitter release from the catecholaminergic neurons in the brain (CAE effect), on the other hand, releasers of catecholamines from their storage sites. Amphetamine and methamphetamine, PEA analogues with a long lasting effect, act like their parent compound, the (−)enantiomers being the more potent CAE substances and the (+)enantiomers being the more potent releasers of catecholamines. All the unwanted effects of the amphetamines which seriously resticted their use in therapy are due to the catecholamine releasing property of these substances.[2]

(−)Deprenyl, the *N*-propargyl analogue of methamphetamine, is at present the only clinically used amphet-

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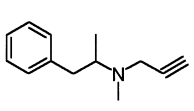
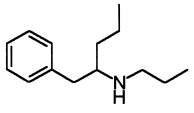
amine derivative devoid of the catecholamine releasing effect.[3] The attachment of a propargyl group to the nitrogen of methamphetamine[4] resulted in the success to separate for the first time the catecholamine releasing property from the CAE effect of the amphetamines. As a CAE substance, (−)deprenyl is more potent than (+)deprenyl.[3] The unique effects of (−)deprenyl such as the prolongation of the life of rats,[5] the neuroprotective effect,[6] the slowing of the functional decline of otherwise untreated subjects with early Parkinson's disease,[7] and the slowing of the progression of Alzheimer's disease,[8] can reasonably be attributed to the CAE effect of this drug[9] (Chart 1).

(−)Deprenyl was also the first described highly selective, potent inhibitor of B-type monoamine oxidase (MAO-B).[10] Because of the great practical importance of this property in exploring the nature of MAO-B, attention was primarily focused on this effect of the drug and consequently thousands of papers have been published on (−)deprenyl, viewing the substance exclusively as a selective MAO-B inhibitor. To furnish direct evidence that the peculiar enhancement of catecholaminergic activity in the brain in animals treated with a small dose of (−)deprenyl is unrelated to MAO inhibition, we previously developed a family of (−)deprenyl analogues devoid of a significant MAO-B inhibitory effect.[11] The selected reference substance, (−)1-phenyl-2-propylaminopentane ((−)PPAP), enhanced the impulse propagation mediated release of catecholamines in the brain, like (−)deprenyl, but it left MAO activity unchanged in contrast to (−)deprenyl.

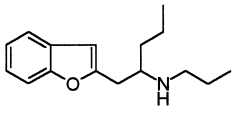
The discovery that also tryptamine, the indole analogue of PEA, is a potent enhancer of the impulse propagation mediated release of catecholamines in the brain, prompted us to design new potential CAE/SAE substances by changing the aromatic ring in PPAP. We synthesized and investigated a series of new 1-aryl-2-alkylaminoalkanes and selected, as a potential follower of (−)deprenyl in the clinic and a promising experimental tool for the analysis of the CAE/SAE mechanism in the mammalian brain, (−)1-(benzofuran-2-yl)-2-propylaminopentane ((−)BPAP), which was a highly selective, potent enhancer of the impulse propagation mediated release of dopamine, noradrenaline and serotonin in the brain. The main aim of this paper is to summarize the experiments leading to the selection of (−)BPAP and to discuss the potential therapeutic significance of this new compound.



(-)Deprenyl



(-)PPAP

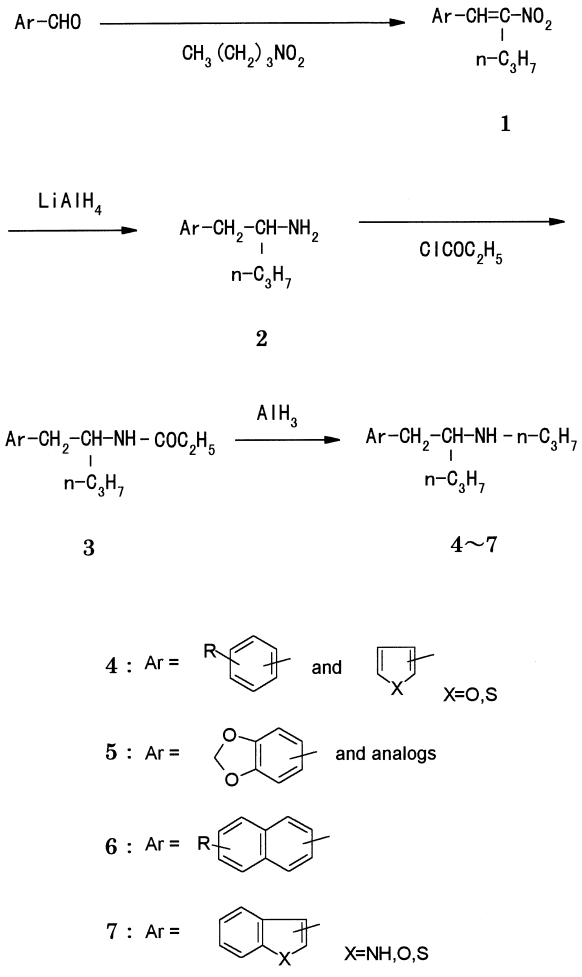


(-)BPAP

Chart 1.

Synthesis and Primary Evaluation

The target compounds, 1-aryl-2-alkylaminopentanes, were synthesized by the route outlined in Scheme 1. The starting 1-aryl-2-nitro-1-pentenes (**1**) were prepared by the condensation of appropriate arylaldehydes with 1-nitrobutane in the presence of ammonium acetate ($AcONH_4$). Reduction of the compounds **1** with lithium aluminum hydride ($LiAlH_4$) gave the corresponding 1-aryl-2-aminopentanes (**2**), which were treated with propionyl choloride to afford the respective *N*-[2-(1-aryl)pentyl]propionamides (**3**). The propionamides **3** thus obtained were reduced with aluminum hydride (AlH_3) to give the racemic 1-aryl-2-propylaminpentanes (**4**–**7**), which were converted into the corresponding hydrochlorides. The newly synthesized compounds were divided into the following four groups for the sake of convenience (Tables 1–4) and were primarily evaluated



Scheme 1. Preparation route to target compounds.

Table 1. Group 1: substituted phenyl, furyl and thienyl derivatives of PPAP, and related compounds

Compound	Aer	R^1	R^2	Formula (analysis)[a]	mp (°C)
PPAP[b]	C_6H_5	*n*-C_3H_7	*n*-C_3H_7	$C_{14}H_{23}N\cdot HCl$ (C,H,N)	123
4a	4-Cl–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{14}H_{22}ClN\cdot HCl$ (C,H,N)	130
4b	3-Cl–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{14}H_{22}ClN\cdot HCl$ (C,H,N)	128
4c	2-Cl–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{14}H_{22}ClN\cdot HCl$ (C,H,N)	115
4d	4-F–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{14}H_{22}FN\cdot HCl$ (C,H,N)	134
4e	3-F–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{14}H_{22}FN\cdot HCl$ (C,H,N)	107
4f	2-F–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{14}H_{22}FN\cdot HCl$ (C,H,N)	119
4g	4-CF_3–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{15}H_{25}N\cdot HCl$ (C,H,N)	125
4h	4-CH_3–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{15}H_{22}F_3N\cdot HCl$ (C,H,N)	118
4i	*i*-C_3H_7–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{17}H_{29}N\cdot HCl$ (C,H,N)	122
4j	4-CH_3O–C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{15}H_{25}NO\cdot HCl$ (C,H,N)	100
4k	3,4-$(CH_3O)_2$–C_6H_3	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{27}NO_2\cdot HCl$ (C,H,N)	107
4l	4-Ph-C_6H_4	*n*-C_3H_7	*n*-C_3H_7	$C_{20}H_{27}N\cdot HCl$ (C,H,N)	158
4m	Furan-2-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{12}H_{21}NO\cdot HCl$ (C,H,N)	111
4n	Furan-2-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{12}H_{21}NO\cdot HCl$ (C,H,N)	93
4o	Thiophen-2-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{12}H_{21}NS\cdot HCl$ (C,H,N)	111
4p[c]	C_6H_5-CH(n-C_3H_7)-NH-n-C_3H_7			$C_{13}H_{21}N\cdot HCl$ (C,H,N)	220
4q	C_6H_5-CH_2-CH_2-CH(n-C_3H_7)-NH-n-C_3H_7			$C_{15}H_{25}N\cdot HCl$ (C,H,N)	106

[a]Analytical results obtained for these elements were within ±0.4% of the theoretical values.
[b]see ref 23.
[c]see ref 24.

Table 2. Group 2: methylendioxyphenyl derivatives of PPAP, and related compounds

Compound	Ar	R^1	R^2	Formula (analysis)[a]	mp (°C)
5a (MPAP)	3,4-(OCH_2O)–C_6H_3	*n*-C_3H_7	*n*-C_3H_7	$C_{15}H_{23}NO_2\cdot HCl$ (C,H,N)	142
5b	2,3-(OCH_2O)–C_6H_3	*n*-C_3H_7	*n*-C_3H_7	$C_{15}H_{23}NO_2\cdot HCl$ (C,H,N)	105
5c	3,4-(OCH_2O)–C_6H_3	*n*-C_3H_7	*n*-C_4H_9	$C_{16}H_{25}NO_2\cdot HCl$ (C,H,N)	115
5d	3,4-(OCH_2O)–C_6H_3	*n*-C_3H_7	*n*-C_5H_{11}	$C_{17}H_{27}NO_2\cdot HCl$ (C,H,N)	88
5e	3,4-(OCH_2O)–C_6H_3	*n*-C_3H_7	sec-C_4H_9	$C_{16}H_{25}NO_2\cdot HCl$ (C,H,N)	167
5f	3,4-(OCH_2O)–C_6H_3	*n*-C_3H_7	$(C_2H_5)_2CH$	$C_{17}H_{27}NO_2\cdot HCl$ (C,H,N)	177
5g	3,4-(OCH_2O)–C_6H_3	*n*-C_3H_7	Ph–CH_2	$C_{19}H_{23}NO_2\cdot HCl$ (C,H,N)	137
5h	3,4-(OCH_2O)–C_6H_3	*n*-C_3H_7	CH_3–C_6H_4	$C_{19}H_{23}NO_2\cdot HCl$ (C,H,N)	136
5i	3,4-(OCH_2CH_2O)–C_6H_3	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{25}NO_2\cdot HCl$ (C,H,N)	148
5j	3,4-(OCH_2CH_2)–C_6H_3	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{25}NO\cdot HCl$ (C,H,N)	140
5k	3,4-$(CH_2)_3$–C_6H_3	*n*-C_3H_7	*n*-C_3H_7	$C_{17}H_{27}N\cdot HCl$ (C,H,N)	155

[a]Analytical results obtained for these elements were within ±0.4% of the theoretical values.

Table 3. Group 3: naphthyl derivatives of PPAP

Compound	Ar	R^1	R^2	Formula (analysis)[a]	mp (°C)
6a (NPAP)	2-Naphthyl	*n*-C_3H_7	*n*-C_3H_7	$C_{18}H_{25}N\cdot HCl$ (C,H,N)	183
6b	1-Naphthyl	*n*-C_3H_7	*n*-C_3H_7	$C_{18}H_{25}N\cdot HCl$ (C,H,N)	109
6c	2-Naphthyl	*n*-C_3H_7	C_2H_5	$C_{17}H_{23}N\cdot HCl$ (C,H,N)	166
6d	2-Naphthyl	*n*-C_3H_7	*n*-C_4H_9	$C_{19}H_{27}N\cdot HCl$ (C,H,N)	143
6e	2-Naphthyl	*n*-C_3H_7	*n*-C_5H_{11}	$C_{20}H_{29}N\cdot HCl$ (C,H,N)	108
6f	2-Naphthyl	*n*-C_3H_7	*iso*-C_4H_9	$C_{19}H_{27}N\cdot HCl$ (C,H,N)	158
6g	2-Naphthyl	*n*-C_3H_7	*iso*-C_5H_{11}	$C_{20}H_{29}N\cdot HCl$ (C,H,N)	146
6h	2-Naphthyl	*n*-C_3H_7	*neo*-C_5H_{11}	$C_{20}H_{29}N\cdot HCl$ (C,H,N)	161
6i	2-Naphthyl	C_2H_5	*n*-C_3H_7	$C_{17}H_{23}N\cdot HCl$ (C,H,N)	182
6j	2-Naphthyl	*n*-C_4H_9	*n*-C_3H_7	$C_{19}H_{27}N\cdot HCl$ (C,H,N)	127
6k	2-Naphthyl	*n*-C_5H_{11}	*n*-C_3H_7	$C_{20}H_{29}N\cdot HCl$ (C,H,N)	118
6l	2-(6-CH_3O-naphthyl)	*n*-C_3H_7	*n*-C_3H_7	$C_{19}H_{27}NO\cdot HCl$ (C,H,N)	187
6m	1-(4-CH_3O-naphthyl)	*n*-C_3H_7	*n*-C_3H_7	$C_{19}H_{27}NO\cdot HCl$ (C,H,N)	190
6n	1-(2-CH_3O-naphthyl)	*n*-C_3H_7	*n*-C_3H_7	$C_{19}H_{27}NO\cdot HCl$ (C,H,N)	135

[a]Analytical results obtained for these elements were within ±0.4% of the theoretical values.

by the shuttle box experiment (vide infra) in comparison with PPAP as a positive reference compound.

Group 1. Substituted phenyl, furyl and thienyl derivatives of PPAP (Table 1)

None of these substances (**4a**–**l**) was remarkably more potent than PPAP. The furan-2-yl (**4m**), furan-3-yl (**4n**) and thiophen-2-yl (**4o**) analogues of PPAP were less potent than PPAP. The compounds in which the distance between the benzene ring and nitrogen was with one carbon atom shorter (1-phenyl-1-propylaminobutane (**4p**)) or longer (1-phenyl-3-propylaminohexane (**4q**)) than in PPAP were less potent than PPAP in the shuttle box experiment.

Group 2. Methylenedioxy and related derivatives of PPAP (Table 2)

The 3,4-methylenedioxyphenyl analogue of PPAP (MPAP, **5a**) was the most potent in the group and then was resolved into the corresponding (−)enantiomer ((−)MPAP) and (+)enantiomer ((+)MPAP) (see Table 5). Ethylenedioxyphenyl (**5i**), dihydrobenzofuryl (**5j**) and indanyl (**5k**) analogues of PPAP were less potent than PPAP. (−)MPAP, the most potent member of the group, was about 5 times more potent in the shuttle box experiment than PPAP.

Group 3. Naphthyl derivatives of PPAP (Table 3)

The 2-naphthyl analogue of PPAP (NPAP, **6a**) and the corresponding (−) and (+)enantiomers ((−)NPAP and (+)NPAP) (see Table 5) were used as reference substances of the group. In the shuttle box experiment (−)NPAP, the most potent compound in this group, was about twice as potent as PPAP.

Group 4. Indolyl, benzothienyl and benzofuryl derivatives of PPAP (Table 4)

The indol-3-yl analogue of PPAP (IPAP, **7a**) and its (−) and (+)enantiomers ((−)IPAP and (+)IPAP) (see Table 5) were used as reference substances for the indol analogues of PPAP. (−)IPAP was about 5 times more potent than PPAP in the shuttle box experiment. The compounds in which the distance between the indole ring and nitrogen was with one carbon atom longer (1-(indol-3-yl)-3-propylaminohexane (**7j**)) than in IPAP was less potent than PPAP. The benzofuran-2-yl analogue of PPAP (BPAP, **7i**) was remarkably more potent than PPAP and then was resolved into the (−) and (+) enantiomers ((−)BPAP and (+)BPAP). Thus (−)BPAP, the most potent member of the group, was about 100 times more potent than PPAP in the shuttle box experiment.

Table 4. Group 4: indolyl benzofuryl and benzothienyl derivatives of PPAP, and related compounds

Compound	Ar	R^1	R^2	Formula (analysis)[a]	mp (°C)
7a (IPAP)	Indol-3-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{24}N_2$·HCl (C,H,N)	151
7b	Indol-2-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{24}N_2$·HCl (C,H,N)	62
7c	Indol-4-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{24}N_2$·HCl (C,H,N)	152
7d	Indol-6-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{24}N_2$·HCl (C,H,N)	173
7e	Indol-7-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{24}N_2$ (C,H,N)	Oil
7f	5-Chloroindol-3-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{23}N_2Cl$·HCl (C,H,N)	67
7g	Benzothiophen-2-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{23}NS$·HCl (C,H,N)	159
7h	Benzothiophen-3-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{23}NS$·HCl (C,H,N)	119
7i (BPAP)	Benzofuran-2-yl	*n*-C_3H_7	*n*-C_3H_7	$C_{16}H_{23}NO$·HCl (C,H,N)	136
7j	(Indol-3-yl)-CH_2-CH_2-CH(n-C_3H_7)-NH-n-C_3H_7			$C_{17}H_{26}N_2$·HCl (C,H,N)	162

Table 5. The respective enantiomers of the most representative new CAE/SAE substances

Racemate	Enantiomer	Formula (Analysis)[a]	mp (°C)	$[\alpha]_D^{20}$
5a (MPAP)	(−)MPAP	$C_{15}H_{23}NO_2$·HCl (C,H,N)	184	−4.29 (*c* = 3.0, MeOH)
	(+)MPAP	$C_{15}H_{23}NO_2$·HCl (C,H,N)	179	+3.90 (*c* = 3.0, MeOH)
6a (NPAP)	(−)NPAP	$C_{18}H_{25}N$·HCl (C,H,N)	210	−10.62 (*c* = 4.0, MeOH)
	(+)NPAP	$C_{18}H_{25}N$·HCl (C,H,N)	209	+9.95 (*c* = 4.0, MeOH)
7a (IPAP)	(−)IPAP	$C_{16}H_{24}N_2$·HCl (C,H,N)	179	−14.03 (*c* = 1.4, MeOH)
	(+)IPAP	$C_{16}H_{24}N_2$·HCl (C,H,N)	178	+13.47 (*c* = 2.0, MeOH)
7i (BPAP)	(−)BPAP	$C_{16}H_{23}NO$·HCl (C,H,N)	166	−4.08 (*c* = 4.0, MeOH)
	(+)BPAP	$C_{16}H_{23}NO$·HCl (C,H,N)	171	+4.01 (*c* = 4.0, MeOH)

[a]Analytical results obtained for these elements were within 0.4% of the theoretical values.

The optical resolutions of the remarkably potent racemates into the corresponding enantiomers were carried out by HPLC on a chiral stationary phase, the results of which were summarized in Table 5.

Pharmacological Analysis

Enhanced activity of the catecholaminergic and serotoninergic neurons in the brain of rats treated with the new CAE/SAE substances

The brain amines, PEA and tryptamine, significantly enhance the electrical stimulation-induced release of ^{3}H-noradrenaline (Fig. 1), ^{3}H-dopamine (Fig. 2) and ^{3}H-serotonin (Fig. 3) from the isolated brain stem of rats. (−)Methamphetamine, (−)deprenyl, and (−)PPAP act similarly and are more potent in this respect than the corresponding (+)enantiomers.[2,3] (−)PPAP strongly enhanced the electrical stimulation-induced release of ^{3}H-noradrenaline and ^{3}H-dopamine in 2.5 mg/l (9.6 μmol/l) concentration and that of ^{3}H-serotonin in 10 mg/l (38.4 μmol/l) concentration. Table 6 shows the effect of CAE/SAE substances on nerve stimulation-induced release of ^{3}H-noradrenaline, ^{3}H-dopamine and ^{3}H-serotonin from isolated rat brain stem in comparison to some drugs acting on the catecholaminergic and/or serotoninergic neurons. (−)BPAP proved to be the most potent CAE/SAE substance. Fig. 4 illustrates the high effectiveness of (−)BPAP in the test.

Treatment of rats with single or repeated doses of 0.25 mg/kg (~1 μmol/kg) sc (−)deprenyl or (−)PPAP significantly enhanced the release of catecholamines from selected distinct brain areas and decreased the amount of serotonin released from the raphe.[12] The newly synthesized CAE/SAE compounds acted similarly. The two most effective substances, (−)IPAP and (−)BPAP enhanced the release of dopamine from the striatum, substantia nigra and tuberculum olfactorium, noradrenaline from the locus coeruleus and serotonin from the raphe in 0.5 and 0.1 μg/kg (1.78 and 0.36 nmol/kg), respectively (Table 7). The release of dopamine from the substantia nigra of rats treated for 3 weeks with (−)IPAP or (−)BPAP demonstrates that the compounds enhanced significantly the release of dopamine in rats treated with low or high doses, while the release of noradrenaline from the locus coeruleus and serotonin from the raphe was significantly increased only in rats treated with a low dose of (−)IPAP or (−)BPAP. In the case of serotonin, high dose treatment even inhibited the release of the transmitter.

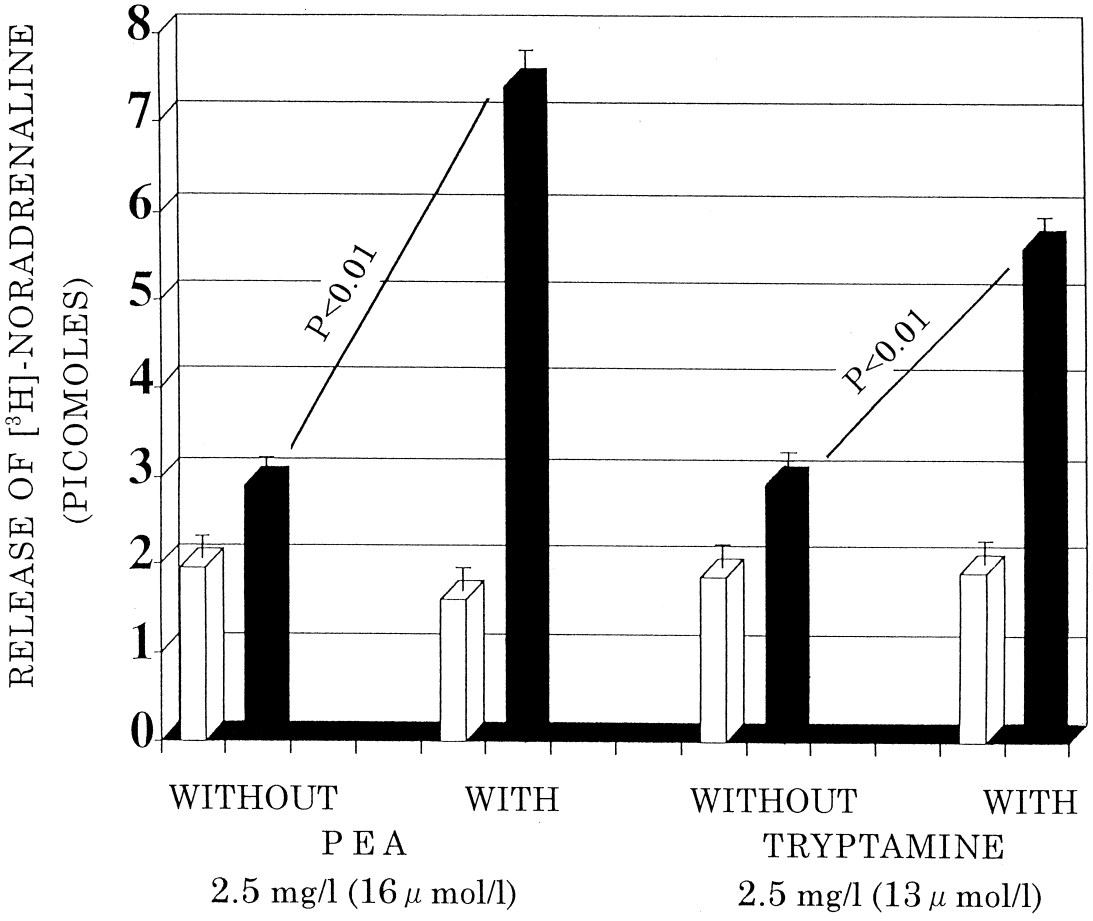


Figure 1. Release of [^{3}H]-noradrenaline from isolated rat brain stem before (open column) and after (filled column) electrical stimulation, in the absence and presence of PEA ($N=8$) and tryptamine ($N=8$), respectively. Each column represents the amount of [^{3}H]-noradrenaline in picomoles released in a 3 min collection period. Vertical lines show SEM Paired Student's t-test. Measured according to Knoll et al.[2] Note the significantly enhanced release of transmitter to electrical stimulation in the presence of PEA and tryptamine, respectively.

The newly synthesized compounds exerted their CAE/SAE effect in ex vivo experiments too. The effect of the most potent compound, (−)BPAP, on the release of noradrenaline from the locus coeruleus (Fig. 5), dopamine from the substantia nigra (Fig. 6) and serotonin from the raphe (Fig. 7) in a concentration range from 10^{-4} to 10^{-17} M, illustrates the ex vivo effects of this substance. (−)BPAP enhanced significantly the release of noradrenaline, dopamine and serotonin even in the lowest, 10^{-14}–10^{-16} concentrations. Regarding the enhancement of the release of noradrenaline from the locus coeruleus, we found two peaks (at 10^{-6} M and at the 10^{-13} M concentration). Regarding the enhancement of the release of serotonin from the raphe the maximum effect was found at 10^{-10}–10^{-12} M concentrations.

The neuroprotective effect of the new CAE/SAE substances

(−)Deprenyl protects the nigrostriatal dopaminergic neuron from the toxic effect of a couple of specific neurotoxic agents (6-hydroxydopamine,[13] MPTP,[14] DSP-4[15]) and an 18-month treatment with the drug protects these neurons from the accumulation of neuromelanin, the typical marker of aging in the substantia nigra.[16] (−)Deprenyl increases, in a small dose, the survival of substantia nigra neurons after MPTP treatment.[6] The neuroprotective, anti-apoptotic effect of (−)deprenyl was confirmed in dozens of papers.

The ability of neurons to change their activity between broad limits according to the physiological need via specific endogenous enhancer substances, is seemingly a widely distributed regulation in the brain and this mechanism is stimulated selectively by the CAE/SAE substances. Accordingly, (−)deprenyl, (−)PPAP and the newly synthesized CAE/SAE substances enhance the activity of many other than the catecholaminergic and serotoninergic neurons in the brain. We tested this effect, using (±)BPAP, on cultured hippocampal neurons according to Watt et al.[17] Thus the cultured cells were exposed to the neurotoxic effect of β-amyloid. Cells evidently mobilize their resources to survive the attack, but only about 20% of the neurons proved to be successful. (±)BPAP, which enhanced the performance of the neurons, increased significantly the rate of the surviving cells (Table 8). Interestingly, (±)BPAP exerted its neuroprotective effect on the hippocampal neurons with a similar peculiar concentration dependency (one peak at 10^{-14} M and another one at 10^{-8} M), to that which characterized the (−)BPAP-induced enhanced

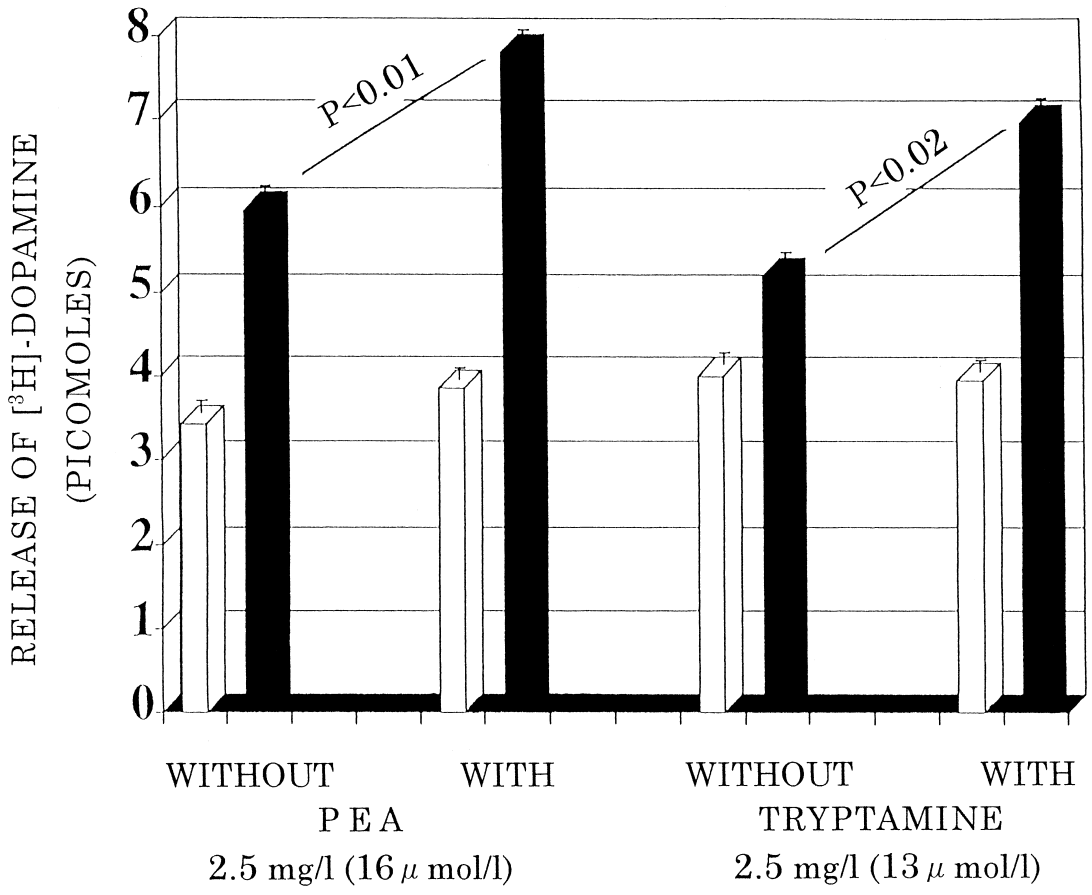


Figure 2. Release of [^{3}H]-dopamine from isolated rat brain stem before (open column) and after (filled column) electrical stimulation, in the absence and presence of PEA ($N=8$) and tryptamine ($N=8$), respectively. Each column represents the amount of [^{3}H]-dopamine in picomoles released in a 3 min collection period. Vertical lines show SEM Paired Students's t-test. Measured according to Knoll et al.[2] Note the significantly enhanced release of transmitter to electrical stimulation in the presence of PEA and tryptamine, respectively.

release of noradrenaline from the locus coeruleus (see Fig. 5).

The antidepressant effect of the new CAE/SAE substances

(−)Deprenyl, though it was never registered for this purpose, is an efficient antidepressant in humans.[18] Considering the key role of the catecholaminergic system in the activation of the mammalian brain and the abundant clinical experience proving in depressed patients the beneficial effect of catecholaminergic stimulants, there can be little doubt that each potent, selective CAE substance must be an efficient antidepressant.

The ability of (−)deprenyl and (−)PPAP to normalize in the shuttle box the learnig performance of rats pretreated with 1 mg/kg tetrabenazine, was of crucial importance in realizing that these PEA derivatives act by enhancing exocytosis in the catecholaminergic neurons of the brain.[3] We analyzed in the shuttle box the acquisition of a two-way conditioned avoidance reflex (CAR) during 5 consecutive days. The total number of CARs displayed during the 5-day training and the number of failures to response within 5 s to the uncondition stimulus (escape failure, EF) characterize the learning ability of the rat. Tetrabenazine (1 mg/kg, sc) administered 1 h prior to testing inhibits the aquisition of CARs by decreasing the amount of catecholamines in the brain. CAE substances, which enhance the impulse propagation mediated release of catecholamines in the brain, fully antagonize the effect of tetrabenazine.

Table 9 shows that a very high dose of (−)deprenyl was needed to antagonize the effect of tetrabenazine in the shuttle box. (−)PPAP was about twice as potent as (−)deprenyl in this test. Of the newly synthesized compounds, NPAP was as active as PPAP, the further order of potency was as follows: IPAP < MPAP < BPAP. The most effective CAE substance of the series, (−)BPAP, was on a molecular weight basis about 130 times more potent than (−)deprenyl. Considering the high potency of (−)BPAP in this test, we may look upon (−)deprenyl and (−)PPAP as relatively weak CAE substances.

Discussion and Conclusion

Members of the described new family of highly selective, potent CAE/SAE substances, of which (−)BPAP was selected as the candidate compound for further studies, stimulate brain activity via a previously unknown

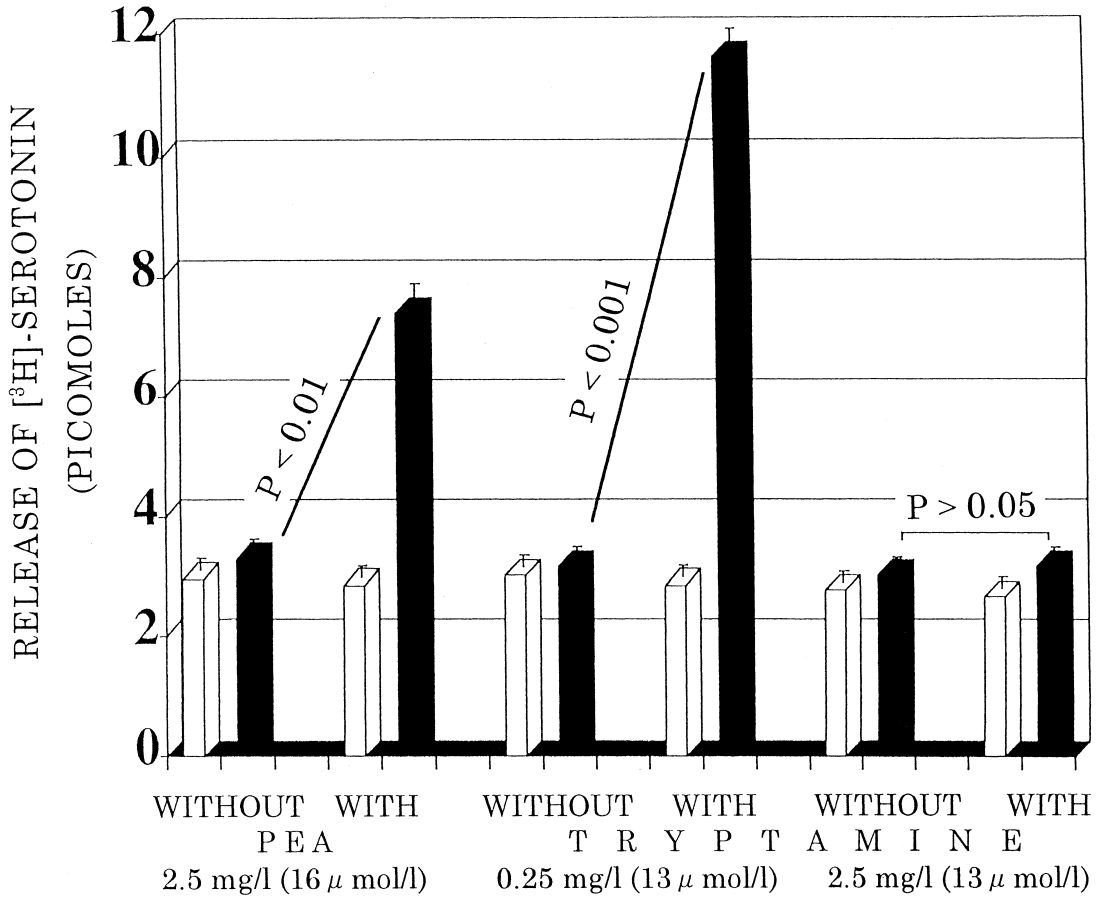


Figure 3. Release of [3H]-serotonin from isolated rat brain stem before (open column) and after (filled column) electrical stimulation, in the absence and presence of 2.5 mg/ml PEA ($N=8$) and 0.25 and 2.5 mg/l tryptamine ($N=8$ each), respectively. Each column represents the amount of [3H]-serotonin in picomoles released in a 3 min collection period. Vertical lines show SEM Paired Students's t-test. Measured according to Knoll et al.[2] Note the significantly enhanced release of transmitter to electrical stimulation in the presence of 2.5 mg/l PEA and 0.25 mg/l tryptamine and the unchanged release of serotonin to stimulation in the presence of 2.5 mg/l tryptamine.

mechanism. They enhanced the impulse propagation mediated release of dopamine, noradrenaline and serotonin in the brain without changing anything on the catecholaminergic and serotoninergic receptors, without inducing a non-specific release of noradrenaline, dopamine and serotonin from the neuron, without inhibiting the uptake system and without inhibiting MAO.

Table 10 shows the relation between structure and pharmacological spectrum illustrating the development

Table 6. The effect of CAE/SAE substances on nerve stimulation induced release of [^{3}H]-noradrenaline, [^{3}H]-dopamine and [^{3}H]-serotonin from isolated rat brain stem in comparison to some drugs acting on the catecholaminergic and/or serotoninergic neurons[a]

	Concentration (mg/L) of the compound which strongly enhanced the nerve stimulation-induced release of:		
	(^{3}H)-noradrenaline	(^{3}H)-dopamine	(^{3}H)-serotonin
PEA	1.0	2.5	2.5
Tyramine	0.5	1.0	2.5
Tryptamine	2.5	2.5	0.25
(−)Deprenyl	2.5	2.5	I
(−)PPAP	2.5	2.5	I
(−)MPAP	2.5	2.5	2.5
(−)NPAP	2.5	2.5	I
(−)IPAP	1.0	1.0	0.1
(−)BPAP	**0.05**	**0.05**	**0.01**
Bromocryptine	2.5	0.25	I
Pergolide	I	0.5	I
Fluoxetine	I	I	5.0
Clorgyline	I	I	I
Lazabemide	I	I	I
Amantadine	I	I	I

[a]Compounds were tested according to their effectiveness in decreasing concentration as follows: 5.0; 2.5; 1.0; 0.5; 0.25; 0.1; 0.05; 0.01; 0.005 mg/l. Each concentration was tested on two brain stems. The concentration which increased on both preparation with at least 25% the amount of the labelled transmitter released to nerve stimulation was taken as the minimum concentration which strongly enhanced transmitter release. Ineffective (I) means that the drug did not reach the required effectiveness in 5 mg/l concentration. Note that (−)**BPAP** is the most potent compound.

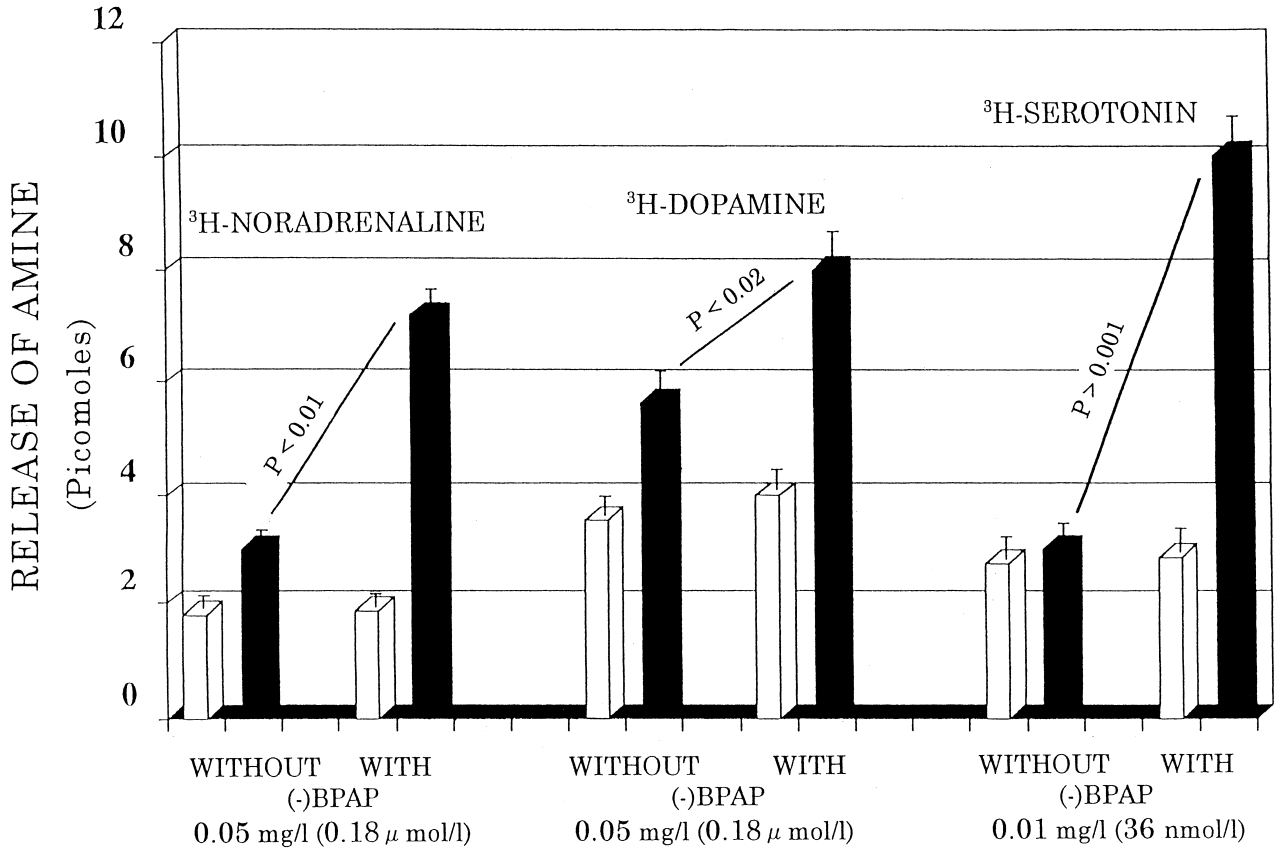


Figure 4. Release of labelled amines from isolated rat brain stem before (open column) and after (filled column) electrical stimulation in the absence and presence of (−)BPAP ($N = 8$ each). Each column represents the amount of labelled amine in picomoles released in a 3 min collection period. Vertical lines show SEM Paired Student's *t*-test. Measured according to Knoll et al.[2] Note the significantly enhanced release of transmitter to electrical stimulation in the presence of (−)BPAP.

from PEA and the amphetamines to the new CAE/SAE substances in this paper. Taking this relation and others into consideration, we summarize at the moment the developments leading from PEA to (−)BPAP as follows. PEA, a short acting brain amine metabolized by MAO-B, is primarily endogenous CAE/SAE substance and in higher concentration a releaser of catecholamines and serotonin.[1,2] The attachement of a methyl group to the α-carbon of PEA leading to amphetamine converts the MAO-B substrate to a weak reversible inhibitor of both types of MAO. Accordingly, amphetamine and then methamphetamine are long acting central nervous system stimulants. It is still believed that amphetamine and methamphetamine exert their stimulating effects in the therapeutic dose-range exclusively by releasing catecholamines (in higher doses also serotonin) from their storage sites in nerve terminals.[19]

The unexpected finding that *N*-propargyl methamphetamine (named later deprenyl) lost the blood pressure increasing effect of its parent compound[4] led us to the selection of (−)deprenyl as a reference substance for the development. The introduction of a propargyl group to the nitrogen resulted in the loss of the noradrenaline releasing property. Thus deprenyl was the first PEA derived CAE substance devoid of the catecholamine

Table 7. Effect of three-weak treatment of male rats with (−)IPAP and (−)BPAP, respectively, on the release of catecholamines and serotonin from selected brain areas[a]

		Amount of biogenic amine (nmol/g wet weight ± SEM) released from the tissue within 20 min		
	Dose μg/kg	Substantia nigra (dopamine)	Locus coeruleus (noradrenaline)	Raphe (serotonin)
Saline	—	5.8 ± 0.18	3.9 ± 0.10	0.403 ± 0.01
(−)IPAP	0.5	7.2 ± 0.15****	7.2 ± 0.10***	1.086 ± 0.08**
	50	11.1 ± 0.12****	4.4 ± 0.05	0.454 ± 0.02
(−)BPAP	0.1	8.8 ± 0.28****	7.4 ± 0.15***	0.870 ± 0.02***
	0.5	8.3 ± 0.23****	4.1 ± 0.05	1.907 ± 0.04****
	50	9.4 ± 0.13****	4.1 ± 0.40	0.136 ± 0.01***

[a]Treatment once daily, sc, for 3 weeks. Measurement 24 h after the last injection. Measured according to Knoll et al.[12c] Paired Student's *t*-test. *$p < 0.05$ **$p < 0.02$ ***$p < 0.01$ ****$p < 0.001$.

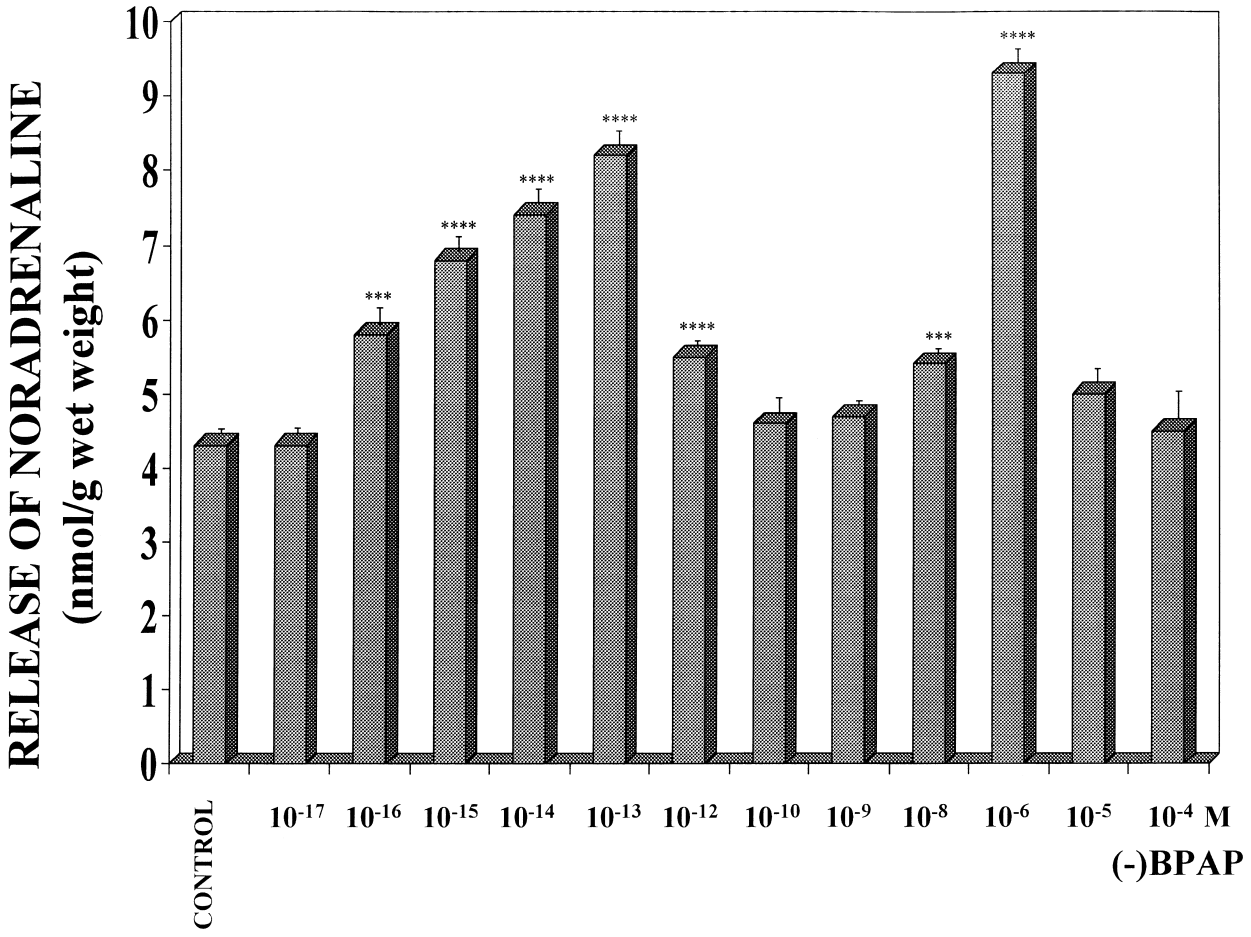


Figure 5. The ex vivo effect of (−)BPAP on the release of noradrenaline from the locus coeruleus isolated from the brain of male rats. The amount of noradrenaline (nmol/g wet weight) released from the tissue within 20 min was measured according to Knoll and Miklya.[12] Vertical lines show SEM Paired Student's *t*-test. *$p < 0.05$, **$p < 0.02$, ***$p < 0.01$, ****$p < 0.001$.

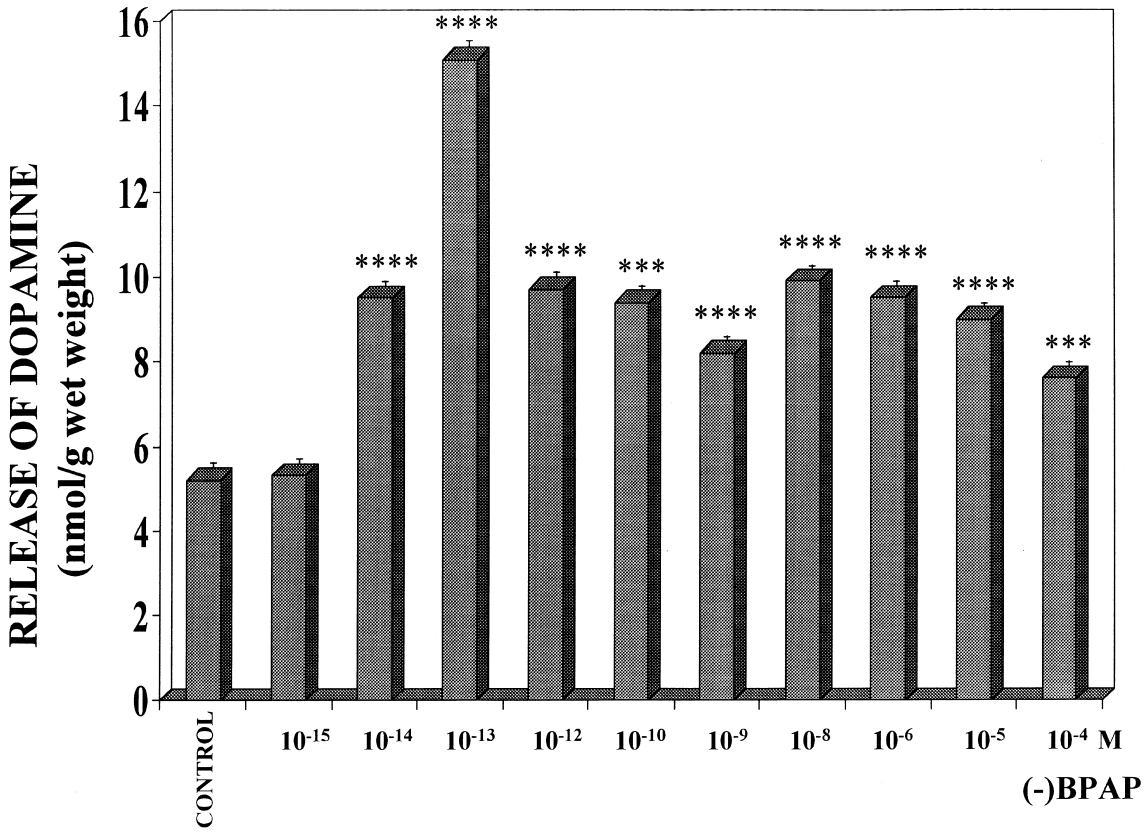


Figure 6. The ex vivo effect of (−)BPAP on the release of dopamine from the substantia nigra isolated from the brain of male rats. The amount of dopamine (nmol/g wet weight) released from the tissue within 20 min was measured according to Knoll and Miklya.[12] Vertical lines show SEM Paired Student's *t*-test. * $p < 0.05$, ** $p < 0.02$, *** $p < 0.01$, **** $p < 0.001$.

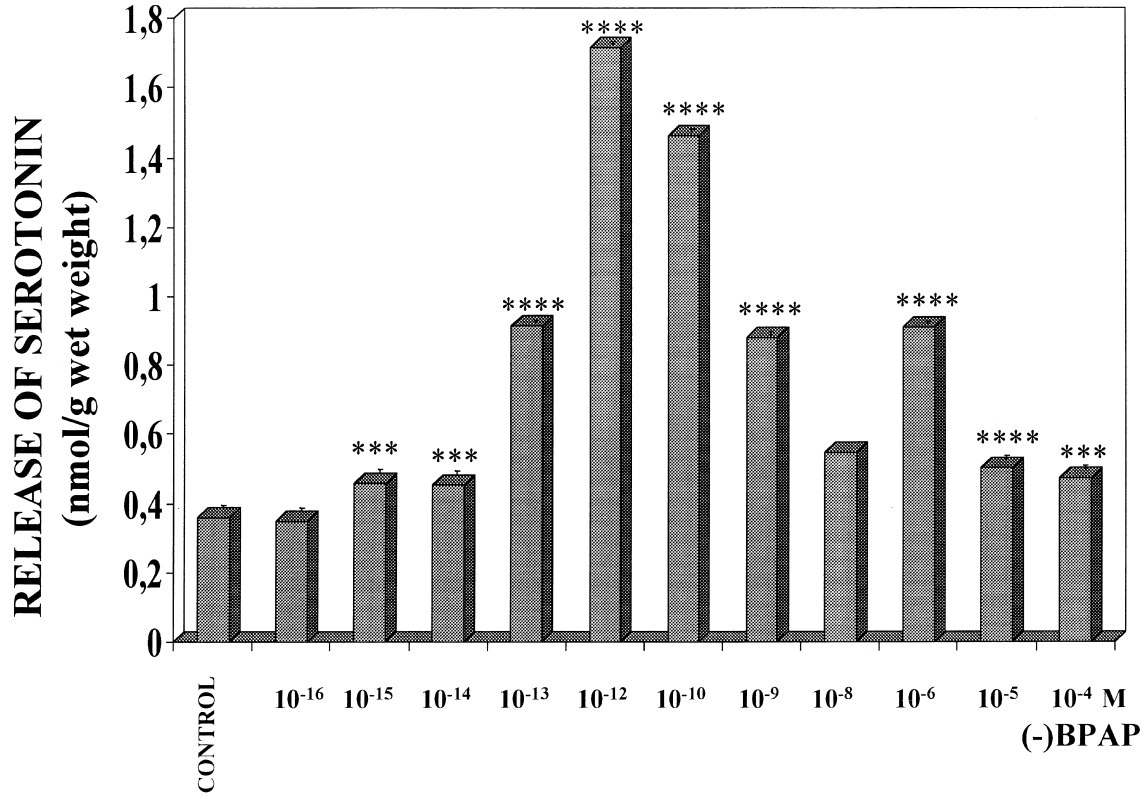


Figure 7. The ex vivo effect of (−)BPAP on the release of serotonin from the raphe isolated from the brain of male rats. The amount of serotonin (nmol/g wet weight) released from the tissue within 20 min was measured according to Knoll and Miklya.[12] Vertical lines show SEM Paired Student's *t*-test. * $p < 0.05$, ** $p < 0.02$, *** $p < 0.01$, **** $p < 0.001$.

releasing effect. Because of the discovery that (−)-deprenyl was a selective inhibitor of MAO-B,[10] attention has primarily been focused on this new property of the compound. However the subsequent development of (−)PPAP[11] proved that the maintenance of the nigrostriatal dopaminergic neurons on a higher activity level, the most remarkable pharmacological effect of the small dose administration of (−)deprenyl, is unrelated to the selective inhibition of MAO-B.[12] Also, the discovery that tryptamine is an enhancer of the impulse propagation mediated release of catecholamines and serotonin as seen in Figs 1–3, prompted us to design and synthesize new compounds including (−)BPAP by changing the benzene ring of PPAP. Thus, some of the new comounds obtained have turned out to be the first potent and selective enhancers of exocytosis of noradrenaline, dopamine and serotonin in the brain, which are structurally unrelated to the amphetamines.

From the data presented in this paper, it is reasonable to expect that (−)BPAP will be more potent than (−)deprenyl in slowing the progression of Parkinson's disease and Alzheimer's disease. As (−)BPAP is 130 times more potent than (−)deprenyl in antagonizing tetrabenazine-induced inhibition of performance in the shuttle box, we may also anticipate that this compound will be a much more efficient antidepressant in the clinic than (−)deprenyl, which was shown to have this effect.[20]

Life-long (−)deprenyl medication, due to its CAE effect, slows the age-related decline of sexual and learning performances of rats and prolongs their life.[9] The unique effect of (−)deprenyl on longevity described by us[6,21] was unequivocally confirmed in studies performed with rats, hamsters and dogs.[22] Considering the potency difference between (−)deprenyl and (−)BPAP, the administration of a very low daily dose of this new substance (e.g. 0.5–0.1 μg/kg) might be sufficient for keeping the catecholaminergic activity of the brain during post-developmental (aging) longevity on a higher basis activity level. This prophylactic medication will work for decades. It will improve the quality of life in the latter decades, hopefully shifting the time of natural death, probably decreasing the precipitation of age-related depression, likely eliminating the precipitation of Parkinson's disease and possibly reducing or delaying the onset of Alzheimer's disease.

Peculiar effects of (−)deprenyl and (−)PPAP like the ones shown on frog heart cells,[2,3] the high number of papers of papers on the neuroprotective effect of (−)deprenyl, as well as, the effect of (±)BPAP on the cultured hippocampal neurons shown in this paper (vide infra) reveal that also the activity of other than the catecholaminergic and serotoninergic neurons in the brain is enhanced by very low concentration of a CAE substance. Table 8 demonstrates the remarkable effect of (±)BPAP on cultured rat hippocampal neurons. We created a life or death situation for the cells by adding a toxic agent to the tissue culture, an amount of β-amyloid. It is assumed that the endangered cell, compelled to fight for survival, is immediately switching over, via the previously unknown (±)BPAP-sensitive activation mechanism, from the resting, 'economy' state into the hyperactive, exceptional, 'emergency' state, in order to mobilize all possible resources to cope with the perilous situation. Due, however, to the huge individual differences between cells regarding any performance, only about 20% of cells, the 'high performing' ones, escaped. (±)BPAP made the cells, in a concentration as low as 10^{-14} M, higher performing and about 70% of the neurons survived. Thus, (±)BPAP inhibited significantly the β-amyloid-induced neurotoxicity in the cultured hippocampal neurons in two distinct ranges of concentration, one with a peak of 10^{-14} M and one with a peak of 10^{-8} M as seen in Table 8. This is surprisingly

Table 8. Survival of cultured rat hippocampal neurons in the absence and presence of β-amyloid and the protective effect of (±)BPAP on β-amyloid induced neurotoxicity[a]

Treatment	Survival (%) Mean±SD	*p* value Dunnett's *t*-test
Control	100.00±14.35	
β-amyloid (20 μmol)	22.41±7.20	
β-amyloid (20 μmol) + (±)BPAP		
10^{-15} M	58.97 ± 4.75	< 0.0001
10^{-14} M	66.97 ± 7.08	< 0.0001
10^{-13} M	43.79 ± 6.79	< 0.0001
10^{-12} M	25.79 ± 6.32	> 0.05
10^{-11} M	31.33 ± 6.81	< 0.001
10^{-10} M	36.56 ± 8.63	< 0.0001
10^{-9} M	29.44 ± 7.51	> 0.05
10^{-8} M	58.15 ± 11.72	< 0.0001
10^{-7} M	42.10 ± 6.30	< 0.0001
10^{-6} M	16.41 ± 3.71	> 0.05

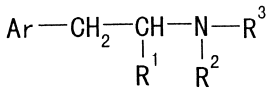
[a]Measurement according to Watt et al.[17]

Table 9. Minimum doses of the CAE compounds which antagonized, in a statistically significant manner, the depressant effect of tetrabenazine on both the CARs and Efs in shuttle box[a]

Compound	Dose (mg/kg)
(±)Deprenyl	5.0
(−)Deprenyl	5.0
(+)Deprenyl	5.0
(±)PPAP	5.0
(−)PPAP	2.5
(+)PPAP	5.0
(±)NPAP	2.5
(−)NPAP	2.5
(+)NPAP	> 5.0
(±)MPAP	1.0
(−)MPAP	0.5
(+)MPAP	1.0
(±)IPAP	2.5
(−)IPAP	0.5
(+)IPAP	2.5
(±)BPAP	1.0
(−)**BPAP**	**0.05**
(+)BPAP	1.0

[a]Measurement according to Knoll et al.[3] In order to find the minimum dose of a new compound which antagonized significantly the effect of tetrabenazine in the shuttle box, we started the experiments with 1 and 5 mg/kg and changed the dose according to the need as follows: 2.5, 0.5, 0.25, 0.1, 0.05 and 0.025 mg/kg. If a substance did not antagonize the effect of tetrabenazine in 5 mg/kg, we did not raise the dose further. Note that (−)BPAP (**boldface**) is the most potent compound.

Table 10. The relation between structure and pharmacological spectrum illustrating the development from PEA and amphetamines to the most representative new CAE substances



Compound	Ar	R^1	R^2	R^3	CAE effect	Catecholamine releasing effect	Relation to MAO
Phenylethylamine (PEA)		H	H	H	+	+	Substrate to MAO-B
Amphetamine		CH_3	H	H	+	+	Weak MAO inhibitor
Methamphetamine		CH_3	CH_3	H	+	+	Weak MAO inhibitor
(−)-*N*,1-Dimethyl-*N*-propargylphenylethylamine ((−)-Deprenyl)		CH_3	CH_3	CH_2-C≡CH	+	–	Potent MAO-B inhibitor
1-Phenyl-2-propylaminopentane (PPAP)		*n*-C_3H_7	H	*n*-C_3H_7	+	–	—
1-(3,4-Methylenedioxyphenyl)-2-propylaminopentane (MPAP)		*n*-C_3H_7	H	*n*-C_3H_7	+	–	—
1-(2-Naphthyl)-2-propylaminopentane (NPAP)		*n*-C_3H_7	H	*n*-C_3H_7	+	–	—
Tryptamine		H	H	H	+	–	Substrate to MAO
1-(Indol-3-yl)-2-propylaminopentane (IPAP)		*n*-C_3H_7	H	*n*-C_3H_7	+	–	Weak MAO inhibitor
1-(Benzofuran-2-yl)-2-propylaminopentane (BPAP)		*n*-C_3H_7	H	*n*-C_3H_7	+	–	Weak MAO inhibitor

identical with the mode of effect of (−)BPAP on the noradrenergic neurons in Fig. 5, indicating the essential identity of the BPAP-sensitive mechanism in the noradrenergic and hippocampal neurons.

In conclusion, endogenous substances, capable to enhance the activity of special groups of neurons according to the physiological need, exist in the brain and renders survival in life and death situation possible.[1a] (−)BPAP, selected from our study as a promising reference compound for further work, a highly selective, potent stimulant of this previously unknown regulation, is capable to enhance the activity of dopaminergic, noradrenergic, serotoninergic and hippocampal neurons in 10^{-14}–10^{-15} M concentration. The high potency of (−)BPAP could make the search in the brain after much more potent endogenous neuronal activity enhancer substances than PEA and tryptamine, reasonable.

Experimental

The purity of each product was checked by thin-layer chromatography (TLC) on silica gel plates (Merck Kieselgel 60 F_{254}, thickness 0.25 nm). Column chromatography was performed on silica gel (Merck, particle size 0.063–0.200 mm for normal chromatography and 15 μm for flash chromatography). All melting points (mp) were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Electron ionization (EI) mass spectra were recorded on a Hitachi M-80B mass spectrometer. Proton nuclear magnetic reasonance (^{1}H NMR) spectra were obtained with a JEOL GX-270 (270 MHz) spectrometer with TMS as internal standard and chemical shifts are expressed as δ values (in ppm). Elemental analyses were carried out on a Yanagimoto MT-3 elemental analyzer. Optical rotations were measured on a Horiba SEPA-200 digital polarimeter.

Reagents and solvents were purchased from common commercial suppliers and used as received.

1-(2-Naphthyl)-2-nitro-1-pentane (1: Ar = 2-naphthyl). A mixture of 2-naphthaldehyde (3.25 g, 20.8 mmol) and 1-nitrobutane (5.04 g, 48.9 mmol) in AcOH (10 mL) was heated at 100 °C in the presence of $AcONH_4$ (1.54 g, 20.0 mmol) for 10 h. The reaction mixture was diluted with H_2O, basified with 28% aqueous NH_3, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography using hexane-$CHCl_3$ (6:1) as eluant to give (**1**; Ar = 2-naphthyl) (2.78 g, 55.4%) as pale yellow oil: EI–MS *m/e* 241$(M)^+$; ^1H NMR($CDCl_3$) δ 1.05 (t, *J* = 7.4 Hz, 3H), 1.74 (tq, *J* = 7.4, 7.4 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 7.42–8.10 (m, 7H), 8.20 (s, 1H). Anal. ($C_{15}H_{15}NO_2$) C, H, N.

1-(2-Naphthyl)-2-aminopentane (2: Ar = 2-naphthyl). A solution of (*1*; Ar = 2-naphthyl) (2.78 g, 11.5 mmol) in THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.88 g, 23.1 mmol) in THF (15 mL) and the mixture was stirred overnight at room temperature. After decomposition of excessive $LiAlH_4$ with H_2O, the mixture was filtered and the filtrate was concentrated. Ether (30 mL) was added to the concentrate and the ether solution was extracted with 0.5 N HCl (20 mL). The obtained water phase was basified with 28% aqueous NH_3 and extracted with ether (30 mL). The ether extracts were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography using $CHCl_3$-MeOH (10:1) for eluting solvent to give (**2**; Ar = 2-naphthyl) (1.27 g, 51.6%) a pale yellow oil: EI–MS *m/e* 213$(M)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 6.7 Hz, 3H), 1.20–1.65 (m, 4H), 2.96 (dd, *J* = 13.4, 4.7 Hz, 2H) 3.10 (m, 1H), 7.27–8.03 (m, 7H). The oil was dissolved in ether and treated with ether solution saturated with HCl to give the hydrochloride as colorless crystalline powder: mp 175–176 °C (from CH_2Cl_2); EI–MS *m/e* 214 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.30–2.10 (m, 4H), 2.50–4.00 (m, 3H), 7.20–8.10 (m, 7H), 8.20–9.30 (br, 3H). Anal. ($C_{15}H_{19}N$·HCl) C, H, N.

***N*-(2-(1-(2-Naphthyl)pentyl)propionamide (3; Ar = 2-naphthyl).** To a THF (15 mL) solution of (**2**; Ar = 2-naphthyl). (1.27 g, 6.0 mmol) and triethylamine (0.90 g, 8.9 mmol), a solution of propinyl chloride (1.10 g, 11.9 mmol) in THF (3 mL) was added dropwise under cooling. The mixture was stirred for 5 h at room temperature, evaporated to dryness, and the residue was dissoleved in ether (15 mL). The ether solution was washed with 5% aquious HCl, 5% aqueous Na_2CO_3 and then saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4, evaporate to dryness, and purified by column chromatography using $CHCl_3$-hexane (5:2) for eluant to afford crude (**3**; Ar = 2-naphthyl). Recrystallization from ether-hexane gave white crystalline powder (1.00 g, 62.4%): mp 92 °C; EI–MS *m/e* 269$(M)^+$; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.7 Hz, 3H), 1.20–1.85 (m, 4H), 2.14 (q, *J* = 7.7 Hz, 2H), 2.95 (d, *J* = 6.4 Hz, 2H), 4.30 (m, 1H), 5.16 (d, *J* = 8.7 Hz, JH), 7.33–7.88 (m, 7H). Anal. ($C_{18}H_{23}NO$) C, H, N.

1-(2-Naphthyl)-2-propylaminepentane (6a) hydrochloride ((±)-NPAP). $LiAlH_4$ (0.50 g, 13.2 mmol) was suspended in ether (7 mL) and a solution of $AlCl_3$ (0.50 g, 3.75 mmol) in ether (5 mL) was added dropwise thereto under ice cooling to prepare an ether solution of aluminum hydride (AlH_3). To this solution, an ether solution (10 mL) of (**3**; Ar = 2-naphthyl) (1.00 g, 3.7 mmol) was added dropwise under ice cooling and the mixture was stirred at 0 °C for 0.5 h and then stirred overnight at room temperature. The reaction mixture was diluted with H_2O little by little, alkalized with 5 N NaOH, and filtered. The filtrate was concentrated and extracted with ether. The ether extracts were dried over anhydrous $MgSO_4$, concentrated and purified by column chromatography using $CHCl_3$:MeOH (30:1) as eluting solvent to give **6a** (0.50 g, 52.8%) as light yellow oil. The oil **6a** was converted by the usual method to **6a** hydrochloride ((±)NPAP) (0.47 g, 80.5%) as white crystalline powder: mp 183 °C (from MeOH); EI–MS *m/e* 256$(M+1)^+$; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.34–1.67 (m, 2H), 1.70–1.90 (m, 2H), 7.34–7.88 (m, 7H), 9.55 (br, 2H).

1-(3,4-Methlendioxyphenyl)-2-nitropentene (1;Ar = 3,4-methylenedioxyphenyl). This compound was obtained by the condensation of 3,4-methylenedioxybenzaldehyde (19.29 g, 128.5 mmol) with 1-nitrobutane (9.88 g, 192.80 mmol) as pale yellow oil (10.56 g, 34.9%) EI–MS *m/e* 235$(M)^+$; ^1H NMR ($CDCl_3$) δ1.03 (t, *J* = 7.4 Hz, 3H), 1.66 (tq, *J* = 7.4, 7.4 Hz, 2H), (t, *J* = 7.4 Hz, 2H), 6.04 (s, 2H), 6.85–7.07 (m, 3H), 7.94 (s, 1H). The oil was used without further purification to the next step.

1-(3,4-Methylenedioxyphenyl)-2-aminopentane (2; Ar = 3,4-methylenedioxyphenyl). A solution of (**1**; Ar = 3,4-methylenedioxyphenyl) (10.56 g, 44.9 mmol) in THF (80 mL) was treated with $LiAlH_4$ (3.17 g, 83.5 mmol) in THF (60 mL) by the same way as described above to give (**2**; Ar = 3,4-methylenedioxyphenyl) (7.12 g, 76.6%) as colorless oil: EI–MS *m/e* 207 $(M)^+$. The oil was converted by the usual method to the hydrochloride of as colorless needles: mp 205 °C (from CH_2Cl_2); EI–MS *m/e* 208 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.41–1.72(m, 4H), 1.14 (q, *J* = 5.7 Hz, 1H), 3.34–3.37 (m, 1H), 5.93 (s, 2H), 6.67–6.77 (m, 3H). Anal. ($C_{12}H_{17}NO_2$·HCl) C, H, N.

***N*-(2-(1-(3,4-Methylenedioxyphenyl))pentyl)propionamide (3;Ar = 3,4-methylenedioxyphenyl).** To a THF (60 mL) solution of (**2**; Ar = 3,4-methylenedioxyphenyl) (7.12 g, 34.4 mmol) and triethylamine (4.80 g, 47.4 mmol), a solution of propionyl chloride (5.85 g, 63.2 mmol) in THF (10 mL) was added and treated by the same way as described above give (**3**; Ar = 3,4-methylenedioxyphenyl) (6.38 g, 70.3%) as colorless needles: mp 73 °C (from CH_2Cl_2); EI–MS *m/e* 263 $(M)^+$; ^1H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 3H), 1.25–1.52 (m, 4H), 2.15 (q, *J* = 7.4 Hz,

2H), 2.75 (d, $J=6.0$ Hz, 1H), 4.05–4.20 (m, 1H), 5.21 (d, $J=9.0$ Hz, 1H), 5.92 (s, 2H), 6.58–6.80 (m, 3H). Anal. ($C_{15}H_{21}NO_3$) C, H, N.

1-(3,4-Methylenedioxyphenyl)-2-propylaminepentane (5a) hydrochloride ((±)MPAP). Compound (**3**; Ar = methylenedioxyphenyl) (6.38 g, 24.2 mmol) was treated with ether solution of AlH_3 prepared from $LiAlH_4$ (3.02 g, 79.6 mmol) in ether (60 mL) and $AlCl_3$ (3.03 g, 22.7 mmol) in either (40 mL) in the same way as described above to afford **5a** (4.24 g, 70.2%) as colorless oil, which was converted by the usual method to **5a** hydrochloride ((±)MPAP) (4.41 g, 90.6%) as colorless needless: mp 142 °C (from MeOH); EI–MS *m/e* 250$(M+1)^+$; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, $J=7.1$ Hz, 3H), 0.95 (t, $J=7.4$ Hz, 3H), 1.37–1.84 (m, 4H), 1.93 (tq, $J=7.4$, 7.4 Hz, 2H), 2.75–2.98 (m, 3H), 3.26 (m, 2H), 5.95 (s, 3H), 6.72–6.88 (m, 2H).

1-(2-(Indol-3-yl)2-nitro-1-pentene (1; Ar = indol-3-yl). A mixture of indol-3-carboxaldehyde (9.39 g, 64.7 mmol) and 1-nitrobutane (10.00 g, 97.0 nmol) in AcOH (10 mL) was heated at 100 °C in the presence of $AcONH_4$ (3.08 g, 40.0 mL) for 8 h. The reaction mixture was diluted with H_2O, basified with 28% NH_3, and extracted with $CHCl_3$ (150 mL). The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography using $CHCl_3$ as eluting solvent to give (**1**; Ar = indol-3-yl) (4.37 g, 31.7%) as pale yellow crystalline powder: mp 139 °C (from EtOH); EI–MS *m/e* 230$(M)^+$; ^{1}H NMR ($CDCl_3$) δ1.90 (t, $J=7.4$ Hz, 3H), 1.71 (m, 2H), 2.92 (t, $J=7.7$ Hz, 2H), 7.25–7.36 (m, 2H), 7.47 (dd, $J=7.0$, 1.4 Hz, 1H), 7.55 (d, $J=2.7$ Hz, 1H) 7.81 (d, $J=6.7$ Hz, 1H), 8.50 (s, 1H), 8.90 (br, 1H). Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

1-(2-(Indol-3-yl))-2-aminopentane (2; Ar = indol-3-yl). A solution of (**1**; Ar = indol-3-yl) (1.56 g, 41.0 mmol) in THF (30 mL) was added dropwise to a suspension of $LiAlH_4$ (4.73 g, 20.5 mmol) in THF (30 mL) under ice cooling and the mixture was stirred for 24 h at room temperature. After decomposition of excessive $LiAlH_4$ with H_2O, the mixture was filtered and the filtrate was concentrated. Ether (100 mL) was added to the concentrate and the ether solution was extracted with 1 N HCl (300 mL). The obtained water phase was basified with 28% aqueous NH_3 and extracted with ether (450 mL). The ether extracts were dried over anhydrous Na_2SO_4 and concentrated to give crude (**2**; Ar = indol-3-yl) (2.52 g, 61.0%) as red oil. The oil was converted by the usual method to the hydrochloride as colorless needles: mp 222 °C (from MeOH); EI–MS *m/e* 203$(M+1)^+$; ^{1}H NMR (CD_3OD) δ 0.98 (t, $J=7.0$ Hz, 3H), 1.40–1.75 (m, 4H), 3.00 (dd, $J=14.3$, 7.4 Hz, 1H), 3.14 (dd, $J=14.8$, 6.4 Hz, 1H), 3.40–3.50 (m, 1H), 7.00–7.18 (m, 3H), 7.40 (d, $J=8.1$ Hz, 1H) 7.55 (d, $J=7.7$ Hz, 1H). Anal. ($C_{13}H_{18}N_2HCl$) C, H, N.

***N*-(2-(1-(Indol-3-yl))pentyl)propionamide (3; Ar = indol-3-yl).** A solution of 3-propionylchloride (2.31 g, 25.0 mmol) in THF (10 mL) was added drop by drop to a solution of (**2**; Ar = indol-3-yl) (2.52 g, 12.5 mmol) and triethylamine (1.90 g, 18.8 mmol) in THF (30 mL) under ice cooling and the mixture was stirred for 3.5 h at room temperature. The reaction mixture was concentrated and the residue was dissolved in ether (150 mL). The ether solution was washed with 5% HCl (50 mL), 5% aqueous Na_2SO_3 (40 mL) and then saturated aqueous NaCl (40 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified with flash column chromatography using CH_2Cl_2 as eluant to give (**2**; Ar = indol-3-yl) (0.97 g, 30.0%) as colorless needless:mp 129 °C (from CH_2Cl_2); EI–MS *m/e* 258$(M)^+$; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, $J=7.1$ Hz, 3H), 1.09 (t, $J=7.7$ Hz, 3H), 1.30–1.64 (m, 4H), 2.12 (q, $J=7.7$ Hz, 2H), 2.95 (dq, $J=12.8$, 6.1 Hz, 2H), 4.31 (m, 1H), 5.23 (d, $J=9.4$ Hz, 1H) 7.02–7.67 (m, 5H), 8.19 (br, 1H).

1-(Indol-3yl)-2-propylaminopentane (7a) hydrochloride ((±)IPAP). $LiAlH_4$ (0.50 g, 13.2 mmol) was suspended in ether (20 mL) and thereto a solution of $AlCl_3$ (0.51 g, 3.82 mmol) in ether (10 mL) was added dropwise under ice cooling to give an ether solution of AlH_3. To this solution, a solution of (**3**; Ar = indol-3-yl) (0.97 g, 3.75 mmol) in THF (20 mL) was added dropwise under ice cooling. The mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with H_2O, alkalized with 5 N NaOH and filtered. The filtrate was concentrated and extracted with ether (300 mL). The ether extracts were dried over anhydrous Na_2SO_4, concentrated and purified with flash column chromatography using $AcOC_2H_5$ as eluant to give a pale yellow oil of **7a** (0.57 g, 62.1%). The oil **7a** was dissolved in ether and treated with ether solution saturated with HCl to give **7a** hydrochloride ((±)IPAP) (0.46 g, 70.0%) as colorless needles: mp 151 °C (from MeOH); EI–MS *m/e* 245$(M+1)^+$; ^{1}H NMR ($CDCl_3$) δ (t, $J=7.1$ Hz, 3H), 1.09 (t, $J=7.7$ Hz, 3H), 1.30–1.64 (m, 4H), 2.12 (q, $J=7.7$ Hz, 2H), 2.95 (m, $J=12.8$, 6.1 Hz, 2H), 4.31 (m, 1H), 5.23 (d, $J=9.4$ Hz, 1H) 7.02–7.67 (m, 5H), 8.19 (br, 1H).

1-(2-(Benzofuran-2-yl))-2-nitro-1-pentene (1; Ar = benzofuran-2-yl). A mixture of benzofuran-2-carboxyldehyde (50.00 g, 342.1 mmol) and 1-nitrobutane (58.00 g, 562.4 mmol) in AcOH (50 mL) wad heated at 100 °C in the presence of $AcONH_4$ (18.48 g, 240.0 mmol) for 1 h. The reaction mixture was diluted with H_2O, basified with 28% aqueous NH_3, and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and concentrated to give a residue, which was distilled under reduced pressure (153–167 °C, 1 mm Hg). The compound (**1**; Ar = benzofuran-2-yl) was obtained as pale yellow crystalline powder (58.61g, 74.1%): mp 47 °C; EI–MS *m/e* 231$(M)^+$; ^{1}H NMR ($CDCl_3$) δ1.06 (t, $J=7.4$ Hz, 3H), 1.72 (tq, $J=7.4$, 7.4 Hz, 2H), 3.18 (t, $J=7.4$ Hz, 2H), 7.12 (s, 1H), 7.25–7.90 (m, 4H), 7.91 (s, 1H). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

1-(2-(Benzofuran-2-yl))-2-aminopentane (2; Ar = benzofuran-2-yl). A solution of (**1**; Ar = benzofuran-2-yl) (58.61 g, 253.4 mmol) in THF (150 mL) was added dropwise to a suspension of $LiAlH_4$ (12.50 g, 329.4 mmol) in THF (150 mL) over 1 h under ice cooling. The mixture was stirred for 15 h at room tempera-

ture. After excessive $LiAlH_4$ was decomposed with H_2O under ice cooling, the mixture was basified with 28% aqueous NH_3, and filtered. After the filtrate was concentrated, ether (500 mL) was added to the concentrate and the ether solution was extracted with 0.5 N HCl (100 mL). The obtained water phase was basified with 28% aqueous NH_3 and extracted with ether (600 mL). The ether extracts were dried over anhydrous Na_2SO_4 and concentrated to give crude (**2**; Ar = benzofuran-2-yl) as coloreless oil (23.98 g, 46.6%): EI–MS *m/e* 203(M)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3H), 1.37–1.64 (m, 4H), 3.46–3.51 (m, 1H), 5.52 (br, 2H), 6.55 (s, 1H), 7.15–7.49 (m, 4H). The crude moduct was used without further purification to the next step.

***N*-(2-(1-(Benzofuran-2-yl))pentyl)propionamide (3; Ar = benzofuran-2-yl).** To a solution of (**2**; Ar = benzofuran-2-yl) (23.98 g, 118.0 mmol) and triethylamine (15.52 g, 153.4 mmol) in THF (250 mL), a solution of propionyl chloride (16.38 g, 177.00 mmol) in THF (100 mL) was added dropwise and the mixture was stirred for 3 h at room temperature. After the reaction, ether (500 mL) was added to the reaction mixture and the ether solution was washed with 1 N HCl (400 mL), 5% aqueous Na_2CO_3 (300 mL) and then saturated aqueous NaCl (300 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude (**3**; Ar = benzofuran-2-yl) (16.35 g, 53.4%) as white crystalline powder: mp 72 °C (from CH_2Cl_2); EI–MS *m/e* 259(M)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 3H), 1.15 (t, J = 7.4 Hz, 3H), 1.32–1.66 (m, 4H), 2.20 (q, J = 7.4 Hz, 2H), 2.98 (dq, J = 15.1, 5.7 Hz, 2H) 4.34 (m, 1H), 5.44 (d, J = 8.1 Hz, 1H), 6.46 (s, 1H), 7.15–7.53 (m, 4H). Anal. ($C_{16}H_{21}NO_2$) C, H, N.

1-(Benzofuran-2-yl)-2-propylaminopentane (7i) hydrochloride ((±)BPAP). $LiAlH_4$ (8.37 g, 220.6 mmol) was suspended in ether (100 mL) and thereto a solution of $AlCl_3$ (8.40 g, 63.0 mmol) in ether (50 mL) was added drop by drop under ice cooling to prepare an ether solution of AlH_3. To this solution, a solution of (**3**; Ar = benzofuran-2-yl) (16.35 g, 63.0 mmol) in THF (100 mL) was added dropwise under ice cooling and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with H_2O little by little, alkalized with 5 N NaOH, and filtered. The filtrate was concentrated and extracted with ether (600 mL). The ether extracts were dried over anhydrous $MgSO_4$, concentrated and distilled under reduced pressure (132–139 °C, 1 mm Hg) to give **7i** (10.51 g, 67.9%) as pale yellow oil. The oil **7i** was dissolved in ether and treated with ether solution saturated with HCl to give **7i** hydrochloride ((±)BPAP) (10.17 g, 84.3%) as colorless needles: mp 136 °C (from MeOH); EI–MS *m/e* 246(M + 1)$^+$; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 1.40–1.68 (m, 2H), 1.68–2.07 (m, 4H), 2.89 (m, 2H), 3.28 (m, 1H), 3.55 (m, 2H), 6.65 (s, 1H), 7.17–7.38 (m, 4H), 9.50 (br, 2H).

The optical resolutions of the racemates. The optical resolutions of the above racemates thus obtained were carried out by HPLC on a chiral stationary phase. Conditions for preparative HPLC are as follows: Column, CHIRALPACK AD (20 mm ϕ×250 mm); Eluant, hexane DEA or TFA (100:0.1). The first fractions were the (−)-enantiomers for (±)NPAP and (±)MPAP and were the (+)-enantiomers for (±)IPAP and (±)BPAP. Each oily enantiomer was dissolved in ether and was treated with ether solution saturated with HCl to afford colorless needles of the respective enantiomer hydrochlorides (see Table 5).

Measurement of the release of radiolabelled noradrenaline, dopamine or serotonin from the isolated brain stem of rats. The method used was described in a previous paper.[2] To measure drug effects on transmitter-release from the brain stem we incorporated either (^{3}H)-noradrenaline (1-(7,8-^{3}H)-noradrenaline; specific activity: 30–50 Ci/mmol), (^{3}H)-dopamine ((2,5,6-^{3}H)-dopamine; specific activity: 5–15 Ci/mmol) or (^{3}H)-serotonin (5-hydroxy-(G-^{3}H)-tryptamine creatinine sulphate; specific activity: 10–20 Ci/mmol) (Amersham, Buckinghamshire, UK), respectively, into the transmitter stores of the brain stem slices by preincubation. The brain stem was stimulated with rectangular pulses (3 Hz, 1 ms, 60 V) for 3 min. At the beginning of the experiment, three consecutive 3-min resting periods preceded the first stimulation. Thereafter seven resting periods were allotted between stimulations.

Measurement of the release of noradrenaline from the locus coeruleus, dopamine from the substantia nigra, striatum and tuberculum olfactorium and serotonin from the raphe. The release of noradrenaline, dopamine or serotonin was measured from selected brain stem areas by HPLC with electrochemical deteciton. After incubation of the quickly removed brain samples for 20 min, the tissue was soaked for 20 min in fresh Krebs solution and the concentration of the biogenic amine released during this period of time was estimated as described in previous paper.[12c]

Measurement of β-amyloid induced neurotoxicity in cultured hippocampal neurons. Primary rat embryonic hippocampal cultures were established according to Watt et al.[17] with some modification. The hippocampus was dissected from the brains of embryonic day 18 rat embryos. At the 10th day, the cultured cells were ingured by exposing them for 3 days to a 20 μM concentration of β-amyloid 25-35 fragment(Aβ) (Peptide Inst., Osaka, Japan). This concentration of β-amyloid decreased the survival of the neurons (control = 100%) to 22.4 ± 7.20% (means ± SD). For testing the neuroprotective effect of (±)BPAP, concurrently with β-amyloid a selected concentration of the compound was present in the culture well and the change in survival of the cells was calculated. Statistical significance of data was evaluated by Dunnett's *t*-test. Significance level was set at $p < 0.05$.

Measurement of the performance of rats in the shuttle box. The method was described in a previous paper.[3] The acquisition of a two-way conditioned avoidance reglex (CAR) was analyzed in the shuttle box during 5 consecutive days. The instrument consists of six boxes, each one separated inside by a barrier with a small gate

in the middle. Animals were trained to cross the barrier under the influence of a conditioned stimulus (CS) (light flash). If they failed to do so, they were punished with a footshock (1 mA), that is an unconditioned stimulus (US). If the rat failed to respond within 5 s to US, it was noted as escape failure (EF). The rats were trained with 100 trials per day. One trial consisted of 15 s intertrial interval, followed by 15 s CS. The last 5 s of CS overlapped the 5 s of US. At each learning session, the number of CARs, EFs and intersignal reactions (Irs) were automatically counted and evaluated by multi-way analysis of variance (ANOVA). Performance of rats was inhibited by the subcutaneous administration of 1 mg/kg tetrabenazine 1 h prior to their testing in the shuttle box. For measuring the antagonistic effect of a compound against tetrabenazine induced inhibition of performance, the test substance was injected subcutaneously, concurrently with tetrabenazine.

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