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Research Article

The memory and learning enhancing effects of Atristamine

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Abstract

The object of the present study, 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (Atristamine), has been deeply studied as a promising antidepressant with the unique spectrum of additional neuropharmacological properties. Previously, the memory-enhancing effects of Atristamine have already been studied in the passive-avoidance test after scopolamine-induced amnesia in mice. Thus, the study of the effects of Atristamine on the spatial learning and memory in the Morris water maze under physiological conditions was the next logical step of our research.

According to the results obtained, Atristamine (100 mg/kg) has almost the same effect on the main markers of the memory-enhancing activity (the escape latency and distance moved) as Piracetam (300 mg/kg) and Phenibut (20 mg/kg) chosen as the well-studied and widely-used memory enhancers. The escape latency decreased in the Atristamine group by 3.2 times compared to the vehicle control group, whereas Piracetam and Phenibut caused a significant reduction of this indicator by 4.3 and 3.7 times, respectively. Moreover, the rats from the Atristamine group swam 5.1 times shorter distance to the platform in the probe trial compared to animals from the vehicle control group. The distance moved was 3-fold shorter in the Piracetam group and decreased by 5.2 times in the Phenibut group.

All drugs used in this study caused considerable changes of inter-quadrant preferences of animals. Based on the analysis of the inter-quadrant behaviour of rats, it has been found that there are considerable differences in search strategies associated, probably, with distinct mechanisms of the memory and learning enhancing action of the drugs used.

Keywords

2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one, Atristamine, the Morris water maze, the memory enhancing effect

Introduction

The present study was grounded on the experimental data of *in vivo* screening research of the series of 3-(N-R,R'-aminomethyl)-2-methyl-1H-quinolin-4-ones. They confirmed the high anti-amnesic activity of all compounds studied in the passive-avoidance test after scopolamine-induced anterograde amnesia (Shtrygol' et al. 2010; Podolsky et al. 2018). The object of the present study, 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (Fig. 1), attracted our attention, while in addition to the mnemotropic properties, it showed the excellent antidepressant activity in the tail suspension test in the dose of 100 mg/kg (Shtrygol' et al. 2010; Shtrygol' et al. 2012).

This compound was chosen as a leader for the in-depth study under the code name of "Atristamine". Currently, it is studied profoundly as a promising antidepressant.

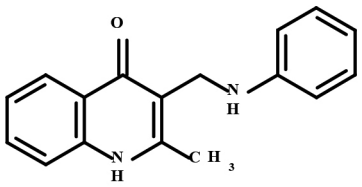

Figure 1. The structural formula of Atristamine (2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one).

The unique spectrum of additional neuropharmacological properties of Atristamine was revealed in numerous further experiments in parallel with the in-depth studies of the antidepressant effect of this molecule (Shtrygol' et al. 2012).

It has been found that Atristamine in the dose of 100 mg/kg possesses cerebroprotective properties discovered in the model of a mild traumatic brain injury in rats (Podolsky and Shtrygol' 2015). This fact correlates well with the antihypoxic effect of Atristamine found in the model of acute hypoxia with hypercapnia in mice (Podolsky et al. 2013; Shtrygol' et al. 2013) and the actoprotective activity in the weight-loaded forced swimming test in mice (Shtrygol' et al. 2013). Furthermore, Atristamine displayed a significant analgesic effect in the tail immersion test in mice (Podolsky and Shtrygol' 2017).

Memory-enhancing properties of Atristamine were previously studied in the passive-avoidance test after scopolamine-induced amnesia in mice. According to the results of two different experiments, the antiamnesic activity of Atristamine was 85.2% (Shtrygol' et al. 2010) and 89.7% (Podolsky and Shtrygol' 2016). The data suggest that scopolamine disrupts processes that are essential for formation of durable memories, whereas Atristamine has strong protective effects against anterograde amnesia produced by a cholinoblocker in mice (Shtrygol' et al. 2010; Podolsky and Shtrygol' 2016).

Predictably, the study of the effects of Atristamine on the spatial memory and learning under physiological conditions became the next logical step to our understanding of the "pharmacological nature" of this molecule.

Safe manoeuvring in the environment is crucial to survival of almost all species. This ability depends on learning and remembering locations. This complex capacity is encoded in the brain by two systems: one using distal cues (outside the organism) is called allocentric navigation and another using nearby proximal cues (self-movement and internal cues) is egocentric navigation. Allocentric navigation involves the hippocampus, entorhinal cortex and surrounding structures. This form of memory is assessed in animals using different paradigms, but the dominant form of assessment is the Morris water maze (MWM) (Vorhees and Williams 2014). Since the MWM was developed by Richard Morris in 1981, it became the most widely-employed behavioural test for assessing the spatial memory and learning in rodents (Wenk 2004). Thus, the aim of our study was experimental investigation of the effects of Atristamine on the spatial memory and learning using the Morris water maze paradigm.

Materials and methods

Chemicals and drugs

Atristamine (2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one) was synthesised from 2-methyl-1H-quinolin-4-one *via* aminomethylation and further interaction of the Mannich base obtained with aniline as described earlier (Zubkov et al. 2005). In this experiment, Atristamine was administered intragastrically (i.g.) in the dose of 100 mg/kg as an aqueous fine suspension stabilised with Tween-80.

Piracetam (2-(2-oxopyrrolidin-1-yl)acetamide) was chosen as the reference drug. This nootropic agent has been shown to improve the cognitive performance in a number of the animal model systems (Moran et al. 2002). Piracetam was used in the dose of 300 mg/kg intraperitoneally (i.p.) (Abdel-Salam et al. 2016) in the form of the solution for injection, 200 mg/ml (the trade name "Piracetam", Arterium, Ukraine).

Phenibut (4-amino-3-phenylbutanoic acid) was used as the second reference drug. In contrast to Piracetam, it belongs to nootropics with sedative and anti-anxiety properties (Lapin 2001). Phenibut was used in the dose of 20 mg/kg i.p. as a solution of the substance in saline.

The animal groups and treatment

Young (2-month-old) female Wistar rats (with the body weight of 120-150 g) were included in the present study. The animals were from the vivarium of the Central Research Laboratory (National University of Pharmacy, Kharkiv, Ukraine). Experiments were carried out in accordance with "Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes". All experimental protocols were approved by the Bioethics Commission of the National University of Pharmacy.

The rats were housed in standard polypropylene cages and kept at 20-26°C and 50% humidity in a well-ventilated room with a 12 h light/dark cycle with free access to food and water (Deacon 2006).

The animals were divided into 4 groups as follows:

1. vehicle control group (n=7) – animals treated with saline i.g. (10 ml/kg) one hour before experimental sessions;
2. Atristamine group (n=7) – rats treated with Atristamine (100 mg/kg, i.g.) one hour before experimental sessions;

3. Piracetam group (n=7) – rats treated with Piracetam (300 mg/kg, i.p.) one hour before experimental sessions;
4. Phenibut group (n=7) – rats treated with Phenibut (20 mg/kg, i.p.) one hour before experimental sessions.

The volume of liquid that the animals of all groups received was similar and equalled to 0.1 ml/10 g of the body weight.

The Morris water maze

The experiment was carried out in a dimly lit and soundproof test room. The Morris water maze consisted of a circular pool (120 cm in diameter and 55 cm in depth) that was filled with water (25°C) to a depth of 45 cm (Vogel 2008). Eight equally spaced coloured cues (made of plastic) with different geometry were disposed around the edge of the pool. An escape platform (9 cm in diameter) was situated in a fixed location, 1 cm above the water surface during the training sessions and at the level of the water surface during the "probe trial" (Garthe and Kempermann 2013).

The animals were trained in the MWM one hour after administration of drugs over two training sessions performed on consecutive days between 10:00 and 12:00 a.m. For each training trial, the animal was taken from the home cage and placed into the pool at the same location (the start position) with its head facing the centre of the water maze. The trial was started when the rat was released to the constant start position. After the rat found and climbed on to the platform, the session was stopped and the escape latency was recorded. During training trials, any rat that failed to find the platform in 180 s was guided to its location by the experimenter. At the end of the session, the animal was returned to the home cage.

Twenty-four hours after the second training session, a "probe trial" was used to assess the rats' spatial retention of the location of the platform. During this stage of the experiment, water was made opaque using powdered milk and the platform was levelled to the water surface (D'Hooge and De Deyn 2001).

Video tracking was performed with a video camera focused on the full diameter of the pool. Navigation parameters were analysed using the Noldus EthoVision XT 14 video tracking software (Noldus et al. 2001). The target quadrant (with the escape platform position) in software metrics was marked as the South-Western (SW).

Statistical analysis

The results were analysed using the "STATISTICA 10.0" software. Analysis of the data ranges using the Kolmogorov-Smirnov test and the Shapiro-Wilk normality test showed that there was sufficient evidence to reject the notion of a normal probability model.

Medians, 25% and 75% percentiles (upper and lower quartiles), as well as the arithmetic means traditionally used and their standard errors (M±SEM) were calculated. The comparison of the central tendencies of independent samples was performed by the Mann–Whitney U test. The level of statistical significance was considered to be $p < 0.05$.

Results and discussion

Analysis of the experimental data presented in Table 1 shows that all drugs significantly enhanced the memory and learning performance of rats compared to the vehicle control group in the probe trials. It was concluded by the changes of the main markers of the memory-enhancing activity – escape latency and distance moved. These indicators dramatically reduced in all experimental groups of animals. As can be seen from Table 1, Atristamine (100 mg/kg) has almost the same effect on these parameters as Piracetam (300 mg/kg) and Phenibut (20 mg/kg) that are well-studied and widely-used memory enhancers. The escape latency decreased in the Atristamine group by 3.2 times ($p < 0.05$) compared to the vehicle control group, whereas Piracetam and Phenibut caused a significant reduction of this indicator by 4.3 and 3.7 times, respectively.

Usually, the path length (distance moved) to the platform correlates well with escape latency. In the present experiment (Table 1), the rats from Atristamine group swam

Table 1. Effects of Atristamine, Piracetam and Phenibut on the memory and learning performance of rats in the MWM (probe trials); Q_{50} (Q_{25}–Q_{75}); M±SEM.

Parameter	Group of animals			
	Vehicle control, n=7	Atristamine, 100 mg/kg, n=7	Piracetam, 300 mg/kg, n=7	Phenibut, 20 mg/kg, n=7
Escape latency, s	103 (67–300)	30 (15–60)*	36 (14-55)*	45 (21-67)*
	168.4±44.8	52.0±21.6	39.1±12.5	44.7±8.0
Distance moved, cm	3911.4	543.5	566.4	686.7
	(1501.9–5973.3)	(377.7–1256.5)**	(368.3–1561.2)*	(326.7–1102.2)**
	3881.5±766.2	751.2±168.6	1277.3±540.6	746.0±175.5
Velocity, cm/s	30.0 (25.7–35.5)	22.0 (13.2–29.3)	32.9 (22.4–42.6)	16.3 (16.0–21.6)**/$$
	30.4±2.6	22.9±4.4	32.1±3.8	17.1±1.7
Meander, degree/cm	17.6 (15.2–168.8)	771.6 (35.3–2811.9)	20.9 (9.9–58.9)	221.1 (59.8–251.2) $
	87.4±36.0	1194.8±570.2	29.6±10.2	167.6±41.0

Notes. *, **, *** – significant with $p < 0.05$, $p < 0.01$ and $p < 0.001$ compared to the vehicle control group; $, $$ – significant with $p < 0.05$ and $p < 0.01$ compared to the Piracetam group (Mann–Whitney U test).

5.1 times shorter distance to the platform ($p < 0.01$) in the probe trial compared to animals from the vehicle control group. A similar situation was observed in other experimental groups – the distance moved was 3-fold shorter in the Piracetam group ($p < 0.05$) and decreased by 5.2 times in the Phenibut group ($p < 0.01$).

It should be noted that rats of Atristamine and Phenibut groups had a considerable greater amount of turning per distance unit (meander) when compared to the Piracetam and vehicle control groups shown the similar results. This may suggest either a different search strategy or a distinct exploratory response toward the environment (Tucker et al. 2018). This view can be supported by the analysis of the linear velocity of the Atristamine, Piracetam and Phenibut groups of animals. Rats in the Piracetam group had comparable velocity with that in the control group, whereas animals of Atristamine and Phenibut groups showed decreased results. This fact cannot be explained only by anti-anxiety properties of Atristamine and Phenibut (Lapin 2001). This phenomenon can be interpreted as a marker of the more confident and energy-saving strategy of the platform search. This is the evidence of improvement of the spatial memory and, consequently, the less energy consumption and purposeful behaviour.

The inter-quadrant analysis of the behaviour of animals was conducted in order to reveal some peculiarities of action of the drugs used (Tucker et al. 2018). The main parameters – the time spent in the quadrant and the frequency of appearance in the quadrant – were obtained using the EthoVision software. Based on these parameters the percentage of the time spent in the quadrant (%) and the average duration of one entry (s) were calculated. The average duration of one entry in seconds was calculated by the formula:

Average duration of one entry = Mean (Time spent in the quadrant) / Mean (Frequency of appearance)

The results of the inter-quadrant analysis of the behaviour of rats are presented in Table 2.

As can be seen from Table 2, rats of the control group had similar parameters in each quadrant without any pre-

Table 2. The inter-quadrant analysis of the behaviour of animals in the probe trials of the MWM; Q_{50} (Q_{25}–Q_{75}); M±SEM

Group	Parameter	In the quadrant			
		SW*	**SE**	**NW**	**NE**
Vehicle control, n=7	Time spent, s	29.3 (13.0–39.0)	26.0 (8.7–81.7)	27.7 (19.3–75.1)	28.4 (8.7–56.4)
		27.7±4.7	42.4±14.8	46.5±11.8	34.6±9.3
	Percentage of time, %	16.5	25.2	27.6	20.6
	Frequency of appearance	15 (9–17)	11 (5–24)	16 (7–26)	12 (10–35)
		13.0±1.9	14.4±3.7	18.0±3.5	19.4±4.7
	Average duration of one entry, s	1.7 (1.5–2.6)	2.9 (1.5–3.4)	2.8 (1.7–2.9)	1.7 (1.2–2.0)
		2.2±0.4	2.5±0.4	2.5±0.2	1.7±0.3
Atristamine, 100 mg/kg, n=7	Time spent, s	5.0 (1.7–6.3)	16.3 (9.7–47.9)	0 (0–0.7)	2.7 (0.3–5.0)
		5.1±1.5	**^^SW**	**^^SW + ^^SE**	**^^SE+^NW**
			39.9±18.7	0.4±0.2	2.8±0.9
	Percentage of time, %	9.8	76.7	0.7	5.4
	Frequency of appearance	2 (2–4)	6 (2–8)	0 (0–1)	4 (1–5)
		2.7±0.5	5.9±1.5	**^^SW + ^^SE**	**^NW**
				0.4±0.2	3.1±0.8
	Average duration of one entry, s	1.3 (0.4–3.0)	4.8 (2.5–8.0)	0 (0–0.7)	0.5 (0.3–1.1)
		2.2±0.8	**^SW**	**^SW+^^SE**	**^SE**
			5.6±1.2	0.4±0.2	1.2±0.6
Piracetam, 300 mg/kg, n=7	Time spent, s	13.3 (8.4–20.7)	3.4 (0.3–6.3)	8.7 (1.0–25.7)	4.3 (0.3–6.0)
		14.4±2.3	**^SW**	13.5±6.1	**^SW**
			5.5±2.7		4.7±2.2
	Percentage of time, %	36.8	14.1	34.5	12.0
	Frequency of appearance	5 (3–9)	2 (1–5)	3 (1–11)	1 (1–4)
		6.3±1.5	4.3±2.5	7.4±3.0	3.4±1.8
	Average duration of one entry, s	2.2 (1.7–4.6)	1.3 (0.3–1.7)	1.3 (0.4–2.3)	1.2 (0.3–1.8)
		2.8±0.6	**^SW**	1.5±0.4	**^SW**
			1.5±0.5		1.3±0.6
Phenibut, 20 mg/kg, n=7	Time spent, s	13.4 (8.7–16.3)	6.7 (1.3–12.7)	8.0 (2.7–8.3)	13.3 (7.7–21.0)
		12.5±1.4	**^SW**	**^SW**	**^SE+^NW**
			6.3±1.9	6.1±1.3	13.8±2.5
	Percentage of time, %	28.0	14.1	13.6	30.9
	Frequency of appearance	2 (1–7)	2 (2–3)	2 (1–5)	4 (3–6)
		3.7±1.1	2.3±0.5	2.4±0.8	4.7±0.9
	Average duration of one entry, s	5.2 (2.4–7.7)	2.0 (0.7–4.2)	2.7 (1.6–4.2)	2.6 (2.2–3.0)
		5.1±1.0	2.3±0.6	3.0±1.0	3.3±0.8

Notes. ^, ^^, ^^^ – significant with $p < 0.05$, $p < 0.01$ and $p < 0.001$ compared to the result of this group in another quadrant (Mann–Whitney U test); SW, SE, NW – the quadrant of comparison.

ferences. At the same time, all drugs used in this study caused considerable changes of inter-quadrant preferences of animals.

Rats from the Atristamine group had a greatly prolonged time spent in the South-Eastern (SE), but not in the target (SW), quadrant. However, significantly prolonged average time of one entry in the SE quadrant compared to others indicated that this change was not accidental – animals spent their time not just swimming, but also investigating visual cues and the environment of this quadrant. This fact reveals an important feature of the memory-enhancing action of Atristamine – activation of the spatial memory recall.

Rats of the Piracetam group had significantly decreased indicators of the time spent in the SE and NE quadrants compared to the target one. Since they correlated well with the frequency of appearance, it was completely predictable that average durations of one entry just in the above-mentioned quadrants significantly reduced.

The animals from the Phenibut group had another preferences – the time spent in the SE and NW quadrants decreased compared to the SW and NE quadrants. Only the average duration of one entry in the SE quadrant was significantly lower compared to the target quadrant results.

Thus, the analysis of the inter-quadrant behaviour of rats allows us to find differences in search strategies that can be associated with distinct mechanisms of the memory and learning enhancing action.

Conclusion

The study of the effects of Atristamine on the spatial memory and learning of rats using the Morris water maze has been conducted. The data from this experiment have shown that Atristamine (100 mg/kg), Piracetam (300 mg/kg) and Phenibut (20 mg/kg) significantly enhances the memory retention of rats in the Morris water maze. In addition, Atristamine administration causes almost the same effects on the learning and memory of animals as Piracetam and Phenibut. Based on the analysis of the inter-quadrant behaviour of rats, it has been found that there are considerable differences in search strategies associated, probably, with distinct mechanisms of the memory and learning enhancing action of the drugs used. The mechanisms, through which Atristamine can improve the cognitive performance, are not clearly delineated, but it can be affirmed that this effect is strongly associated with the antiamnesic properties of this compound against scopolamine-induced amnesia and, consequently, the positive impact on the cholinergic neurotransmitter system, which is important for the nootropic action of drugs. Furthermore, the above-mentioned properties of Atristamine, together with the protective activity against the traumatic brain injury, antihypoxic and actoprotective effects found previously, indicate the complex and many-sided positive impact of this molecule on the animal brain under different conditions.

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