CNS Drug Reviews
Vol. 11, No. 3, pp. 273–288

Pharmacological Properties, Central Nervous System Effects, and Potential Therapeutic Applications of Atipamezole, a Selective α_2-Adrenoceptor Antagonist

Antti Pertovaara[1], Antti Haapalinna[2], Jouni Sirviö[2] and Raimo Virtanen[2]

[1]*Institute of Biomedicine/Physiology, University of Helsinki, Helsinki, Finland, and*
[2]*Orion Corporation, Orion Pharma, Turku, Finland*

Keywords: α_2-Adrenoceptor antagonist — Anesthesia — Atipamezole — Cognition — Epilepsy — Ischemic brain damage — MPV-1248 — Memory — Pain — Parkinson's disease — Sexual behavior.

ABSTRACT

Atipamezole is an α_2-adrenoceptor antagonist with an imidazole structure. Receptor binding studies indicate that its affinity for α_2-adrenoceptors and its α_2/α_1 selectivity ratio are considerably higher than those of yohimbine, the prototype α_2-adrenoceptor antagonist. Atipamezole is not selective for subtypes of α_2-adrenoceptors. Unlike many other α_2-adrenoceptor antagonists, it has negligible affinity for 5-HT_{1A} and I_2 bindings sites. Atipamezole is rapidly absorbed and distributed from the periphery to the central nervous system. In humans, atipamezole at doses up to 30 mg/subject produced no cardiovascular or subjective side effects, while at a high dose (100 mg/subject) it produced subjective symptoms, such as motor restlessness, and an increase in blood pressure. Atipamezole rapidly reverses sedation/anesthesia induced by α_2-adrenoceptor agonists. Due to this property, atipamezole is commonly used by veterinarians to awaken animals from sedation/anesthesia induced by α_2-adrenoceptor agonists alone or in combination with various anesthetics. Atipamezole increased sexual activity in rats and monkeys. In animals with sustained nociception, atipamezole increased pain-related responses by blocking the noradrenergic feedback inhibition of pain. In tests assessing cognitive functions, atipamezole at low doses has beneficial effects on alertness, selective attention, planning, learning, and recall in experimental animals, but not necessarily on short-term working memory. At higher doses atipamezole impaired performance in tests of cognitive functions, probably due to noradrenergic overactivity. Recent experimental animal studies suggest that atipa-

Address correspondence and reprint requests to: Dr. A. Pertovaara, Biomedicum Helsinki, Institute of Biomedicine/Physiology, P.O. Box 63, University of Helsinki, FIN-00014 Helsinki, Finland.
Fax: +358 (9) 19-12-53-02; E-mail: Antti.Pertovaara@helsinki.fi.

mezole might have beneficial effects in the recovery from brain damage and might potentiate the anti-Parkinsonian effects of dopaminergic drugs. In phase I studies atipamezole has been well tolerated by human subjects.

α_2-ADRENOCEPTORS IN THE CENTRAL NERVOUS SYSTEM

α_2-Adrenoceptors in the central nervous system are involved in mediating modulatory actions of norepinephrine. In central synapses, α_2-adrenoceptors may exist presynaptically, postsynaptically, or both. It has been proposed that α_2-adrenoceptors located in noradrenergic neurons mediate presynaptic autoreceptor functions, while α_2-adrenoceptors located in noradrenergic projection areas contribute to postsynaptic effects of norepinephrine (56). Blockade of α_2-adrenoceptors, particularly presynaptic autoreceptors in noradrenergic neurons, promotes the release of norepinephrine (55). Three subtypes of α_2-adrenoceptors (α_{2A}, α_{2B}, and α_{2C}) have been isolated and characterized in the brain (28). α_{2A} mRNA is most abundant in the locus coeruleus, but it is also widely distributed in the brainstem, cerebral cortex, septum, hypothalamus, hippocampus and amygdala (56). α_{2B} mRNA is observed only in the thalamus. α_{2C} mRNA is mainly localized to the basal ganglia, olfactory tubercle, hippocampus, and cerebral cortex (56). In the spinal cord, α_{2A}-adrenoceptors are predominantly found on central terminals of nociceptive primary afferent nerve fibers (61), whereas α_{2C}-adrenoceptors are located on axonal endings of excitatory interneurons in the spinal dorsal horn (35) or the lateral spinal nucleus (36). The distribution of α_2- adrenoceptor subtypes in the central nervous system has been confirmed using α_2-adrenoceptor subtype preferring ligands and tissue from genetically modified transgenic mice lines. Yohimbine is the prototype of synthetic α_2-adrenoceptor antagonists blocking the action of norepinephrine and that of other adrenergic compounds on α_2-adrenoceptors. In this review, we describe the pharmacological properties and central nervous system effects of atipamezole, which is a more recent and more selective α_2-adrenoceptor antagonist than yohimbine.

PHARMACOLOGICAL CHARACTERISTICS OF ATIPAMEZOLE

Atipamezole (MPV-1248) or 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole] is an α_2-adrenoceptor antagonist synthesized by Orion Pharma Ltd., Turku, Finland (Fig. 1; 55,67). In receptor binding studies, atipamezole has about 100 times higher affinity for α_2-adrenoceptors and an over 200 times higher α_2/α_1 selectivity ratio than either idazoxan or yohimbine (Table 1; 11,67). High potency and selectivity is apparent also in functional studies with isolated organ preparations (67). Atipamezole has high affinity for α_{2A}-, α_{2B}-, and α_{2C}-adrenoceptor subtypes in both humans and rodents, suggesting

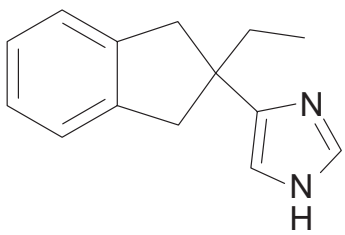

Fig. 1. Chemical structure of atipamezole.

that there are no species-specific differences in its effects (11). The affinity of atipamezole for α_{2D}-adrenoceptor, which is the species variant of the human α_{2A}-adrenoceptor, is in the same range as that for α_{2A}-adrenoceptor, whereas affinity of yohimbine is considerably higher for the α_{2A}- than the α_{2D}-adrenoceptor (11,48). Based on receptor binding studies and studies with isolated organ preparations, atipamezole has no affinity or effects on numerous other receptors, including β_1, β_2, H_1, H_2, 5-HT_1, 5-HT_2, muscarinic, dopamine D_2, tryptamine, $GABA_A$, opiate (μ, δ) and brain or heart benzodiazepine receptors (Tables 2 and 3). In contrast to many other α_2-adrenoceptor antagonists, atipamezole has negligible affinity for 5-HT_{1A} and imidazoline I_2 binding sites (11,54). Pharmacologic receptor specificity together with behavioral observations indicate that atipamezole does not markedly affect systems other than α_2-adrenoceptors (11). It should be noted, however, that the in-

TABLE 1. Affinity of atipamezole to α_1- and α_2-adrenoceptors in rat brain membranes

	α_2	α_1	α_2/α_1
Compound	K_i (nM)	K_i (nM)	Selectivity ratio
Atipamezole	1.6	13,300	8300
Idazoxan	148	3960	27
Yohimbine	130	5130	40

α_1, [^{3}H]prazosin displacement; α_2, [^{3}H]clonidine displacement.

TABLE 2. IC_{50} (M) values of atipamezole for 40 non-human (rodent) receptors

Receptor/binding site	IC_{50} for atipamezole	Receptor/binding site	IC_{50} for atipamezole
Adenosine A_1	$>10^{-5}$	Muscarinic M_2	$>10^{-5}$
Adenosine A_2	$>10^{-5}$	Muscarinic M_3	$>10^{-5}$
Adrenergic α_{1A}	1.3×10^{-6}	Nicotinic	$>10^{-5}$
Adrenergic α_{1B}	6.5×10^{-6}	NMDA	$>10^{-5}$
Adrenergic β_1	$>10^{-5}$	Kainate	$>10^{-5}$
Adrenergic β_2	$>10^{-5}$	AMPA	$>10^{-5}$
Dopaminergic D_1	$>10^{-5}$	Opiate μ	$>10^{-5}$
Dopaminergic D_2	$>10^{-5}$	Opiate δ	$>10^{-5}$
$GABA_A$	$>10^{-5}$	Opiate κ	$>10^{-5}$
GABAB	$>10^{-5}$	Chloride ionophore	$>10^{-5}$
Histaminergic H_1	$>10^{-5}$	Calcium channel T + L	$>10^{-5}$
Histaminergic H_2	$>10^{-5}$	Calcium channel N	$>10^{-5}$
Histaminergic H_3	5.4×10^{-7}	Sodium channel	$>10^{-5}$
5-HT_{1A}	$>10^{-5}$	Potassium channel	$>10^{-5}$
5-HT_{1B}	$>10^{-5}$	Glycine	$>10^{-5}$
5-HT_{1C}	$>10^{-5}$	MK-801	$>10^{-5}$
5-HT_{1D}	$>10^{-5}$	Sigma	4.3×10^{-6}
5-HT_2	$>10^{-5}$	Dopamine uptake	8.4×10^{-6}
5-HT3	2.5×10^{-5}	5-HT uptake	1.3×10^{-6}
Muscarinic M_1	3.7×10^{-6}	Norepinephrine uptake	$>10^{-5}$

TABLE 3. Displacement values (%) of atipamezole for 76 human receptors or binding sites

Receptors	Atipamezole HCl (1 μM)	Receptors	Atipamezole HCl (1 μM)
A_1 (h)	—	ML1	—
A_{2A} (h)	—	M1 (h)	17
A_3 (h)	23	M_2 (h)	11
α_1 (non-selective)	42	M_3 (h)	—
α_2 (non-selective)	99	M_4 (h)	17
β_1 (h)	—	M_5 (h)	11
β_2 (h)	—	NK_1 (h)	—
NE transporter (h)	37	NK_2 (h)	—
AT_1 (h)	10	NK_3 (h)	25
AT_2 (h)	—	Y_1 (h)	—
ANP	—	Y_2 (h)	—
Bombesin (non-selective)	—	NT_1 (h) (NTS_1)	—
B_2 (h)	—	δ (h)	—
CGRP (h)	—	κ	—
CB_1 (h)	—	μ (h)	—
CB_2 (h)	—	5-HT_{1A} (h)	19
CCK_A (h) (CCK_1)	—	5-HT_{1B}	—
CCK_B (CCK_2)	—	5-HT_{2A} (h)	11
D_1 (h)	—	5-HT_{2C} (h)	11
D_2 (h)	—	5-HT_3 (h)	13
D_3 (h)	—	5-HT_{5A} (h) (5-HT_{5a})	—
D_4 (h)	—	5-HT_6 (h) (5-HT_6)	26
D_5 (h)	—	5-HT_7 (h)	15
DA transporter (h)	25	5-HT transporter (h)	25
ET_A (h)	—	σ (non-selective)	—
ET_B (h)	—	sst (non-selective)	—
GABA (non-selective)	—	VIP_1 (h) ($VPAC_1$)	—
GAL_1 (h)	—	V_{1A} (h)	—
ET_A (h)	—	Ca^{2+} channel (L, verapamil site)	—
ET_B (h)	—	K_V^+ channel	—
GABA (non-selective)	—	SK_{Ca}^+ channel	—
BZD (central)	11	Na^+ channel (site 2)	—
BZD (peripheral)	—	Cl^- channel	—
GAL1 (h)	—	ORL1 (h)	—
PDGF	—	PACAP	—
IL-8B (h) (CXCR2)	—	PCP	—
TNF-α (h)	—	TXA_2/PGH_2 (h) (TP)	—
CCR1 (h)	—	PGI_2 (h) (IP)	11
H_1 (central)	37	P2X	—
H_2	—	P2Y	—

For atipamezole hydrochloride, the results are expressed as a percent inhibition of control specific binding (mean values; $n = 2$). —, An inhibition of less than 10%.

crease in norepinephrine release following blockade of α_2-adrenoceptors may indirectly activate other receptor systems in *in vivo* conditions (14).

Atipamezole completely reversed the mydriasis, sedation and hypothermia induced by medetomidine, a selective α_2-adrenoceptor agonist. A ten times higher dose of yohimbine was needed to produce an equally strong central α_2-adrenoceptor blocking effect than that of atipamezole (11). Neurochemical measurements in the brain have indicated that atipamezole causes a dose-dependent elevation in the concentration of 3-methoxy-4-hydroxyphenylethyleneglycol sulphate (MHPG-SO_4), a metabolite of norepinephrine, indicating increased turnover rate of norepinephrine (Table 4; 11,14,55). Interestingly, atipamezole increased turnover rate of norepinephrine significantly more in the brain of aged (24 months old) than in adult control (3 months old) rats (Table 4; 14). Furthermore, atipamezole tended to increase the turnover rate of 5-HT and dopamine, particularly in the aged animals (Table 4; 14).

When compared with equally effective α_2-antagonizing doses in the rat mydriasis model, either atipamezole or yohimbine increased the central norepinephrine turnover rate to the same extent (11). In contrast, while yohimbine significantly increased the central turnover rate of dopamine and decreased that of 5-HT, atipamezole at an equally effective dose in the mydriasis test had no significant effect on the turnover rates of dopamine or 5-HT (11).

TABLE 4. The effect of atipamezole (0.3 mg/kg s.c.) on the levels, including the main metabolites (nmol/g), and the turnover rate of norepinephrine (NE), 5-hydroxytryptamine (5-HT) and dopamine (DA) in the brains of adult and aged rats at three hours after treatment

Age/treatment	NE	MHPG-SO_4	MHPG-SO_4/NA	5-HT	5-HIAA	5-HIAA/5-HT	DA	HVA	HVA/DA
Adult/control	3.48 ± 0.16	0.42 ± 0.02	0.12 ± 0.01	2.59 ± 0.05	1.54 ± 0.02	0.60 ± 0.02	5.69 ± 0.03	0.42 ± 0.02	0.074 ± 0.003
Adult/atipamezole	3.20 ± 0.07	0.53 ± 0.02[a]	0.16 ± 0.01[a]	2.45 ± 0.07	1.63 ± 0.02	0.67 ± 0.02	5.92 ± 0.06[a]	0.46 ± 0.02	0.077 ± 0.005
Aged/control	3.53 ± 0.08	0.44 ± 0.01	0.12 ± 0.01	2.93 ± 0.01[b]	1.77 ± 0.05[b]	0.60 ± 0.02	5.55 ± 0.08	0.32 ± 0.01[b]	0.058 ± 0.002[b]
Aged/atipamezole	3.45 ± 0.03	0.72 ± 0.03[ac]	0.21 ± 0.01[ac]	2.78 ± 0.05[c]	2.18 ± 0.16[a]	0.79 ± 0.06[ac]	5.66 ± 0.1[c]	0.40 ± 0.03[a]	0.072 ± 0.005[a]
ANOVA									
$F =$	2.13	37.64	38.81	15.4	14.17	7.39	5.13	6.93	3.89
$P <$	0.2	0.0001	0.0001	0.0001	0.001	0.01	0.05	0.01	0.05

The results are expressed as mean ± S.E.M., $n = 5$ in the groups of adult rats and 4 in the groups of aged rats. ANOVA was followed by the Fisher's PLSD test. [a]Significant difference ($P < 0.05$) atipamezole group from the corresponding age control group; [b]significant difference between adult and aged control groups ($P < 0.05$); [c]significant difference between adult and aged atipamezole treated groups ($P < 0.05$); NE-norepinephrine, MHPG-SO_4 methoxyhydroxyphenylglycol sulfate; 5-HIAA, 5-hydroxyindoleacetic acid; DA, dopamine; HVA, homovanillic acid. Reproduced with permission from ref. 14.

GENERAL EFFECTS AND PHARMACOKINETICS

Atipamezole is well tolerated in rodents. In anesthetized, normotensive rats, the cardiovascular effects of atipamezole (0.01–1 mg/kg, i.v.) are rather modest. An initial, short-lasting hypertensive effect can be detected. The LD_{50} is >30 mg/kg after i.v., s.c., or i.p. administration to male or female mice and rats. In the LD_{50} experiments, animals died due to cardiac and/or pulmonary disturbances. Following s.c. administration, atipamezole is rapidly absorbed and distributed. Peak concentrations in tissues, including the brain, are two- to three-fold higher than the corresponding plasma levels (11,13). In rat, the elimination half-life is 1.3 h after s.c. administration of a single dose. Atipamezole undergoes extensive first-pass metabolism (11,13).

Phase I studies performed in humans indicate that atipamezole is well tolerated after a single i.v. or oral dose (10–100 mg; 21) as well as after single-dose buccal or sublingual administration (up to 40 mg; 17). Atipamezole is absorbed from the buccal mucosa to circulation with a bioavailability of about 33% (17). The time to reach peak concentration of atipamezole in plasma is about ¾ hours following buccal administration to humans (17). When up to 100 mg of atipamezole was infused i.v. to healthy volunteers, the elimination half-life of the drug was 1.7–2.0 h (21). Subjective drug effects, such as motor restlessness, sweating, shivering, coldness and increased salivation, were reported after the dose of 100 mg, but not after doses of 10 mg or 30 mg (21). The highest atipamezole dose (100 mg) increased systolic and diastolic blood pressure (mean increases 17 ± 7 and 14 ± 2 mm Hg, respectively) and plasma NE concentration in healthy human subjects, while lower doses (10 and 30 mg) had no significant effects on the blood pressure or the plasma NE level (21).

EFFECTS ON COGNITIVE AND RELATED FUNCTIONS

Anatomical and electrophysiological properties of noradrenergic neurons projecting from the locus coeruleus to the forebrain suggest that this system plays a role in selective attention, learning and memory (2). Therefore, α_2-adrenoceptor antagonists, like atipamezole, by stimulating endogenous norepinephrine release, potentially influence alertness, selective attention, distractibility, learning and memory consolidation. Effects of atipamezole on various cognition-related tasks have been assessed in a series of studies performed in experimental animals.

Normal cognitive functions result from the interaction of several neurotransmitter systems. Dysfunction of the noradrenergic system, possibly in conjunction with dysfunction of the cholinergic system, may underlie some aspects of age-related cognitive deficits (32). Quantitative electroencephalographic (EEG) analysis provides one way to measure this interaction, to predict deficits in cognitive functions, and also to study the effects of drugs on pathological EEG alternations. A lesion of a cholinergic nucleus (nucleus basalis or septal area), blockade of cholinergic receptors (e.g., scopolamine), or aging cause changes in EEG and deficits in the performance of different kinds of learning tests in animals. For example, an increase in slow wave activity and in the number neocortical high voltage spindles (HVS) provides an example of an alternation in the cortical EEG that has been associated with performance deficits in learning tests. Atipamezole atten-

uated nucleus basalis lesion-induced slowing in EEG as effectively as the cholinesterase inhibitor tacrine (49,51,53). The transfer of ascending sensory information through the thalamus to the cerebral cortex is suggested to be accurate only when the thalamic neurons are in the transfer mode and not in the burst-firing mode such as reflected by HVS activity. Both atipamezole (1–10 mg/kg s.c.) and tacrine were able to suppress HVS activity in aged and nucleus basalis-lesioned rats; i.e., these drugs decreased spontaneous activity in the thalamus and presumably ameliorated information transfer to the cerebral cortex (49, 51,53). Interestingly, a combination of atipamezole with a muscarine agonist, pilocarpine, or an anticholinesterase, tacrine, blocked HVS more effectively than any of these treatments alone (50–53).

Atipamezole (3 mg/kg s.c.) increased the baseline amplitude of the non-rhythmical hippocampal EEG in the dentate gyrus and increased slightly spike activity in the CA1 area in young and aged rats (64). Another study (65) showed that atipamezole (1 mg/kg s.c.) is able to shift population spike-field postsynaptic potential to the left in the dentate gyrus of adult rats and this effect was abolished following a lesion of the fimbria-fornix. These results suggest that stimulation of the noradrenergic system by atipamezole facilitates neuronal transmission in the dentate gyrus of the hippocampus. Atipamezole has also facilitated the excitability of granular cells in the rat hippocampus *in vivo* and improved intermediate-term memory retention in the radial arm maze task (70).

In the five-choice reaction time test atipamezole did not affect the performance of the average control rat under normal conditions. However, in a subpopulation of rats, seven of the eight rats with a poor choice accuracy improved their discriminative accuracy after atipamezole treatment (18). Similarly, atipamezole improved also the choice accuracy of poorly performing rats in a delayed (20 min) three-choice maze test (12). When the intensity (brightness) of visual stimuli was reduced in the five-choice reaction time test (i.e., an additional attentional load was placed), the choice accuracy of rats was markedly impaired (60). In this condition atipamezole significantly and dose-dependently improved the choice accuracy of the rats. The improved choice accuracy may be explained by atipamezole-induced increases in arousal and attention, although a possible facilitation in the processing of visual information still needs to be excluded (60).

The effects of atipamezole on maze performance and learning in adult and aged rats have been tested using the linear arm maze-learning test. In adult control rats, atipamezole enhanced acquisition of a linear-arm maze test (12). The aged animals with a decreased activity of choline acetyltransferase in the frontal cortex had clear performance deficits in the task when compared with adult control rats. Atipamezole-treated aged rats made significantly less errors than saline-treated ones and also the mean time/trial was shortened correspondingly (14).

The effect of atipamezole on memory consolidation has been studied in a food-rewarded task in the rat. The food-rewarded task consists of an elevated plus-maze with an illuminated, baited arm. The arms visited and time used until the rat finds food pellets is monitored for one week after the training trial. Atipamezole was injected s.c. immediately after the training trial and the memory retrieval was tested one week later. The animals receiving low doses of atipamezole remembered the task better than the saline-treated controls (12).

The effect of atipamezole on the performance in the delayed non-matching to position task (short-term memory of 0–30-sec duration) has been assessed in young and aged rats. Atipamezole was unable to improve short-term memory in this task (57,58). In line with

this, while medetomidine, an α_2-adrenoceptor agonist, improved performance of aged rats in a spatial delayed alternation task, neither systemic (4) nor intracortical (62) administration of atipamezole had any significant effect on spatial working memory performance. In aged non-human primates, atipamezole increased reaction times (47) but did not influence delayed response performance (46). In contrast, α_2-adrenoceptor agonists have improved short-term working memory in aged non-human primates (2,46).

In the Morris water maze, a test of spatial learning and memory, atipamezole did not improve performance (59). Curiously, some of the atipamezole-treated animals exhibited floating behavior in the water maze (59). Interestingly, atipamezole impaired the performance of rats in a two-way active avoidance-learning test after an acute treatment, but improved the learning after subchronic treatment (13). This change in behavior occurred in parallel with attenuation in the MHPG-SO_4-increasing effect of atipamezole. Notably, after acute treatment there was an increase in the number of failures in the atipamezole-treated group, resembling the behavioral depression state produced by uncontrollable stress. However, atipamezole did not disturb the avoidance performance of the fully trained rats (12,13). In the active avoidance-learning test, the test situation (fear of electric shock or forced swimming) itself may be so stressful that it could interfere with the performance of the animals in the test. For example, it has been reported that stress-sensitive rat strains exhibited floating behavior in a water T-maze or in a Morris water maze, without motivation to solve the task, whereas low stress responders quickly mastered the task (8,68). Accordingly, it has been reported that, after acute treatment, atipamezole potentiates reaction to novelty and stress, causing a decrease in exploratory activity and an impairment in shock avoidance learning (13). After subchronic treatment, however, there was a decrease in the NE release that was accompanied by lack of effect on exploratory behavior and improved learning in the active avoidance test (13).

Aging is associated with some decline in the function of the cholinergic system and anticholinergic drugs can cause confusion, especially in aged subjects (32,34). In rats, atipamezole (0.3 mg/kg) was able to alleviate hyperactive locomotion caused by the antimuscarinic agent scopolamine (34). It remains to be studied whether atipamezole might have similar beneficial effects in aged humans.

Effect of atipamezole on EEG and neuropsychological test performance has been assessed in healthy humans following i.v. administration of atipamezole at doses up to 0.1 mg/kg (33). Atipamezole decreased the spontaneous thalamocortical oscillation of EEG and improved focused attention (digit span task), but impaired divided attention (increased errors in word recognition task) of the human subjects (33). These atipamezole-induced changes may be explained by noradrenergic overactivity, although a contribution of other mechanisms, such as dopaminergic influence, cannot be excluded.

Based on above results it is proposed that atipamezole, at low doses, may have beneficial effects on alertness, selective attention, planning, learning and recall, but not necessarily on short term working memory. Effects on consolidation and plasticity in tasks assessing learning and memory are likely to be due to atipamezole-induced stimulation of NE release. The noradrenergic dose response curve is non-linear and at higher doses atipamezole-induced noradenergic overactivity may impair performance in cognitive functions, especially in stressful situations. This is in general agreement with numerous experimental and clinical studies obtained with other α_2-adrenoceptor antagonists such as yohimbine, idazoxan and efaroxan (32). It may also be suggested that achieving an optimal noradrenergic tone is likely to be beneficial for performance in various cognitive

tasks. If the baseline noradrenergic tone is low, its increase by atipamezole is likely to improve cognitive performance. In contrast, if the baseline noradrenergic tone is already at an optimal level or above it, e.g., due to stress, then the additional atipamezole-induced increase in the noradrenergic tone is likely to impair cognitive performance.

EFFECTS ON EMOTION-RELATED BEHAVIOR

Atipamezole-induced modulation of emotion-related behavior has been assessed in the rat and mice. In the open-field test, atipamezole at s.c. doses of 1.5–4.5 mg/kg decreased ambulation, rearing and defecation in a novel environment. In the two compartment exploratory test in rats, atipamezole increased the onset latency of exploration of a novel environment, without affecting the total amount of locomotor activity (23), but had no significant effect in mice (11). In the plus maze test in mice, atipamezole had no significant anxiogenic effect (6). In the staircase test in mice and rats, atipamezole potentiated the reaction to novelty and decreased exploratory behavior (11,13). In a familiar environment, atipamezole slightly stimulated behavior as seen in fixed ratio responding (11) and in the open field after habituation (13,34). Although atipamezole has had no clear effects in the traditional tests of anxiety such as the plus maze test, it has potentiated behavioral responses induced by novelty or aversive stimulation (11,13). Together these findings suggest that atipamezole has only mild effects on emotional behavior.

ATIPAMEZOLE AND ANESTHESIA

α_2-Adrenoceptor agonists, such as clonidine and (dex)medetomidine, have sedative-anesthetic properties and they have synergistic effects with general anesthetics such as halothane or isoflurane (22). Therefore, α_2-adrenoceptor agonists can be used as anesthesia adjuvants or even alone for minor surgery, particularly in veterinary medicine. Atipamezole has proved effective in rapidly reversing the anesthesia and immobilization as well as possible undesirable side effects induced by α_2-adrenoceptor agonists alone or in combination with a number of anesthetics such as isoflurane or ketamine (7,19,63). Thus, following administration of atipamezole the animals are fully awake within a few minutes after the operation, which is an additional advantage in minor veterinary surgery. Atipamezole is registered for veterinary use in several European countries and the USA to reverse sedation and other effects induced by the α_2-adrenoceptor agonist, medetomidine. In the presence of barbiturates, however, the capacity of atipamezole to reverse the sedative/anesthetic effects of α_2-adrenoceptor agonists may be reduced (24).

PAIN MODULATION

There is abundant evidence indicating that synthetic and endogenous noradrenergic compounds induce analgesia due to action on α_2-adrenoceptors. α_2-Adrenoceptors in the spinal cord have a critical role in mediating noradrenergic analgesia, although supraspinally located α_2-adrenoceptors may contribute to suppression of some components of pain

(38,39). While α_2-adrenergic sedative/anesthetic actions may confound assessment of analgesia following systemic administration of α_2-adrenoceptor agonists, earlier microinjection results indicate that the spinal antinociceptive action of a selective α_2-adrenoceptor agonist dissociates from its supraspinal sedative/anesthetic effect (41). In non-painful conditions, the intrinsic noradrenergic activity in descending pain regulatory pathways is low, since α_2-adrenoceptor antagonists, including atipamezole, have weak effects in tests of baseline pain sensitivity in the rat (38). Baseline responses may be modulated by atipamezole as well as other α_2-adrenoceptor antagonists in some behavioral tests also in animals without sustained pain, but this test-specific modulation is rather due to action on motor expression of pain than modulation of pain sensitivity (25). Sustained pain, such as induced by formalin or capsaicin, activates the descending noradrenergic pain inhibitory circuitry reducing pain due to action on spinal α_2-adrenoceptors. In rats and mice with a sustained nociceptive stimulus, administration of atipamezole blocks the action of descending noradrenergic pain inhibitory pathways and leads to an increase of pain-related responses (9,31,40). In the rabbit, however, an α_2-adrenoceptor antagonist RX821002, markedly enhanced withdrawal reflexes, although there was no sustained nociceptive stimulation (5). This finding indicates that in some species the tonic adrenergic descending inhibition may be strong without sustained pain.

In contrast to their pain suppressive role at the spinal cord level, α_2-adrenoceptors appear to have a pronociceptive role in some brainstem sites. Namely, microinjection of atipamezole into the noradrenergic area of the caudal ventrolateral medulla attenuated hypersensitivity induced by neurogenic inflammation in the rat (30). Block of pronociceptive α_2-adrenoceptors supraspinally may explain the paradoxical antinociceptive effect induced by atipamezole under some experimental conditions (29).

SEXUAL BEHAVIOR EFFECTS OF ATIPAMEZOLE

Sexual behavioral effects of atipamezole have been assessed in rats and non-human primates. In male rats, atipamezole increased sexual activity at s.c. doses 0.1–0.3 mg/kg (66). Further studies in sexually naïve male rats have shown that while yohimbine at doses of 1–4 mg/kg s.c. had no effect on any measure of sexual motivation, atipamezole at doses of 0.1–0.3 mg/kg s.c. increased the time the male spent in the receptive female incentive zone, lengthened the visits to her and reduced the duration of visits to another male rat (3). These results suggest that atipamezole selectively enhances sexual incentive motivation. In male macaques, atipamezole produced a dose-related (0.01–0.3 mg/kg, i.m.) increase in the number of ejaculations (27). Aphrodisiac properties of atipamezole have been tested also in female macaques by observing the sexual behavior of the female with a male (Fig. 2). Following i.m. administration to the female, atipamezole dose-dependently (0.03–0.3 mg/kg) increased the number of short-time mountings and copulations (42). This result indicates that atipamezole administered to the female increases sexual behavior of the male with the female. A plausible explanation for this finding is that atipamezole increases sexual arousal in female macaques and this, possibly due to a change in psychosocial behavior of the female, triggers increased sexual activity in the male. Central α_2-adrenoceptors might play an important role in the aphrodisiac effects of atipamezole. This proposal is supported by the findings that α_2-adrenoceptors are

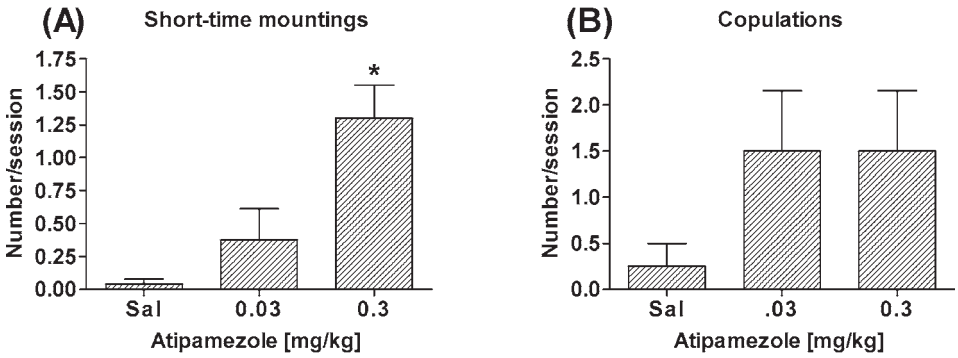

Fig. 2. Sexual behavior of the male with the female macaque following i.m. administration of atipamezole in the female. A, Short-time mountings; B, copulations. The error bars represent S.E.M. ($n = 4$). According to two-way analysis of variance, blinded, randomized administration of atipamezole to the female macaque induced an increase in short-time mountings and copulations. *$p < 0.05$ (Tukey's test; reference: the saline-treated group). Adapted with permission from ref. 42.

abundant in brain nuclei presumably involved in central regulation of sexual behavior such as the septum and the hypothalamus (56). Microinjection of NE or yohimbine into the brain increases sexual activity in the rat (10), and peripheral administration of atipamezole increases NE release in various brain regions, including those participating in the central control of sexual behavior (26,55).

ATIPAMEZOLE IN THE TREATMENT OF EXPERIMENTAL MODELS OF ISCHEMIA, BRAIN DAMAGE-INDUCED EPILEPTOGENESIS, AND PARKINSON'S DISEASE

There is earlier evidence indicating that pretreatment of experimental animals with an α_2-adrenoceptor agonist may reduce the development of brain damage in neuronal overactivity states, while pretreatment with an α_2-adrenoceptor antagonist, atipamezole, may potentiate the development of brain damage (16). Following development of brain damage, however, administration of an α_2-adrenoceptor antagonist may have a beneficial effect on the recovery from the damage. This is suggested by recent studies reporting that combined with training, atipamezole may improve behavioral performance of rats subjected to focal cerebral ischemia (1,44,45).

Brain trauma is a clear cause of epilepsy. In line with this, patients recovering from brain trauma have a decreased threshold to seizures. Therefore, it is important that compounds used during rehabilitation of brain-injured patients do not promote epileptogenesis. In an experimental model of epilepsy, chronic administration of atipamezole (100 μg/kg/h) from a subcutaneous minipump had a disease-modifying effect in rats recovering from status epilepticus-induced brain damage; i.e., when compared with the saline-treated controls, atipamezole-treated animals had a lower frequency of seizures and the seizure-frequency was non-progressive (43). Although these recent findings still warrant further confirmations, they raise the possibilities that atipamezole might improve motor recovery from brain trauma and it could even have a disease-modifying effect on

TABLE 5. The main pharmacological properties of atipamezole

High affinity for α_2-adrenoceptors and high α_2/α_1-adrenoceptor selectivity ratio
Not selective for subtypes of α_2-adrenoceptors
Negligible affinity for other neurotransmitter receptors, including 5-HT_{1A} and I_2
Rapidly absorbed and distributed (also through the blood-brain-barrier)
Elimination half-life 1.3–2.0 h (rat, human)
LD_{50} > 30 mg/kg (rat)
Up to 30 mg/subject no subjective or cardiovascular side effects (humans)

epileptogenesis induced by brain damage, so that the epilepsy that develops is milder and non-progressive.

In an experimental rat model of Parkinson's disease, unilateral lesion of the nigrostriatal system, atipamezole potentiated circling behavior induced by d-amphetamine, apomorphine or L-DOPA (15). This finding suggests that atipamezole may potentiate anti-Parkinsonian effects of dopaminergic drugs. Atipamezole-induced potentiation of striatal DA release (69) might explain its synergistic effect with L-DOPA. Interestingly, atipamezole potentiated the anti-Parkinsonian effects of dopaminergic drugs at a dose (0.3 mg/kg) that did not influence blood pressure, while it attenuated the sedative effect of apomorphine. Furthermore, atipamezole (0.3 mg/kg) was also able to reduce the sedative and hypotensive effects of apomorphine (15). Thus, atipamezole improved the efficacy of L-dopa and apomorphine in an animal model of Parkinson's disease and also reduced dopaminergic adverse effects on vigilance and cardiovascular functions. These results suggest that further investigations of the anti-Parkinsonian effects of α_2-adrenoceptor antagonists are warranted.

CONCLUSIONS

In the study of central nervous system functions, atipamezole provides a highly specific, selective and potent tool for blocking central α_2-adrenoceptors (Table 5). In veterinary practice, atipamezole has proved useful in rapidly reversing the anesthesia, immobilization and undesirable side effects induced by α_2-adrenoceptor agonists alone or in combination with other anesthetics. The effect of atipamezole on cognitive performance has varied depending on experimental parameters such as the dose, the type of test, stress related to the task, the duration of the drug infusion, and the age of the animal. At low doses, it has improved alertness, selective attention, planning, learning and recall of experimental animals, but not necessarily short-term working memory. At higher doses, atipamezole has impaired performance in cognitive tasks, probably due to overactivation of the noradrenergic system. Sexual activity of experimental animals was increased by atipamezole. Recent experimental animal studies suggest that atipamezole might have beneficial effects in recovery from brain damage and it also might enhance the anti-Parkinsonian effects and reduce adverse actions of dopaminergic compounds. Concerning potential clinical applications (Table 6), it is noteworthy that in phase I studies atipamezole has

TABLE 6. Potential indications for atipamezole

A selective tool in the study of α_2-adrenergic functions
Rapid reversal of α_2-adrenergic sedation/anesthesia
Aphrodisiac
Improvement of low cognitive performance associated with low alertness
Promotion of recovery from brain damage
Potentiation of anti-Parkinsonian effects of dopaminergic drugs

been well tolerated by human subjects. Thus, controlled clinical studies are warranted to test the potential therapeutic applications of atipamezole.

Acknowledgments. Antti Pertovaara has been supported by the Academy of Finland and the Sigrid Jusélius Foundation, Helsinki, Finland.

REFERENCES

1. Barbelivien A, Jolkkonen J, Rutkauskaite E, Sirviö J, Sivenius J. Differentially altered cerebral metabolism in ischemic rats by α_2-adrenoceptor blockade and its relations to improved limb-placing reactions. *Neuropharmacology* 2002;42:117– 126.
2. Berridge CW, Arnsten AFT, Foote SL. Noradrenergic modulation of cognitive function — clinical implications of anatomical, electrophysiological and behavioural studies in animal models. *Psychol Med* 1993;23: 557–564.
3. Bidtnes V, Bals M, Viitamaa T, Ågmo A. The adrenergic α_2-antagonist atipamezole enhances sexual incentive motivation in the male rat whereas yohimbine is ineffective. *Soc Neurosci Abstr* 2001;27:958.11
4. Carlson S, Tanila H, Rämä P, Mecke E, Pertovaara A. Effects of medetomidine, an alpha-2 adrenoceptor agonist, and atipamezole, an alpha-2 adrenoceptor antagonist, on spatial memory performance in adult and aged rats. *Behav Neural Biol* 1992;58:113–119.
5. Clarke RW, Harris J. RX 821002 as a tool for physiological investigation of α_2-adrenoceptors. *CNS Drug Rev* 2002;8:177–192.
6. Durcan MJ, Lister RG, Linnoila M. Behavioral effects of α_2 adrenoceptor antagonists and their interactions with ethanol in tests of locomotion, exploration and anxiety in mice. *Psychopharmacology* 1989;97: 189–193.
7. Ewing KK, Mohammed HO, Scarlett JM, Short CE. Reduction of isoflurane anesthetic requirement by medetomidine and its restoration by atipamezole in dogs. *Am J Vet Res* 1993;54:294–299.
8. Grauer E, Kapon Y. Wistar–Kyoto rats in the Morris water maze: Impaired working memory and hyper-reactivity to stress. *Behav Brain Res* 1993;59:147–151.
9. Green GM, Lyons L, Dickenson AH. Alpha$_2$-adrenoceptor antagonists enhance responses of dorsal horn neurones to formalin induced inflammation. *Eur J Pharmacol* 1998;347:201–204.
10. Gulia KK, Kumar VM, Mallick HN. Role of the lateral septal noradrenergic system in the elaboration of male sexual behavior in rats. *Pharmacol Biochem Behav* 2002;72:817–823.
11. Haapalinna A, Viitamaa T, MacDonald E et al. Evaluation of the effects of a specific alpha 2-adrenoceptor antagonist, atipamezole, on alpha 1- and alpha 2-adrenoceptor subtype binding, brain neurochemistry and behaviour in comparison with yohimbine. *Naunyn Schmiedeberg's Arch Pharmacol* 1997;356:570–582.
12. Haapalinna A, Sirviö J, Lammintausta R. Facilitation of cognitive functions by a specific α_2-adrenoceptor antagonist, atipamezole. *Eur J Pharmacol* 1998;347:29–40.
13. Haapalinna A, MacDonald E, Viitamaa T, Salonen JS, Sirviö J, Virtanen R. Comparison of the effects of acute and subchronic administration of atipamezole on reaction to novelty and active avoidance learning in rats. *Naunyn Schmiedeberg's Arch Pharmacol* 1999;359:194–203.
14. Haapalinna A, Sirviö J, MacDonald E, Virtanen R, Heinonen E. The effects of a specific α_2-adrenoceptor antagonist, atipamezole, on cognitive performance and brain neurochemistry in aged Fisher 344 rats. *Eur J Pharmacol* 2000;387:141- 150.

15. Haapalinna A, Leino T, Heinonen E. The α_2-adrenoceptor antagonist atipamezole potentiates anti-Parkinsonian effects and can reduce the adverse cardiovascular effects of dopaminergic drugs in rats. *Naunyn Schmiedeberg's Arch Pharmacol* 2003;368:342–351.
16. Halonen T, Kotti T, Tuunanen J, et al. Alpha$_2$-adrenoceptor agonist, dexmedetomidine, protects against kainic acid-induced convulsions and neuronal damage. *Brain Res* 1995;693:217–224.
17. Huupponen R, Karhuvaara S, Anttila M, Vuorilehto L, Scheinin M. Buccal delivery of an α_2-adrenergic receptor antagonist, atipamezole, in humans. *Clin Pharmacol Ther* 1995;58:506–511.
18. Jäkälä P, Sirviö J, Riekkinen P Jr, Haapalinna A, Riekkinen P. Effects of atipamezole, an α_2-adrenoceptor antagonist, on the performance of rats in a five-choice serial reaction time task. *Pharmacol Biochem Behav* 1992;42:903–907.
19. Jalanka H. The use of medetomidine, medetomidine-ketamine combinations and atipamezole at Helsinki Zoo — a review of 240 cases. *Acta Vet Scand Suppl* 1989;85:193–197.
20. Jolkkonen J, Puurunen K, Rantakomi S, Härkönen A, Haapalinna A, Sivenius J. Behavioral effects of the α_2-adrenoceptor antagonist, atipamezole, after focal cerebral ischemia in rats. *Eur J Pharmacol* 2000;400: 211–219.
21. Karhuvaara S, Kallio A, Scheinin M, Anttila M, Salonen JS, Scheinin H. Pharmacological effects and pharmacokinetics of atipamezole, a novel α_2-adrenoceptor antagonist — a randomized, double-blind cross-over study in healthy male volunteers. *Br J Clin Pharmacol* 1990;30:97–106.
22. Kaukinen S, Pyykkö K. The potentiation of halothane anaesthesia by clonidine. *Acta Anaesthesiol Scand* 1979;23:107–111.
23. Kauppila T, Tanila H, Carlson S, Taira T. Effects of atipamezole, a novel alpha 2-adrenoceptor antagonist, in open-field, plus-maze, two compartment exploratory, and forced swimming tests in the rat. *Eur J Pharmacol* 1991;205:177–182.
24. Kauppila T, Jyväsjärvi E, Pertovaara A. Effects of atipamezole, an α_2-adrenoceptor antagonist, on the anesthesia induced by barbiturates and medetomidine. *Anesth Analg* 1992;75:416–420.
25. Kauppila T, Jyväsjärvi E, Hämäläinen MM, Pertovaara A. The effect of selective α_2-adrenoceptor antagonist on pain behavior of the rat varies depending on experimental parameters. *Pharmacol Biochem Behav* 1998;59:477–485.
26. Laitinen KS, Tuomisto L, MacDonald E. Effects of a selective α_2-adrenoceptor antagonist, atipamezole, on hypothalamic histamine and noradrenaline release *in vivo*. *Eur J Pharmacol* 1995;285:255–260.
27. Linnankoski I, Grönroos M, Carlson S, Pertovaara A. Increased sexual behavior in male *Macaca arctoides* monkeys produced by atipamezole, a selective α_2-adrenoceptor antagonist. *Pharmacol Biochem Behav* 1992;42:197–200.
28. MacDonald E, Kobilka BK, Scheinin M. Gene targeting — homing in on α_2-adrenoceptor-subtype function. *Trends Pharmacol Sci* 1997;18:211–219.
29. Mansikka H, Pertovaara A. Influence of selective α_2-adrenergic agents on mustard oil-induced hyperalgesia in rats. *Eur J Pharmacol* 1995;281:43–48.
30. Mansikka H, Idänpään-Heikkilä JJ, Pertovaara A. Different roles of α_2-adrenoceptors of the medulla versus the spinal cord in modulation of mustard oil-induced hyperalgesia in rats. *Eur J Pharmacol* 1996;297:19–26.
31. Mansikka H, Lähdesmäki J, Scheinin M, Pertovaara A. α_{2A}-Adrenoceptors contribute to feedback inhibition of capsaicin-induced hyperalgesia. *Anesthesiology* 2004;101:185–190.
32. Marien, MR, Colpaert FC, Rosenquist AC. Noradrenergic mechanisms in neurodegenerative diseases: A theory. *Brain Res Rev* 2004;45:38–78.
33. Mervaala E, Alhainen K, Helkala EL, et al. Electrophysiological and neuropsychological effects of a central α_2-adrenoceptor antagonist in healthy volunteers. *Behav Brain Res* 1993;55:85–91.
34. Niittykoski M, Hakkarainen V, Puumala T, et al. Systemic administration of atipamezole, an α_2-antagonist, can reduce scopolamine-induced hyperactivity in rats. *Behav Pharmacol* 1997;8:465–470.
35. Olave MJ, Maxwell DJ. Neurokinin-1 projection cells in the rat dorsal horn receive synaptic contacts from axons that possess α_{2C}-adrenergic receptors. *J Neurosci* 2003;23:6837–6846.
36. Olave MJ, Maxwell DJ. Axon terminals possessing α_{2C}-adrenergic receptors densely innervate neurons in the rat lateral spinal nucleus which respond to noxious stimulation. *Neuroscience* 2004;126:391–403.
37. Penttilä J, Kaila T, Helminen A, et al. Effects of atipamezole, a selective alpha-adrenoceptor antagonist, on cardiac parasympathetic regulation in human subjects. *Auton Autacoid Pharmacol* 2004;24:69–75.
38. Pertovaara A. Antinociception induced by α_2-adrenoceptor agonists, with special emphasis on medetomidine studies. *Prog Neurobiol* 1993;40:691–709.
39. Pertovaara A. Antinociceptive properties of fadolmidine (MPV-2426), a novel α_2-adrenoceptor agonist. *CNS Drug Rev* 2004;10:117–126.

40. Pertovaara A, Bravo R, Herdegen T. Induction and suppression of immediate-early genes by a selective alpha-2-adrenoceptor agonist and antagonist following peripheral stimulation. *Neuroscience* 1993;54: 117–126.
41. Pertovaara A, Hämäläinen MM, Mecke E, Carlson S, Pertovaara A. Dissociation of the α_2-adrenergic antinociception from sedation following microinjection of medetomidine into the locus coeruleus in rats. *Pain* 1994;57:207–215.
42. Pertovaara A, Linnankoski I, Artchakov D, Rämä P, Carlson S. A potential aphrodisiac for female macaques. *Pharmacol Biochem Behav* 2004;79:137- 141.
43. Pitkänen A, Narkilahti S, Bezvenyuk Z, Haapalinna A, Nissinen J. Atipamezole, an α_2-adrenoceptor antagonist, has disease modifying effects on epileptogenesis in rats. *Epilepsy Res* 2004;61:119–140.
44. Puurunen K, Sirviö J, Koistinaho J, et al. Studies on the influence of enriched-environment housing combined with systemic administration of an α_2-adrenergic antagonists on spatial learning after global ischemia in rats. *Stroke* 1997;28:623–631.
45. Puurunen K, Jolkkonen J, Sirviö J, Haapalinna A, Sivenius J. An α_2-adrenergic antagonist, atipamezole, facilitates behavioral recovery after focal cerebral ischemia in rats. *Neuropharmacology* 2001;40:597–606.
46. Rämä P, Linnankoski I, Tanila H, Pertovaara A, Carlson S. Medetomidine, atipamezole, and guanfacine in delayed response performance of aged monkeys. *Pharmacol Biochem Behav* 1996;55:415–422.
47. Rämä P, Linnankoski I, Carlson S. The effects of α_2 agonist, medetomidine and its antagonist, atipamezole on reaction and movement times in a visual choice reaction time task in monkeys. *Brain Res Bull* 1997;44: 171–175.
48. Renouard A, Widdowson S, Millan MJ. Multiple α_2 adrenergic receptor subtypes. I. Comparison of [^{3}H]RX821002-labeled rat R alpha-2A adrenergic receptors in cerebral cortex to human H alpha-2A adrenergic receptor and other populations of alpha-2 adrenergic subtypes. *J Pharmacol Exp Ther* 1994;270: 946–957.
49. Riekkinen P Jr., Sirviö J, Jäkälä P, Lammintausta R, Riekkinen P. Effect of α_2 antagonists and an agonist on EEG slowing induced by scopolamine and lesion of the nucleus basalis. *Neuropharmacology* 1990;29: 993–999.
50. Riekkinen PJ, Sirviö J, Jäkälä P, Lammintausta R, Riekkinen P. Interaction between the alpha-2 noradrenergic and muscarinic systems in the regulation of neocortical high voltage spindles. *Brain Res Bull* 1990;25: 147–149.
51. Riekkinen PJ, Riekkinen M, Jäkälä P, Lammintausta R, Riekkinen P. Combination of atipamezole and tetrahydroaminoacridine/pilocarpine treatment suppresses high voltage spindle activity in aged rats. *Brain Res Bull* 1991;27:237–239.
52. Riekkinen PJ, Sirviö J, Jäkälä P, Riekkinen M, Lammintausta R, Riekkinen P. Effects of alpha-2 noradrenergic drugs and pilocarpine on the high voltage spindle activity of young and aged control and DSP-4-lesioned rats. *Physiol Behav* 1991;50:955–959.
53. Riekkinen PJ, Sirviö J, Valjakka A, Riekkinen M, Lammintausta R, Riekkinen P. Effects of atipamezole and tetrahydroaminoacridine on nucleus basalis lesion-induced EEG changes. *Brain Res Bull* 1991;27:231–235.
54. Savontaus S, Raasmaja A, Rouru J, et al. Anti-obesity effect of MPV-1743 A III, a novel imidazoline derivative, in genetic obesity. *Eur J Pharmacol* 1997;328:207–215.
55. Scheinin H, MacDonald E, Scheinin M. Behavioural and neurochemical effects of atipamezole, a novel α_2-adrenoceptor antagonist. *Eur J Pharmacol* 1988;151:35–42.
56. Scheinin M, Lomasney JW, Hayden-Hixson DM, et al. Distribution of α_2-adrenergic receptor subtype gene expression in rat brain. Mol *Brain Res* 1994;21:133–149.
57. Sirviö J, Lukkarinen K, Riekkinen P Jr, et al. The effects of atipamezole, and alpha-2 antagonist, on the performance of young and aged rats in the delayed nonmatching to position task. *Pharmacol Biochem Behav* 1991;39:1015–1019.
58. Sirviö J, Harju M, Riekkinen P Jr., Haapalinna A, Riekkinen PJ. Comparative effects of alpha-2 receptor agents and THA on the performance of adult and aged rats in the delayed non-matching to position task. *Psychopharmacology* 1992;109:127–133.
59. Sirviö J, Riekkinen P Jr, MacDonald E, Airaksinen M, Lammintausta R, Riekkinen PJ. The effects of alpha-2 adrenoceptor antagonist, atipamezole, on spatial learning in scopolamine-treated and aged rats. *J Neural Transm* 1992;4:99–106.
60. Sirviö J, Jäkälä P, Mazurkiewicz M, Haapalinna A, Riekkinen P Jr, Riekkinen PJ. Dose- and parameter-dependent effects of atipamezole, an α_2-antagonist, on the performance of rats in a five-choice serial reaction time task. *Pharmacol Biochem Behav* 1993;45:123–129.

61. Stone LS, MacMillan LB, Kitto KF, Limbird LE, Wilcox GL. The alpha-2A-adrenergic receptor subtype mediates spinal analgesia evoked by alpha-2-agonists and is necessary for spinal adrenergic-opioid synergy. *J Neurosci* 1997;17:7157–7165.
62. Tanila H, Rämä P, Carlson S. The effects of prefrontal intracortical microinjections of an alpha-2 agonist, alpha-2 antagonist and lidocaine on the delayed alternation performance of aged rats. *Brain Res Bull* 1996; 40:117–119.
63. Vainio O, Vähä-Vahe T. Reversal of medetomidine sedation by atipamezole in dogs. *J Vet Pharmacol Ther* 1990;13:15–22.
64. Valjakka A, Lukkarinen K, Koivisto E, et al. Modulation of EEG rhythmicity and spike activity in the rat hippocampus by systemically administered tetrahydroamonoacridine, scopolamine and atipamezole. *Brain Res Bull* 1991;26:739–745.
65. Valjakka A, Lukkarinen K, Koivisto E, Lammintausta R, Airaksinen M, Riekkinen P. Evoked field responses, recurrent inhibition, long-term potentiation and immobility-related nonrhythmical EEG in the dentate gyrus of fimbria-fornix-lesioned and control rats. *Brain Res Bull* 1991;26:525–532.
66. Viitamaa T, Haapalinna A, Heinonen E. The effect of the α_2-adrenoceptor antagonist, atipamezole, on the sexual behavior of sexually low-active male rats. *Behav Pharmacol* 1995;6:634–635.
67. Virtanen R, Savola JM, Saano V. Highly selective and specific antagonism of central and peripheral α_2-adrenoceptors by atipamezole. *Arch Int Pharmacodyn Ther* 1989;297:190–204.
68. Vogel WH, Harris N. Learning and memory of a water T-maze by rats selectively bred for low or high plasma catecholamine stress response. *Behav Neural Biol* 1991;56:113–117.
69. Yavich L, Sirviö J, Haapalinna A, Ylinen A, Männistö PT. Atipamezole, an α_2-adrenoceptor antagonist, augments the effects of L-DOPA on evoked dopamine release in rat striatum. *Eur J Pharmacol* 2003;462:83–89.
70. Ylinen A, Pitkänen M, Pussinen R, et al. A selective antagonists of alpha-2 adrenoceptors, facilitates the excitability of the dentate gyrus and improves the retention of the radial arm maze. *Soc Neurosci Abstr* 1996;22:680.

crease in norepinephrine release following blockade of α_2-adrenoceptors may indirectly activate other receptor systems in *in vivo* conditions (14).

Atipamezole completely reversed the mydriasis, sedation and hypothermia induced by medetomidine, a selective α_2-adrenoceptor agonist. A ten times higher dose of yohimbine was needed to produce an equally strong central α_2-adrenoceptor blocking effect than that of atipamezole (11). Neurochemical measurements in the brain have indicated that atipamezole causes a dose-dependent elevation in the concentration of 3-methoxy-4-hydroxyphenylethyleneglycol sulphate (MHPG-SO_4), a metabolite of norepinephrine, indicating increased turnover rate of norepinephrine (Table 4; 11,14,55). Interestingly, atipamezole increased turnover rate of norepinephrine significantly more in the brain of aged (24 months old) than in adult control (3 months old) rats (Table 4; 14). Furthermore, atipamezole tended to increase the turnover rate of 5-HT and dopamine, particularly in the aged animals (Table 4; 14).

When compared with equally effective α_2-antagonizing doses in the rat mydriasis model, either atipamezole or yohimbine increased the central norepinephrine turnover rate to the same extent (11). In contrast, while yohimbine significantly increased the central turnover rate of dopamine and decreased that of 5-HT, atipamezole at an equally effective dose in the mydriasis test had no significant effect on the turnover rates of dopamine or 5-HT (11).

TABLE 4. The effect of atipamezole (0.3 mg/kg s.c.) on the levels, including the main metabolites (nmol/g), and the turnover rate of norepinephrine (NE), 5-hydroxytryptamine (5-HT) and dopamine (DA) in the brains of adult and aged rats at three hours after treatment

Age/treatment	NE	MHPG-SO_4	MHPG-SO_4/NA	5-HT	5-HIAA	5-HIAA /5-HT	DA	HVA	HVA/DA
Adult/control	3.48 ± 0.16	0.42 ± 0.02	0.12 ± 0.01	2.59 ± 0.05	1.54 ± 0.02	0.60 ± 0.02	5.69 ± 0.03	0.42 ± 0.02	0.074 ± 0.003
Adult/atipamezole	3.20 ± 0.07	0.53 ± 0.02[a]	0.16 ± 0.01[a]	2.45 ± 0.07	1.63 ± 0.02	0.67 ± 0.02	5.92 ± 0.06[a]	0.46 ± 0.02	0.077 ± 0.005
Aged/control	3.53 ± 0.08	0.44 ± 0.01	0.12 ± 0.01	2.93 ± 0.01[b]	1.77 ± 0.05[b]	0.60 ± 0.02	5.55 ± 0.08	0.32 ± 0.01[b]	0.058 ± 0.002[b]
Aged/atipamezole	3.45 ± 0.03	0.72 ± 0.03[ac]	0.21 ± 0.01[ac]	2.78 ± 0.05[c]	2.18 ± 0.16[a]	0.79 ± 0.06[ac]	5.66 ± 0.1[c]	0.40 ± 0.03[a]	0.072 ± 0.005[a]
ANOVA									
F =	2.13	37.64	38.81	15.4	14.17	7.39	5.13	6.93	3.89
P <	0.2	0.0001	0.0001	0.0001	0.001	0.01	0.05	0.01	0.05

The results are expressed as mean ± S.E.M., $n = 5$ in the groups of adult rats and 4 in the groups of aged rats. ANOVA was followed by the Fisher's PLSD test. [a]Significant difference ($P < 0.05$) atipamezole group from the corresponding age control group; [b]significant difference between adult and aged control groups ($P < 0.05$); [c]significant difference between adult and aged atipamezole treated groups ($P < 0.05$); NE-norepinephrine, MHPG-SO_4 methoxyhydroxyphenylglycol sulfate; 5-HIAA, 5-hydroxyindoleacetic acid; DA, dopamine; HVA, homovanillic acid. Reproduced with permission from ref. 14.