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Pharmacology of amineptine, an antidepressant agent acting on the dopaminergic system: a review

Silvio Garattini

Istituto Mario Negri, Via Eritrea 62, I-20157 Milan, Italy

Amineptine is a tricyclic antidepressant agent with a unique capacity to reduce dopamine uptake selectively *in vitro*: this effect is also obtained *in vivo*. *In vivo*, amineptine increases striatal homovanillic acid without affecting the levels of other metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine. However, relatively high doses of amineptine preferentially lower the extracellular DOPAC level, assessed by pulse voltammetry, in the nucleus accumbens but not in the striatum. Microdialysis techniques confirm an increase in extracellular dopamine in various brain areas (striatum, nucleus accumbens and frontal cortex) and an increase in extracellular noradrenaline in the frontal cortex and dorsal hippocampus. Chronic treatment with amineptine induces downregulation of dopamine D_2, β- and α_2-adrenergic receptors. Amineptine enters the brain and its pharmacological effects are probably induced by the unchanged drug, rather than its two main metabolites.

Keywords: Amineptine, antidepressants, dopamine uptake, noradrenaline uptake, receptor downregulation

INTRODUCTION

Amineptine differs from other tricyclic agents because of its 7-aminoheptanoic acid side-chain, shown in Fig. 1. The drug is rapidly absorbed and metabolized to form two major metabolites through β-oxidation of the side-chain, giving rise to a tricyclic agent with a 5-aminoheptanoic or 3-aminopropionic acid (Fig. 1; Sbarra *et al.*, 1979, 1981). In addition, five other metabolites, resulting from transformation of the side-chain and hydroxylation of the dibenzocycloheptyl ring on carbon atom C10, have been detected (Grislain *et al.*, 1990). In rats, amineptine enters the brain without showing a selective distribution between different brain areas (Sbarra *et al.*, 1979). In humans, the half-life of amineptine is 0.8 h, while that of the major metabolite (the 5-amino-heptanoic acid derivative) is 2.5 h. The half-life does not change with repeated treatment, and is similar in younger adults and in the elderly (Riche *et al.*, 1989) and in patients with liver impairment (Tsaconas *et al.*, 1989).

Pharmacologically, amineptine has mild stimulant activity (Samanin *et al.*, 1977; Vassout *et al.*, 1993) and a clear effect in a number of antidepressant tests, including antireserpine (Poignant, 1979) and anti-immobility activities (Borsini *et al.*, 1981). It increases exploratory activity in mice (Poignant, 1979), and improves the social behaviour of the recessive monkey (Poignant and Avril, 1978).

Amineptine has aroused interest because of its neurochemical peculiarities and the apparent rapidity of its effects in clinical trials (Billion *et al.*, 1979; Bornstein, 1979; Deniker *et al.*, 1982; Kemali, 1989; Rampello *et al.*, 1991; Dalery *et al.*, 1992). The drug is well tolerated, with a potency of effect comparable to that of the classic antidepressant agents. A considerable number of studies have investigated the mechanism of action of amineptine on central monoaminergic systems. *In vitro* studies with rat brain synaptosomes (Ceci *et al.*, 1986) have established that amineptine inhibits the uptake of dopamine and, to a lesser extent, noradrenaline, without affecting the uptake of serotonin (5-hydroxytryptamine, 5-HT). The inhibition exerted by amineptine was shared, although to a lesser extent, by its two metabolites. The release of monoamines by amineptine *in vitro* was limited to dopamine, without any effect on noradrenaline and 5-HT; again, the two metabolites were less effective than the parent drug. Amineptine released dopamine more efficiently in reserpinized synaptosomes, suggesting a preferential release of dopamine from a small extragranular pool (Ceci *et al.*, 1986). However, it was about 10 times less potent than amphetamine for dopamine release, and its effect on inhibition of dopamine uptake was seen at lower concentrations than was stimulation of dopamine release (Ceci *et al.*, 1986).

The effects of amineptine and reference drugs on the uptake and release of monoamines are summarized in Table 1. These were confirmed (Bonnet *et al.*, 1987) using [^{3}H]-GBR 12783, a compound that binds specifically to a component of the dopamine uptake complex. Amineptine had no effect on a number of receptors, as labelled by the following ligands: [^{3}H]-5-HT, [^{3}H]-spiroperidol (cortex and striatum), [^{3}H]-ADTN, [^{3}H]-WB 4101, [^{3}H]-clonidine, [^{3}H]-dihydroalprenolol, [^{3}H]-γ-aminobutyric acid, [^{3}H]-mepy-

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Table 2. Dihydroxyphenylaceti c acid (DOPAC) and homovanillic acid (HVA) levels in limbic area and striatum of rats at different times after the administration of amineptine at 40 mg/kg intraperitoneally

	Limbic area				Striatum			
	DOPAC		HVA		DOPAC		HVA	
Min	ng/g	%	ng/g	%	ng/g	%	ng/g	%
0	460 ± 25	100	204 ± 12	100	1010 ± 60	100	530 ± 40	100
15	381 ± 10	83*	196 ± 10	96	1030 ± 70	102	560 ± 40	106
30	405 ± 23	88	242 ± 16	119	890 ± 50	88	630 ± 30	119
60	402 ± 26	87	264 ± 8	130**	1150 ± 30	113	880 ± 63	167**

Data are means ± SEM of six determinations. *$P < 0.05$, **$P < 0.01$. Data from De Simoni *et al.* (1986).

Table 3. Effect of amineptine on depletion of dopamine and noradrenaline induced by 6-hydroxydopamine (6-OHDA) in rat brain

Treatments (mg/kg intraperitoneally)	Dopamine (ng/g)	Noradrenaline (ng/g)
Vehicle (controls)	1.100 ± 60	350 ± 15
6-OHDA	430 ± 20**	62 ± 10**
Amineptine 10 + 6-OHDA	580 ± 60	59 ± 9
Amineptine 20 + 6-OHDA	830 ± 70††	85 ± 12
Amineptine 40 + 6-OHDA	830 ± 80††	80 ± 10
d-Amphetamine 5 + 6-OHDA	850 ± 60††	220 ± 13††

The rats were treated with amineptine or *d*-amphetamine 1 h before 6-OHDA, which was injected intraventricularly at a dose of 300 µg in 20 µl. They were killed by decapitation 10 days later. Data are means ± SEM of six determinations. Statistical significance was analysed by a modification of Dunnett's test: **$P < 0.01$, versus controls; ††$P < 0.01$, versus 6-OHDA.

dose-dependent (1.25–20 mg/kg intraperitoneally), lasted about 60 min, and was not accompanied by changes in the dopamine metabolites, DOPAC and homovanillic acid. It was also reported that the increase in extracellular dopamine induced by amineptine depends on neuronal action potentials, as shown by the blockade induced by tetrodotoxin, a blocker of voltage-dependent sodium conductance (Narahashi, 1974). Furthermore, amineptine's effect on dopamine was dependent on the local concentration of the drug, as shown by the increase in extracellular dopamine in striatum and nucleus accumbens when amineptine was infused in the microdialysis tube (Invernizzi *et al.*, 1992). At 10 and 20 mg/kg, amineptine significantly raised dopamine extracellular levels in the frontal cortex also, a result at variance with the observation that other specific dopamine uptake blockers such as GBR 12909 have no effect on dopamine output in the frontal cortex (Carboni *et al.*, 1990). In these experiments, amineptine surprisingly raised extracellular noradrenline in the frontal cortex and in the dorsal hippocampus (Invernizzi *et al.*, 1992; Fig. 2). This contrasts with its low activity on noradrenaline uptake *in vitro* (Table 1) and with the lack of effect against the depletion of brain noradrenaline induced by 6-OHDA *in vivo* (Table 3). Further studies will be needed to explain the effect of amineptine on noradrenaline in the frontal cortex, an action similar to that induced by desipramine (Carboni *et al.*, 1990). Therefore, amineptine is similar to desipramine in increasing noradrenaline and dopamine in the frontal cortex, but it differs in its capacity to raise the dopamine level in the nucleus accumbens and striatum.

If amineptine enhances dopaminergic transmission through its dual effect as a releaser and inhibitor of dopamine uptake, stimulation of dopaminergic transmission should result in a feedback mechanism, leading to reduced synthesis of dopamine (Ponzio *et al.*, 1981). This was investigated by following the accumulation of L-dopa in the striatum and limbic areas after blockade of L-dopa decarboxylase. This study showed that amineptine did indeed reduce the accumulation of L-dopa, indicating a compensatory decrease of dopamine synthesis (Ponzio *et al.*, 1986).

Since antidepressant agents do not act acutely, but require chronic treatment to produce their effect, changes in monoaminergic transmission were investigated after chronic amineptine treatment. After 3 weeks of daily treatment, amineptine lost its effect on brain dopamine metabolism, since a challenge with 40 mg/kg did not elicit the usual increase in striatum homovanillic acid. However, dopamine release by amineptine *in vitro*, after chronic treatment *in vivo*, was slightly increased (from 14.6 ± 1.1 to 18.9 ± 1.1%). An interesting observation was that the basal dopamine uptake of synaptosomes from rats chronically treated with amineptine was lower (2.99 ± 0.20 pmol/min per mg protein) than in normal synaptosomes (3.53 ± 0.20 pmol/min per mg protein), while dopamine uptake was inhibited less by amineptine after chronic treatment (Ceci *et al.*, 1986).

Because of the changes in monoamine receptors after chronic treatment with tricyclic antidepressants, amineptine was also studied in this respect. Table 4 shows that chronic treatment with amineptine led to a significant de-

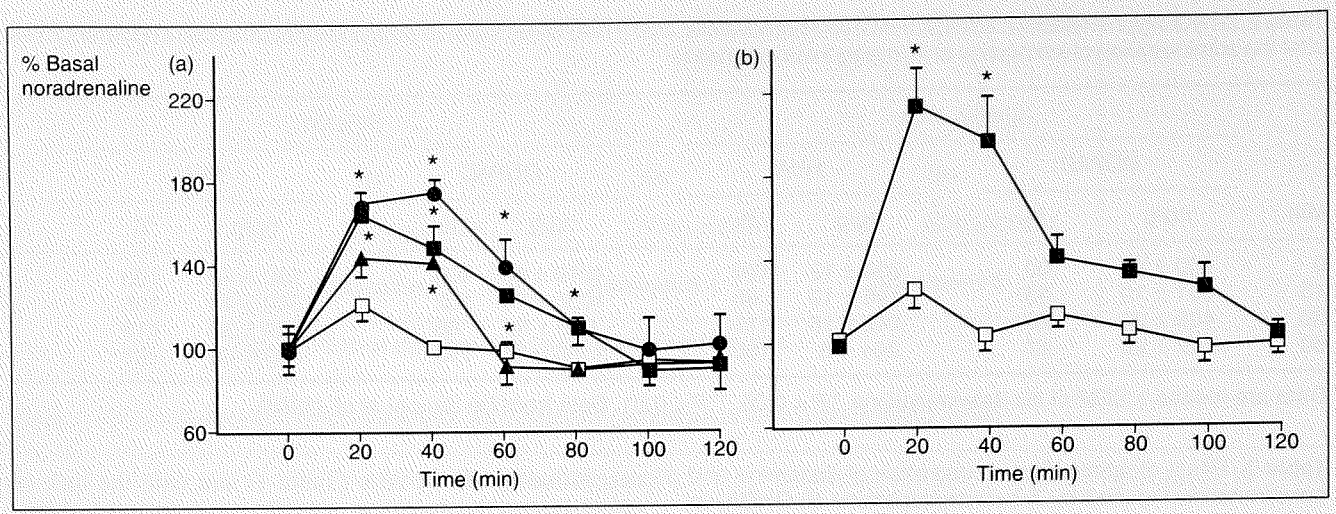

Fig. 2. Effects of amineptine on extracellular concentrations of noradrenaline in (a) frontal cortex and (b) dorsal hippocampi, shown as means ± SEM (not corrected for recovery) of four to five rats. Basal levels of noradrenaline in the frontal cortex were 54.2 ± 2.17, 52.94 ± 1.90, 56.27 ± 4.76 and 59.68 ± 6.64 fmol/20 min for vehicle, 5, 10 and 20 mg/kg amineptine, respectively. Basal levels of noradrenaline in the dorsal hippocampi were 33.92 ± 1.99 and 34.71 ± 2.72 fmol/20 min for vehicle and 10 mg/kg amineptine, respectively. Open squares, vehicle; closed triangles, amineptine at 5 mg/kg; closed squares, amineptine at 10 mg/kg; closed circles, amineptine at 20 mg/kg. $^*P < 0.05$ versus vehicle, by Tukey's test. From Invernizzi *et al.* (1992) with permission.

crease in the maximum number of D_2 receptors in striatum (ligand [^{3}H]-spiroperidol), of β-adrenergic receptors in the forebrain (ligand [^{3}H]-dihydroalprenolol) and of α_2-adrenergic receptors (ligand [^{3}H]-clonidine). No changes were found in 5-HT_1 and 5-HT_2 receptors (ligands [^{3}H]-5-HT in the forebrain and [^{3}H]-spiroperidol in cortex) or α_1-adrenergic receptors (ligand [^{3}H]-WB 4101; Ceci *et al.*, 1986). Amineptine is therefore similar to several other antidepressants in its ability to reduce β-adrenergic receptors, but differs in the downregulation of dopaminergic and α_2-adrenergic receptors. These changes reflect the stimulation of these receptors by amineptine. However, while there is evidence that amineptine is an indirect dopaminergic agonist for the downregulation of D_2-receptors, there is no evidence that it interferes directly with the central adrenergic system. The only exceptions are a blockade of noradrenaline uptake, measurable only *in vitro*, and the increase in extracellular noradrenaline in the frontal cortex and in the dorsal hippocampus described above. Whatever the mechanism involved, it is significant that the decrease induced by amineptine in the immobility test is inhibited by dopaminergic antagonists (sulpiride and haloperidol; Table 5), but not by other monoaminergic inhibitors (Borsini *et al.*, 1985).

DISCUSSION

Amineptine is an antidepressant agent with a predominant effect on the dopaminergic system. Its enhancing effect on dopamine is shown both *in vitro* and *in vivo*. *In vitro*, it inhibits dopamine uptake and increases dopamine release, with little effect on noradrenaline and none on 5-HT. *In*

Table 4. Effects of chronic amineptine on neurotransmitter receptor binding, shown as dissociation constants (K_D) and maximum binding (B_{max}) values

	5-HT_1	5-HT_2	Dopamine (D_2)	α_1-Noradrenaline	α_2-Noradrenaline	β-Noradrenaline
Vehicle						
K_D	4.6 ± 1.0	0.8 ± 0.02	0.4 ± 0.04	0.24 ± 0.06	2.4 ± 0.2	2.0 ± 0.03
B_{max}	18.4 ± 3.3	15.2 ± 0.7	19.9 ± 0.9	6.7 ± 0.8	6.7 ± 0.1	12.4 ± 0.6
Chronic amineptine						
K_D	4.1 ± 0.7	0.8 ± 0.04	0.3 ± 0.06	0.22 ± 0.06	2.6 ± 0.1	2.2 ± 0.1
B_{max}	18.9 ± 2.1	15.0 ± 0.3	15.3 ± 0.5**	6.3 ± 0.4	6.0 ± 0.2**	11.0 ± 0.9*

K_D (nmol/l) and B_{max} (pmol/g tissue) are means ± SD of five animals per group. 5-HT, 5-hydroxytryptamine (serotonin). Amineptine (20 mg/kg, intraperitoneally) was given twice a day for 15 days, and the rats were killed 3 days after the end of treatment. $^*P < 0.05$, $^{**}P < 0.01$, versus vehicle, by Student's *t*-test. Data from Ceci *et al.* (1986).

Table 5. Effect of various monoaminergic inhibitors on the reduction in immobility caused by 7 days' treatment with amineptine. Data from Borsini *et al.* (1981, 1985)

Drug	Monoamine inhibited	Effect on decrease in immobility test by amineptine
Sulpiride	Dopamine	Inhibition
Haloperidol	Dopamine	Inhibition
Phenoxybenzamine	α-Noradrenaline	No effect
Propranolol	β-Noradrenaline	No effect
Metergoline	5-Hydroxytryptamine	No effect

vivo, this drug raises the extracellular levels of dopamine in the striatum, nucleus accumbens and frontal cortex; it also raises extracellular noradrenaline levels in the frontal cortex and dorsal hippocampus. Amineptine has no direct effect on various monoamine receptors, but after continued treatment, it reduces the density of α_2- and α_β-adrenoceptors and D_2 receptors. The mechanism of action of amineptine is therefore distinct from that of other antidepressant agents. Whether this difference is significant in clinical practice can only be established by new controlled clinical studies.

REFERENCES

Billion A, Kamal S, Grivois J (1979) Ambulatory treatment of depressed states in a general hospital setting and in private practice. *Vol Thér Entretiens Bichat* 117–122.

Bonnet JJ, Chagraoui A, Protais P, *et al.* (1987) Interactions of amineptine with the neuronal dopamine uptake system: neurochemical *in vitro* and *in vivo* studies. *J Neural Transm* **69**:211–220.

Bornstein S (1979) Cross-over trial comparing the antidepressant effects of amineptine and maprotiline. *Curr Med Res Opin* **6**:107–110.

Borsini F, Bendotti C, Velkov V, *et al.* (1981) Immobility test: effects of 5-hydroxytryptaminergic drugs and role of catecholamines in the activity of some antidepressants. *J Pharm Pharmacol* **33**:33–37.

Borsini F, Pulvirenti L, Samanin R (1985) Evidence of dopamine involvement in the effect of repeated treatment with various antidepressants in the behavioural 'despair' tests in rats. *Eur J Pharmacol* **110**:253–256.

Carboni E, Tanda GL, Frau R, *et al.* (1990) Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up *in vivo* by noradrenergic terminals. *J Neurochem* **55**:1067–1070.

Ceci A, Garattini S, Gobbi M, *et al.* (1986) Effect of long-term amineptine treatment on pre- and postsynaptic mechanisms in rat brain. *Br J Pharmacol* **88**:269–275.

Dalery J, Rochat C, Peyron E, *et al.* (1992) Comparative study of the efficacy and acceptability of amineptine and fluoxetine in patients with major depression. *Encephale* **18**:257–262.

De Simoni MG, Dal Toso G, Algeri S, *et al.* (1986) Differences in the effect of the antidepressant amineptine on striatal and limbic DOPAC measured by HPLC-ECD and *in vivo* voltammetry. *Eur J Pharmacol* **123**:433–439.

Deniker P, Besancon G, Colonna L, *et al.* (1982) Extensive multicentric study of 1354 cases of depressed subjects treated with amineptine [in French]. *Encephale* **8**:355–370.

Grislain L, Gele P, Bromet N, *et al.* (1990) Metabolism of amineptine in rat, dog and man. *Eur J Drug Metab Pharmacokinet* **15**:339–345.

Invernizzi R, Pozzi L, Vallebuona F, *et al.* (1992) Effect of amineptine on regional extracellular concentrations of dopamine and noradrenaline in the rat brain. *J Pharmacol Exp Ther* **262**:769–774.

Jenck F, Moreau JL, Mutel V, *et al.* (1993) Evidence for a role of 5-HT_{1C} receptors in antiserotonergic properties of some antidepressant drugs. *Eur J Pharmacol* **231**:223–229.

Kemali D (1989) A multicenter Italian study of amineptine (Survector 100). *Clin Neuropharmacol* **12** (suppl 2):S41–S50.

Narahashi T (1974) Chemicals as tools in the study of excitable membranes. *Physiol Rev* **54**:814–869.

Poignant JC (1979) Pharmacological review on amineptine [in French]. *Encephale* **5**:709–720.

Poignant JC, Avril A (1978) Pharmacological studies on drugs acting on the social behaviour of the squirrel monkey. *Arzneimittelforschung* **28**:267–271.

Ponzio F, Achilli G, Perego C, *et al.* (1981) Differential effects of certain dopaminergic drugs on the striatal concentration of dopamine metabolites, with special reference to 3-methoxytyramine. *Neurosci Lett* **27**:61–67.

Ponzio F, Achilli G, Garattini S, *et al.* (1986) Amineptine: its effect on the dopaminergic system of rats. *J Pharm Pharmacol* **38**:301–303.

Rampello L, Nicoletti G, Raffaele R (1991) Dopaminergic hypothesis for retarded depression: a symptom profile for predicting therapeutical responses. *Acta Psychiatr Scand* **84**:552–554.

Riche C, Lachatre G, Guedes Y, *et al.* (1989) Pharmacokinetics of amineptine after single-dose, repeated treatment and study of the at-risk populations. *Clin Neuropharmacol* **12** (suppl 2):S32–S40.

Samanin R, Bernasconi S, Garattini S (1975) The effect of nomifensine on depletion of brain serotonin and catecholamines induced respectively by fenfluramine and 6-hydroxydopamine in rats. *Eur J Pharmacol* **34**:377–380.

Samanin R, Jori A, Bernasconi S, *et al.* (1977) Biochemical and pharmacological studies on amineptine (S 1694) and (+)-amphetamine in the rat. *J Pharm Pharmacol* **29**:555–558.

Sbarra C, Negrini P, Fanelli R (1979) Quantitative analysis of amineptine (S-1694) in biological samples by gas chromatography–mass fragmentography. *J Chromatogr* **162**:31–38.

Sbarra C, Castelli MG, Noseda A, *et al.* (1981) Pharmacokinetics of amineptine in man. *Eur J Drug Metab Pharmacokinet* **6**:123–126.

Tsaconas C, Padieu P, d'Athis P, *et al.* (1989) Gas chromatographic–mass spectrometric assessment of the pharmacokinetics of amineptine and its main metabolite in volunteers with liver impairment. *J Chromatogr* **487**:313–329.

Vassout A, Bruinink A, Krauss J, *et al.* (1993) Regulation of dopamine receptors by bupropion: comparison with antidepressants and CNS stimulants. *J Recept Res* **13**:341–354.