

Studies on Cognitive Enhancing Agents. I. Antiamnestic and Antihypoxic Activities of 2-Dimethylaminoethyl Ethers and Related Compounds

Satoshi ONO,* Tetsuo YAMAFUJI, Hisaaki CHAKI, Yozo TODO, Mutsuko MAEKAWA, Kazunori KITAMURA, Masaru TAI, and Hirokazu NARITA

Research Laboratories, Toyama Chemical Co., Ltd., 2-4-1 Shimookui, Toyama 930, Japan.

Received January 5, 1995; accepted April 17, 1995

N-(2-Dimethylaminoethyl)carboxamide (1a—d), 2-dimethylaminoethyl alkyl ether (2a, b), and 2-dimethylaminoethyl 2-hydroxy-2-phenethyl ether (3a—c) and its amino and methylene analogues (3d, 4) have been screened for antiamnestic and antihypoxic activities in mice. A clear reversing effect on electroconvulsive shock-induced amnesia was found with 1a—d, 2a, b, and 2-dimethylaminoethyl 2-hydroxy-2-phenylethyl ether (3a). However, a protective effect against hypoxia was only observed with 3a. Compound 3a, which displayed the dual activity, was further investigated for ameliorating effect on CO₂-induced memory impairment, and it was found to be more potent than indeloxazine and bifemelane. In addition, the acute toxicity of 3a in mice was significantly lower than that of tacrine, but its serum-to-brain penetration ability in rats was less than that of the reference drugs.

Key words antihypoxic activity; antiamnestic activity; cognition enhancement; dementia; 2-dimethylaminoethyl ether

With the rapid increase in the number of elderly people throughout the world, senile dementia of Alzheimer's type (SDAT) and multi-infarct dementia, which is associated with aging, are becoming increasingly important diseases. SDAT is apparently associated with the loss of cholinergic activity in the cortex and hippocampus.¹⁾ In addition, it has been reported that monoaminergic systems, which also control brain functions, are disturbed in Alzheimer's patients.²⁾ Based on this neurochemical background, a number of cholinesterase inhibitors including tacrine³⁾ and its analogues⁴⁾ and some monoamine oxidase inhibitors such as L-deprenyl⁵⁾ (Chart 1) have been developed for the treatment of SDAT, but all of the known agents have some drawbacks in terms of toxicity and/or effectiveness.⁶⁾

Multi-infarct dementia, on the other hand, is linked primarily with disruption of cerebral blood flow, which leads to insufficient supply of oxygen and glucose to the brain cells, ultimately resulting in irreversible damage to neurons.⁷⁾ This oxygen deprivation is pathologically characterized by hypoxia, a state in which impairments of memory and learning abilities have been reported for some animals⁸⁾ and humans.⁹⁾ Agents for the clinical treatment of multi-infarct disease include an array of cerebral vasodilators¹⁰⁾ and also some cerebral metabolism-enhancers such as indeloxazine¹¹⁾ and bifemelane,¹²⁾ which are believed to have protective effects against cerebral damage due to oxygen deprivation. However, the currently available drugs are only moderately effective in reversing memory and cognition deficits,¹³⁾ and, therefore, are occasionally administered in combination with a psychotropic drug (an antidepressant or a tranquilizer).¹⁴⁾

Our present investigation, which was directed to developing a new cognitive enhancing agent with antihypoxic activity as well as neurotransmitter-activating action, started with the search for a prototype compound among *N*-(2-dimethylaminoethyl)carboxamides and 2-dimethylaminoethyl ethers, which are chemically more stable analogues of choline *O*-acetate. The idea of such structural modification of acetylcholine was obtained from the report of Fries and Andrako in 1977;

they showed that 2-dialkylaminoethyl 2,2-diphenyl-2-hydroxyethyl ethers such as 3c display significant anticholinergic activity, much higher than that of the corresponding esters, in the assay of inhibitory activity against perphenazine-induced catatonia in rats.¹⁵⁾ In addition, the amino ether function in our designed compounds can be seen in the antihypoxia drugs indeloxazine and bifemelane, both of which are known to inhibit the uptake of cerebral noradrenaline and serotonin.¹⁶⁾

In this paper, we report the results of bioassay of our designed compounds listed in Chart 2 for antiamnestic and antihypoxic activities in mice, as determined by using contemporary techniques. 2-(2-Dimethylaminoethoxy)-1-phenylethanol (3a) displays both activities and has significantly lower acute toxicity than tacrine, and so has been chosen as a prototype compound for further structural modifications.

Chemistry

All the tested compounds except 1d, 3b, and 3d have been reported in the literature,¹⁷⁾ mostly as free amines. The amide 1d was obtained by heating ethyl mandelate with *N,N*-dimethylethylenediamine and isolated as its hydrochloride. The 2-hydroxy-2-phenylpropyl ether (3b)

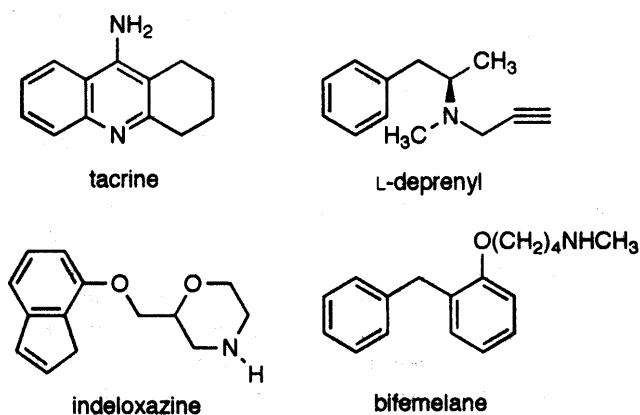
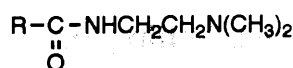


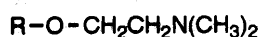
Chart 1

* To whom correspondence should be addressed.

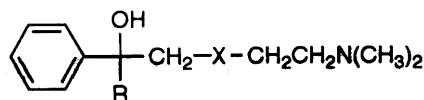


1a-d	R	salt
a	CH ₃	NDS
b	CH ₃ CH ₂	NDS
c	C ₆ H ₅ CH ₂	HCl
d	C ₆ H ₅ CH(OH)	HCl

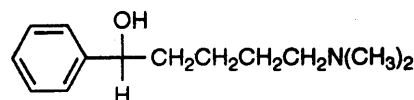
NDS = naphthalene-1,5-disulfonic acid



2a,b	R	salt
a	CH ₃ CH ₂ CH ₂	HCl
b	C ₆ H ₅ CH ₂ CH ₂	NDS



3a-d	R	X	salt
a	H	O	HCl
b	CH ₃	O	HCl
c	C ₆ H ₅	O	HCl
d	H	NH	fumaric acid



4

Chart 2

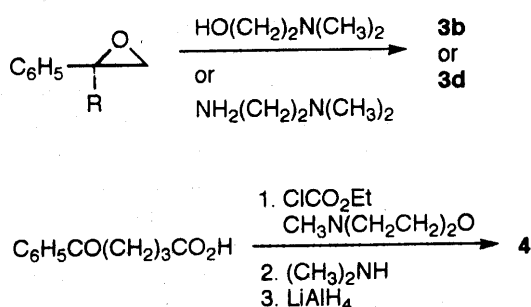


Chart 3

and 2-hydroxyphenethylamine (3d) were prepared from the corresponding phenyloxiranes by reaction with the requisite aminoethanol or ethylenediamine (Chart 3). Compound 4 was prepared in our hands starting with 5-oxo-5-phenylvaleric acid and using standard functional group transformations. For biological assays, all amino compounds were converted to their salts by using an appropriate acid, depending on ease of crystallization. The characterization data of the salts are recorded in Table 1.

Pharmacological Results and Discussion

It has been reported that electroconvulsive shock (ECS) treatment causes amnesia and confusion in humans¹⁸⁾ and also in rodents¹⁹⁾ and decreases the acetylcholine level in rat brain.²⁰⁾ The compounds listed in Chart 2 were examined for the ability to reverse ECS-induced amnesia in mice, by using the step-through passive avoidance response procedure.²¹⁾ The test compounds (3 mg/kg) were administered intraperitoneally 1 h before the passive avoidance training, and memory-retention testing was performed 24 h after ECS treatment. Antihypoxic activity was evaluated in mice using a hypoxia model obtained by exposure to an oxygen-deficient atmosphere. Test samples (100 mg/kg) were given orally 30 min before the hypoxia treatment, and survival times were recorded. Results of the assays for the anti-amnesic (AA) and antihypoxic (AH)

activities are summarized in Table 2.

All of the amides (1a–d) displayed AA activity, but no AH activity. The same phenomenon can be seen with the propyl and phenethyl ethers (2a,b), though their AA activities are equal to or less than those of the amides 1a–d. However, as the data for 3a indicate, introduction of a hydroxy group at the benzylic position of 2b enhances not only AA activity but also, more importantly, leads to a remarkable advent of AH activity. In contrast, compounds 3b and 3c, which are tertiary alcohol analogues of 3a, show neither AA nor AH activity. Furthermore, NH and CH₂ analogues (3d,4) of 3a were totally inactive.

Compound 3a, which showed both AA and AH activities, was further evaluated for ability to ameliorate CO₂-induced memory loss in mice, since it has been reported that appearance of some memory disorder can be observed in patients with cerebrovascular disorders and that memorizing and learning abilities are impaired by hypoxia in animals⁸⁾ and humans.⁹⁾ This assay was performed by using a passive avoidance training technique. The results obtained with 3a and the reference drugs (tacrine, indeloxazine, and bifemelane) are shown in Table 3, together with acute toxicity data in mice. Although the minimum effective dose (MED) of 3a (30 mg/kg) in oral administration proved significantly greater than that of tacrine (1 mg/kg), the acute toxicity of 3a was found to be much less than that of tacrine (LD₅₀: > 500 mg/kg vs. 68 mg/kg). Furthermore, it should be noted that the MED of 3a is smaller than those of indeloxazine and bifemelane.

We then determined the brain-to-serum concentration ratio of 3a in rats in order to examine its penetration ability into brain cells. As shown in Table 3, the ratio for 3a (4.96) proved to be smaller than those observed with tacrine and indeloxazine by 60% and 25%, respectively.

In conclusion, we have discovered the prototype compound 3a (Chart 4) among simple analogues of acetylcholine. It is characterized by moderate ability to

Table 1. Characterization Data for 1a–d, 2a, b, 3a–d, and 4

Compd.	Formula	mp (°C) (Solvent for crystallization) ^{a)}	Combustion analysis Calcd (Found) (%)			¹ H-NMR spectral data δ in D ₂ O solvent, <i>J</i> in Hz
			C	H	N	
1a ^{b)}	C ₆ H ₁₄ N ₂ O·0.5NDS ·0.4H ₂ O	152–153.5 (MeOH–IPA)	46.92 (47.04)	6.73 6.84	9.95 9.71	1.97 (3H, s), 2.83 (6H, s), 3.0–3.3 (2H, m), 3.3–3.6 (2H, m), 7.78 (1H, dd, <i>J</i> =8.5, 6), 8.22 (1H, d, <i>J</i> =6), 8.94 (1H, d, <i>J</i> =8.5)
1b ^{b)}	C ₇ H ₁₆ N ₂ O·0.5NDS	153–154.5 (EtOH)	49.98 (49.75)	6.99 6.99	9.71 9.49	1.05 (3H, t, <i>J</i> =7.5), 2.22 (2H, q, <i>J</i> =7.5), 2.83 (6H, s), 3.0–3.3 (2H, m), 3.3–3.6 (2H, m), 7.78 (1H, dd, <i>J</i> =8.5, 6), 8.28 (1H, d, <i>J</i> =6), 8.94 (1H, d, <i>J</i> =8.5)
1c ^{b)}	C ₁₂ H ₁₈ N ₂ O·HCl	142–143 (EtOH)	59.38 (59.28)	7.89 8.06	11.54 11.40	2.91 (6H, s), 3.1–3.4 (2H, m), 3.4–3.7 (4H, m), 7.40 (5H, s)
1d	C ₁₂ H ₁₈ N ₂ O ₂ ·HCl	168–169 (IPA)	55.70 (55.55)	7.40 7.39	10.83 10.65	2.90 (6H, s), 3.1–3.5 (2H, m), 3.5–3.8 (2H, m), 5.22 (1H, s), 7.47 (5H, s)
2a ^{b)}	C ₇ H ₁₇ NO·HCl	Oil		ND ^{c)}		0.88 (3H, t, <i>J</i> =7), 1.3–1.8 (2H, m), 2.91 (6H, s), 3.36–3.6 (4H, m), 3.7–3.9 (2H, m)
2b ^{b)}	C ₁₂ H ₁₉ NO·0.5NDS	148–149 (IPA)	60.51 (60.43)	6.87 7.01	4.15 4.08	2.67 (6H, s), 2.7–2.9 (2H, m), 3.0–3.2 (2H, m), 3.4–3.8 (4H, m), 7.27 (5H, s), 7.70 (1H, dd, <i>J</i> =8.5, 6.5), 8.24 (1H, d, <i>J</i> =6.5), 8.93 (1H, d, <i>J</i> =8.5)
3a	C ₁₂ H ₁₉ NO ₂ ·HCl	184–185 (EtOH) (Lit. ^{16a)} 186–187)	58.65 (58.44)	8.20 8.29	5.70 5.63	2.84 (6H, s), 3.1–3.5 (2H, m), 3.6–4.0 (4H, m), 4.95 (1H, t, <i>J</i> =5.5), 7.44 (5H, s)
3b	C ₁₃ H ₂₁ NO ₂ ·HCl	158–159.5 (EtOH)	60.11 (59.98)	8.54 8.65	5.39 5.30	1.53 (3H, s), 2.75 (6H, s), 3.1–3.4 (2H, m), 3.6–3.9 (4H, m), 7.46 (5H, s)
3c	C ₁₈ H ₂₃ NO ₃ ·HCl	168.5–169 (EtOH) (Lit. ^{16a)} 167–168)	67.17 (66.89)	7.52 7.50	4.35 4.26	2.82 (6H, s), 3.2–3.5 (2H, m), 3.7–4.0 (2H, m), 4.28 (2H, s), 7.47 (10H, s)
3d	C ₁₂ H ₂₀ N ₂ O· (fumaric acid) ₂	164–166 (MeOH–EtOH)	54.54 (54.43)	6.41 6.43	6.36 6.33	3.00 (6H, s), 3.4–3.7 (6H, m), 5.09 (1H, t, <i>J</i> =6), 6.68 (4H, s), 7.46 (5H, s)
4 ^{b)}	C ₁₃ H ₂₁ NO·HCl	Oil		ND ^{c)}		1.2–2.1 (6H, m), 2.84 (6H, s), 2.9–3.3 (2H, m), 4.7–4.9 (1H, m), 7.45 (5H, s)

a) IPA: iso-PrOH. b) Free base data are given in the literature for 1a–c,^{17a)} 2a,^{17b)} 2b,^{17c)} and 4.^{17f)} c) Not determined.

Table 2. Antiamnesic and Antihypoxic Activities in Mice

Compound	Antiamnesic activity ^{a)} (3 mg/kg i.p. dosing)	Antihypoxic activity ^{b)} (100 mg/kg p.o. dosing)
1a	+	–
1b	++	–
1c	+++	–
1d	++	–
2a	+	–
2b	+	–
3a	++	++
3b	–	–
3c	–	–
3d	–	–
4	–	–
Tacrine	++ ^{c)}	ND ^{d)}
Indeloxazine	–	++
Bifemelane	–	+

a) Determined by testing reversal of electroconvulsive shock-induced amnesia. Symbols represent mean latency: –, <60 s; +, 60–100 s; ++, 101–150 s; +++, 151–300 s. b) Determined with hypoxia models. Symbols represent % increase in survival time against untreated animals: –, <25%; +, 26–50%; ++, 51–75%. c) 0.3 mg/kg. d) Not determined.

reverse memory impairment as well as protective effects against hypoxia, and also by low acute toxicity, while having sufficient lipophilicity to cross the blood-brain barrier.

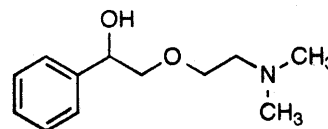
Experimental

Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer. ¹H-NMR spectra were recorded on a JEOL FX-60

Table 3. Memory-Ameliorating Activity, Acute Toxicity, and Brain-to-Serum Ratio of 2-(2-Dimethylaminoethoxy)-1-phenylethanol (3a) in Oral Administration

Compound	Ameliorating activity of CO ₂ -induced memory impairment in mice ^{a)} MED ^{b)} (mg/kg)	Acute toxicity in mice ^{c)} LD ₅₀ (mg/kg)	Brain/serum ratio in rats ^{d)}
3a	30	>500	4.96
Tacrine	1	68	8.47
Indeloxazine	>30	444 ^{e)}	18.46
Bifemelane	>100	1034 ^{f)}	ND ^{g)}

a) Amnesia was induced by exposure to CO₂ immediately after the acquisition trial. b) Minimum effective dose. c) LD₅₀ were calculated from lethality during 7 d after dosing. d) Rats were killed 30 min after administration of test compounds (30 mg/kg). e) Ref. 23. f) Ref. 24. g) Not determined.



3a (R,S)

Chart 4

spectrometer. Chemical shifts are expressed in δ (ppm) downfield from internal tetramethylsilane (for CDCl₃ solvent) or sodium 3-(trimethylsilyl)propionate (for D₂O solvent). Splitting patterns are described as s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Mass spectra were recorded on a JEOL JMA-D300 spectrometer. Column chromatography was carried out with E. Merck Silica gel 60 (70–230 mesh). Distillation of oily products were carried out on a Kugelrohr apparatus and boiling points are uncorrected. High-

performance liquid chromatography (HPLC) was carried out with a Shimadzu LC-64A equipped with an SPD-6A UV detector. All organic solvent extracts were dried over anhydrous magnesium sulfate and concentrated with a rotary evaporator under reduced pressure.

***N*-[2-(*N,N*-Dimethylamino)ethyl]mandeloamide Hydrochloride (1d)** A mixture of ethyl mandelate (10 g, 56 mmol) and *N,N*-dimethylethylenediamine (7.4 g, 84 mmol) was heated at 100°C under stirring. After 2 h the mixture was cooled to room temperature, and ether (100 ml) was added to precipitate crude mandeloamide. This material was dissolved in acetone (200 ml), and dry HCl was passed through the solution at 10–20°C. The resulting crystalline precipitate was collected and recrystallized from iso-PrOH to give analytically pure 1d (11.1 g, 77%) as colorless needles, mp 168–169°C.

2-[2-(*N,N*-Dimethylamino)ethoxy]-1-methyl-1-phenylethanol Hydrochloride (3b) 2-Methyl-2-phenyloxirane (10.6 g, 79 mmol) was added to a stirred and heated (65°C) mixture of potassium *tert*-butoxide (26 g, 0.23 mol) and *N,N*-dimethylethanolamine (43 g, 0.48 mol) in dimethyl sulfoxide (DMSO) (50 ml). After continued stirring at 65–70°C for 30 min, the mixture was poured into a mixture of ice-water (300 ml) and CHCl₃ (200 ml). The layers were separated and the organic layer was washed with water (100 ml × 3), dried, and concentrated. The residual oil was dissolved in EtOH (50 ml) and dry HCl was passed through the solution at 10–20°C. The crystalline precipitate was collected and recrystallized from EtOH to give 3b (7.8 g, 33%) as colorless needles, mp 158–159.5°C.

2-[2-(*N,N*-Dimethylamino)ethyl]amino-1-phenylethanol Difumarate (3d) A solution of styrene oxide (3.0 g, 25 mmol) and *N,N*-dimethylethylenediamine (2.4 g, 27 mmol) in iso-PrOH (60 ml) was heated under reflux for 3 h. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (elution with CHCl₃:MeOH = 5:1) to give a diamine as an oil. This material was dissolved in EtOH (10 ml) and the solution was treated with fumaric acid (0.62 g, 5 mmol). The precipitate was collected by filtration and recrystallized from a 1:1 mixture of MeOH and EtOH to give analytically pure 3d (1.0 g, 9%) as colorless needles, mp 164–166°C.

5-(*N,N*-Dimethylamino)-1-phenylpentanol Hydrochloride (4) Ethyl chloroformate (0.50 g, 4.6 mmol) was added over 5 min to a stirred and cooled (ice-water) mixture of 5-oxo-5-phenylvaleric acid (0.8 g, 4.2 mmol) and *N*-methylmorpholine (0.46 g, 4.6 mmol) in dry CH₂Cl₂ (10 ml) at 0–5°C. After 1 h the reaction mixture containing a mixed anhydride was added over 5 min to a stirred and cooled (0–5°C) mixture of 50% aqueous Me₂NH (4 g, 89 mmol), CH₂Cl₂ (10 ml), and ice-water (20 ml). After continued stirring of the two-phase mixture for 15 min, the organic layer was separated, washed with brine, dried, and concentrated. The residual oil was purified by silica gel chromatography (elution with hexane:AcOEt = 10:1) to give *N,N*-dimethyl-5-oxo-5-phenylvalerol-1-amine (0.80 g, 88%) as a colorless oil. IR (neat): 1685, 1638 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.9–2.2 (2H, m), 2.2–2.6 (2H, m), 2.8–3.2 (8H, m), 7.2–7.6 (3H, m), 7.8–8.0 (2H, m). MS *m/z*: 219 (M⁺).

A solution of the keto amide obtained above (0.70 g, 3.2 mmol) in tetrahydrofuran (THF) (5 ml) was added to a stirred suspension of LiAlH₄ (0.24 g, 6.3 mmol) in THF (10 ml). The mixture was heated under reflux for 3 h before quenching with AcOEt followed by addition of 10% NaOH (5 ml). The whole was filtered through a layer of Celite and the remaining solid was washed with MeOH. The combined filtrates were concentrated, and the residue was subjected to silica gel chromatography (elution with CHCl₃:EtOH = 10:1) to give the free base of 4 (0.64 g, 97%) as a colorless oil, bp 115–120°C/0.5 Torr (lit.^{16f}) bp 126.3°C/1 Torr. ¹H-NMR (CDCl₃) δ: 1.2–1.8 (6H, m), 2.14 (6H, s), 2.2–2.4 (2H, m), 3.26 (1H, br s), 4.63 (1H, t, *J* = 6 Hz), 7.1–7.4 (5H, m). MS *m/z*: 207 (M⁺). Treatment of this material with dry HCl gas in EtOH followed by removal of the solvent provided 4 as a colorless oil.

Reversal of ECS-Induced Impairment of a Passive Avoidance Response Ten male ddY mice, 6–7 weeks old and weighing 26–37 g, were used in each group. Assay was carried out according to a reported procedure²⁰ by using a two-compartment step-through passive avoidance apparatus consisting of an illuminated compartment (10 × 13 × 15 cm) and a darkened grid-floor-equipped compartment (25 × 13 × 23 cm) with an opening (3 × 4 cm) between the boxes. The passive avoidance training was given by application of 1.5 mA current for 3 s to the grid. Each test compound dissolved in physiological saline was dosed intraperitoneally 1 h before the training. Immediately after the training, ECS (20 mA, 0.5 s) was administered to the eyes, then after 24 h, retention of the inhibitory avoidance response was measured over

a period of 300 s.

Antihypoxic Activity Ten female ddY mice (6 weeks old) were used in each group. Two mice were placed in a 300 ml glass container into which a 4:96 (v/v) mixed gas of O₂ and N₂ was passed continuously at a flow rate of 5 l/min. A test compound was orally administered 30 min before this treatment. Time in seconds to respiratory cessation was recorded as the survival time.

Reversal of CO₂-Induced Impairment of a Passive Avoidance Response Ten male ddY mice (6–7 weeks old) were used in each group. This assay was performed according to a published procedure.²² Immediately after being given the passive avoidance training described in the foregoing section, each mouse was brought to suspended animation by placing it in a 300 ml glass container into which CO₂ gas was passed continuously at a flow rate of 5 l/min for 30 s. The mouse was then animated by artificial respiration, and a test compound was administered orally. Retention of the passive avoidance response was evaluated. Dosages for MED determination were: 3a = 1.0, 3.0, 10 and 30 mg/kg; tacrine = 0.1, 0.3, 1.0, 3.0, and 10 mg/kg; indeloxazine = 1.0, 3.0, 10, and 30 mg/kg; bifemelane = 10, 30, and 100 mg/kg. MED as determined by the Kruskal-Wallis test followed by the Mann-Whitney *U*-test were statistically significant (*p* < 0.05).

Determination of Serum and Brain Levels Five male Wistar rats (8 weeks old) were used in each group. Serum (1 ml) or a brain tissue homogenate prepared with 4 volumes of saline (1 ml) was treated with acetonitrile (1 ml), and the mixture was centrifuged to precipitate proteins. The supernatant was concentrated to dryness and the residue was dissolved in a 0.1 M sodium carbonate buffer of pH 10.5 (1 ml). The solution was applied to a Chem Elut column (Varian, 1.2 × 2.6 cm), which was eluted with CH₂Cl₂ (9 ml). The eluate was concentrated, and the residue was dissolved in a 0.1 M phosphate buffer (pH 2) before extraction with hexane-AcOEt (1:1). The aqueous layer was separated by centrifugation and extracted with CH₂Cl₂ (5 ml × 2) after addition of sodium 1-heptanesulfonate (40 mg). The combined CH₂Cl₂ solution was concentrated, and the residue was analyzed by HPLC using an ODS-II column (4 mm × 15 cm) and with the solvent system of acetonitrile–0.5 M phosphate buffer (pH 3)–0.5 M C₆H₁₃SO₃Na–H₂O, 14:2:1:83 for serum samples and 12:5:1:82 for brain samples.

Acknowledgment The authors are grateful to Professor E. Yoshii, Toyama Medical and Pharmaceutical University, for his help and useful suggestions during the preparation of the manuscript.

References and Notes

- 1) Marchbanks R. M., *J. Neurochem.*, **39**, 9–15 (1982).
- 2) Adolfsson R., Gotterfries C. G., Roos B. E., Winbland B., *Br. J. Psychiatry*, **135**, 216–223 (1979).
- 3) Summers W. K., Majovski L. V., Marsh G. M., Tachiki K., Kling A., *N. Engl. J. Med.*, **315**, 1241–1245 (1986).
- 4) Shutske G. M., Pierrat F. A., Kapples K. J., Cornfeldt M. L., Szwczak M. R., Huger F. P., Bores G. M., Haroutunian V., Davis K. L., *J. Med. Chem.*, **32**, 1805–1813 (1989).
- 5) Tarot N., Sunderland T., Weingartner H., Murphy D. L., Welkowitz J. A., Thompson K., Cohen R. M., *Psychopharmacology*, **91**, 489–495 (1987).
- 6) a) Kameyama M., *Dementia*, **8**, 484–485 (1994); b) Summers W. K., Kaufman K. R., Altman F., Jr., Fischer J. M., *Clin. Toxicol.*, **16**, 269–282 (1980); c) Wilcock G. K., Surmon D., Forsyth D., Morgan R., *Lancet*, **2**, 1305 (1988); d) Tariot P. N., Sunderland T., Weingartner H., Murphy D. L., Welkowitz J. A., Thompson K., Cohen R. M., *Psychopharmacology*, **91**, 489–495 (1987).
- 7) Siesjo B. K., *J. Cereb. Blood Flow Metab.*, **1**, 155–185 (1981).
- 8) Frieder B., Allweis C., *Behav. Biol.*, **22**, 178–189 (1978).
- 9) Schaffler K., Klausnitzer W., *Alzheim.-Forsch.*, **38**, 288–291 (1988).
- 10) Rossignol P., Margarret E. I., *Trend Science*, **1**, 287–289 (1980).
- 11) Yamamoto M., Shimizu M., Harada M., Terai M., Yamaguti T., *Kiso To Rinsyo*, **19**, 4563–4583 (1985).
- 12) Tobe A., Egawa M., Hashimoto N., *Folia Pharmacol. Japon.*, **81**, 421–429 (1983).
- 13) Sarai K., *Rinsyo To Kenkyu*, **64**, 1138–1143 (1987).
- 14) Shimizu M., *Nichidokuihou*, **36**, 336–343 (1991).
- 15) Fries D. S., Andracko J., *J. Med. Chem.*, **20**, 1250–1254 (1977).
- 16) a) Harada M., Maeda H., *Biochem. Pharmacol.*, **28**, 2645–2651 (1979); b) Ohizumi Y., Takahashi M., Tobe A., *Br. J. Pharmacol.*, **75**, 377–382 (1982).

- 17) a) Legheand J., Cuisinaud G., Sabbagh M., Pabiot M. N., Seccia M. M., Cier A., *Ann. Pharm. Fr.*, **35**, 45—51 (1977); b) Grail G. F., Tenenbaum L.E., Tolstouhov A. V., Duca C. J., Reinhard J. F., Anderson F. E., Scudi J. V., *J. Am. Chem. Soc.*, **74**, 1313—1315 (1952); c) Maillard J., Langlois M., Meingan J. P., Remond G., Jolly R., *Chim. Ther.*, **5**, 1—9 (1970); d) Bottari F., Macchia B., *Gazz. Chim. Ital.*, **92**, 165—173 (1962); e) Fries D. S., Andraško J., *J. Med. Chem.*, **20**, 1250—1254 (1977); f) Vasileva T. T., Cherkasova E. M., Korolkova T. M., Borisova E. Y., Kost T. A., Kozlenkova R. V., *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1970**, 2654—2656.
- 18) Ruff R. L., *Am. J. Psychiatry*, **137**, 1615—1616 (1980).
- 19) Cumin R., Bandle E. F., Gamuzu E., Haefely W. E., *Psychopharmacology*, **78**, 104—111 (1982).
- 20) Spignol G., Pepeu G., *European J. Pharmacol.*, **126**, 253—257 (1986).
- 21) Amami K., Yamamoto Y., Setoguchi M., *Nippon Yakurigaku Zasshi*, **85**, 71—77 (1985).
- 22) Yamazaki N., Shintani M., Saji Y., Nagawa Y., *Jpn. J. Psychopharmacol.*, **5**, 1—9 (1985).
- 23) Suzuki H., Imamura K., Kitamura K., Yoshida T., Hanada T., Sakurai Y., Miki H., *Kiso To Rinsyo*, **19**, 223—235 (1985).
- 24) Toshida K., Suzuki Y., Takechi M., Kojima Y., *Oyo Yakuri*, **31**, 587—600 (1986).