Dipeptide "alaptide" prevented impairments in spontaneous behavior produced with trimethyltin in male rats

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Abstract

OBJECTIVES: On the animal model of trimethyltin (TMT) induced behavioral deficits the effect of chronic treatment with spirocyclic dipeptide cyclo/alanyl-l-amino-l-cyclopentane-carbonyl (alaptide, AL) was evaluated in adult male rats.
METHODS: Changes in the spontaneous behavioral repertoire were investigated in the open-field test on Day 21 (Session 1) and Day 28 (Session 2) after a single oral TMT administration.
RESULTS: In Experiment 1, rats given the highest TMT dose (7.5 mg/kg) exhibited significantly increased total number of behavioral patterns, the floor sniffing being the most frequent pattern. While the medium TMT dose (5 mg/kg) had a similar effect only in Session 1, the lowest TMT dose (2.5 mg/kg) was entirely ineffective. In Experiment 2, an explicit beneficial influence of both AL doses (5 and 10 mg/kg) given for 10 days before and 10 days after TMT (7.5 mg/kg) on the spontaneous behavior repertoire was observed in both Session 1 and Session 2. The total number of patterns and the time spent in individual patterns of AL+TMT treated animals did not differ from the controls and those given AL alone.
CONCLUSION: We conclude that sufficiently long AL treatment interfered with deleterious effects of TMT and forestalled changes in the structure and timing of spontaneous behavioral patterns. Thus, AL can be designated as a substance having "neuroprotective" effects.

INTRODUCTION

Numerous studies have implicated neuropeptide vasopressin in facilitation of cognitive processes (Dantzer, 1998; de Wied, 1997). Another neuropeptide oxytocin has been found to affect learning and memory in a reversed manner than vasopressin, namely in terms of deterioration (Bohus *et al.* 1993; Kovacs *et al.* 1978; Krejčí *et al.* 1981). Shorter fragments of vasopressin and oxytocin molecule also affected learning and memory (de Wied *et al.* 1984; Kovacs *et al.* 1986]. In rats, a smaller oxytocin molecule fragment prolyl-leucyl-glycine amide prevented puromycin-induced amnesia (Walter *et al.* 1975), delayed the extinction of active avoidance (Walter *et al.* 1978), invigorated learning abilities in the passive avoidance test (Krejčí *et al.* 1986) and in discrimination learning (Krejčí & Dlabač, 1984). However, there are some limitations to the use of this peptide frag-

ORIGINAL ARTICLE

Abbreviations

AL – alaptide (cyclo/alanyl-l-amino-l-cyclopentane-carbonyl)
AL5 – alaptide in dose 5 mg/kg b.w.
AL10 – alaptide in dose 10 mg/kg b.w.
GABA – gamma-amino-butyric acid
SEM – standard error of the mean
TMT – trimethyltin
TMT 7.5 – trimethyltin in dose 7.5 mg/kg b.w.

ment in therapy, in particular, for its peptidase-induced splitting which prevents oral administration (Rádl *et al.* 1990). Therefore, several analogues of this peptide were prepared in order to reduce or abolish enzymatic degradation, including the spirocyclic dipeptide cyclo/alanyl-1-amino-1-cyclopentane-carbonyl/, named alaptide (Kasafirek *et al.* 1992a; Kasafirek *et al.* 1992b).

Beneficial effects of alaptide (AL) on learning and memory performance of rats were estimated using various experimental paradigms (Hliňák & Krejčí, 1991; Hliňák & Krejčí, 1992; Krejčí *et al.* 1981; Krejčí 1987). These studies showed that AL exerts a long-lasting effect and can influence all phases of the memory process. Of particular interest was the finding that spatial information was retained for several days in mice given AL or its analogues (Hliňák *et al.* 1996). Further, AL administered in a preventive-curative way ameliorated the deficits in spontaneous behavior consequent to the $NaNO_2$ effect (Hliňák *et al.* 1990). A protective though incomplete potency of AL against quinolinic acid induced neurotoxicity has also been demonstrated (Keilhoff *et al.* 1991). Thus, AL seems to represent a potential drug influencing significantly cognitive and behavioral functions.

For more than a century, the neurotoxicity of organotin compounds has been recognized. Severe structural, biochemical and functional deficits have been documented in animals treated with trimethyltin (TMT), an organotin compound (e.g. McMillan & Wenger, 1985; Reiter & Ruppert, 1984; Koczyk & Jablonska, 1998; Martin *et al.* 1997). As to the functional deficits, TMT causes increased seizure susceptibility, hyperactivity, aggression, vocalization as well as severe deficits in cognition. These deficits are related to the extensive cell destruction in the limbic system of the brain (e.g. Dyer *et al.* 1982; Earley *et al.* 1992; Shin *et al.* 2007; Nishimura *et al.* 2001). For example, loss of pyramidal cells in the CA1 and CA3 fields, mossy fiber sprouting and impairment of spatial memory were observed after TMT intoxication (Tsutsumi *et al.* 2002). In general, the characteristic neurobehavioral syndrome occurs at the third week after a single TMT injection and persists for a long period of time (Earley *et al.* 1990; Ruppert *et al.* 1982; Moser, 1996). It has been postulated that TMT-induced deficits can be considered as a suitable model for neurodegenerative changes characteristic of aging and dementia in humans (Dorman, 2000; Ishikawa *et al.* 1997; Martin *et al.* 1997).

The findings on both the neurotoxic effect of TMT and the beneficial effect of AL led us to study an interaction of these two compounds. We addressed the following questions: (a) will a single TMT administration induce long-lasting changes in the structure of spontaneous behavior repertoire (Experiment 1); (b) will a chronic AL treatment alleviate and/or prevent the manifestation of TMT-induced changes in spontaneous behavior (Experiment 2)? We predicted that sufficiently long AL pre + post treatment could ameliorate behavioral changes produced by TMT dose (7.5 mg/kg) that appeared highly effective in the first experiment. It is important to note that in the open-field test the changes in spontaneous behavior of TMT-treated rats were exclusively expressed either by the total number of squares crossed or by the total number of arbitrary counts, using the open-field test. Till now, the complete repertoire of spontaneous behavior was not estimated in TMT-treated rats.

MATERIAL AND METHODS

Animals

At arrival, adult (90 days old, 250–280 g) albino male rats (Hannover-Wistar strain, Konarovice Breeding, Czech Republic) were housed in groups of three in standard plastic cages and kept in a temperature-controlled room (20–22 °C) in a natural photoperiod for 2 weeks before the start of the experiment. Animals were handled daily. Commercial pellet food and water were available ad libitum.

Treatment of animals was in accordance with the Declaration of Helsinki Guiding Principles on Care and Use of Animals (DHEW Publication, NHI 80–23).

Treatment

Always, animals aged 114 days were randomly assigned to groups. Experiment 1: trimethyltin chloride (Aldrich Chemical Co.) dissolved in distilled water in a volume of 1 ml/kg at doses of 2.5, 5 and 7.5 mg/kg (calculated as the weight of the base) was used (n = 10/group, 4 groups total); the controls received distilled water. Based on the results the dose of 7.5 mg/kg was used in Experiment 2 (n = 9/group, 6 groups total: control, TMT, TMT+AL5, TMT+AL10, AL5, AL10). AL at a dose of 5 mg/kg dissolved in a volume of 10 ml/kg was administered once (group 5 mg/kg) or twice (group 10 mg/kg) daily for 10 days before and 10 days after TMT treatment. On the day of TMT insult, AL was given 4 h before and 4 h later, respectively. Always, both TMT and AL and distilled water (when appropriate) were administered orally.

Procedure

In both experiments, animals were tested on Day 21 (Session 1) and Day 28 (Session 2) after TMT treatment, always between 8.00 and 12.00 (a.m.) following 24 hours lasting adaptation to the experimental room.

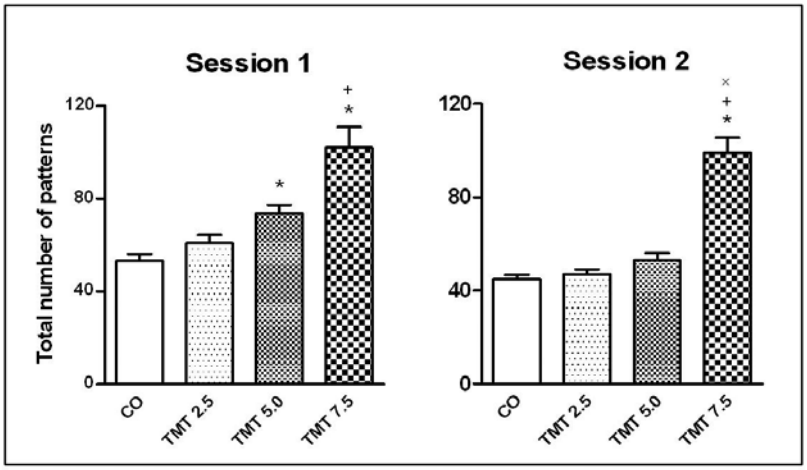

Fig.1. Effect of trimethyltin (TMT) on spontaneous behavior of adult male rats (Experiment 1). The total number of all registered patterns expressed as the mean ± SEM (n =10). Session 1 = testing on Day 21, Session 2 = testing on Day 28 after TMT administration. CO = control group; TMT dose given in 2.5, 5.0 and 7.5 mg/kg b.w. Statistical significance for the total number of patterns is shown above a given column; $p < 0.05$: * vs control group, $^{+}$ vs TMT 2.5 mg group, ^{x} vs TMT 5 mg group.

A transparent plexiglass arena (60 x 60 x 30 cm) with 4 holes (each 4 cm in the diameter) located on the floor equidistantly at the distance of 20 cm from the corners was used. The arena was lit from the ceiling of the room with a 25W fluorescent tube. Experimental room was separated from the observational one by a two-way window. Always, an animal was gently placed at the centre of the arena and spontaneous behavioral patterns were recorded by an experienced observer for 5 min using the typing preset keys on the key-board of a computer. The arena was cleaned after each animal.

Behavioral patterns

The following behavioral patterns were distinguished: *floor sniffing* – the rat probes with the snout along and around surfaces by a discrete head movement during which the tip of the snout and the whiskers are also in a brisk motion; *hole sniffing* – the rat dips the head in the hole; *air sniffing* – the pattern is defined as stationary sniffing the air indicated by whiskers movement and twitching with the nose not near the wall or the floor; *rearing* – standing upright on the hind legs while both forepaws are raised above the floor or leaned against the wall; *grooming* – the rat takes care of the body; *immobility* – sitting or lying on the place (i.e. motionless of the body). As each behavioral pattern occurred, its corresponding key was pressed. The procedure created a computer record of the number and the duration of particular behavioral patterns.

Statistics

Both the total number and the total time spent in particular patterns were subjected to the statistical analysis (Sigma Stat® SPSS package). The nonparametric technique that appears as very suitable for the behavioral sciences (Siegel, 1956) was used to evaluate the data. To compare differences among groups within a definite session the Kruskal-Wallis one-way analysis of variance by ranks (H =) followed by Tukey´s method with a $p <$ 0.05 adjusted significance level was used when appropriate to identify significant differences between groups (*df* 3 in Experiment 1, *df* 5 in Experiment 2).

RESULTS

To simplify the results the total number of all registered behavioral patterns and the total time spent in individual patterns are only included.

Experiment 1: As shown in Fig.1 there are significant group differences in the total of registered patterns in Session 1 [$H = 29.7$, $p < 0.001$] and Session 2 [$H = 23.9$, $p < 0.001$]. Compared to the controls, rats given the highest TMT dose exhibited significantly increased total number of patterns in both sessions. A similar effect in rats given the medium TMT dose was found only in Session 1. The lowest TMT dose was ineffective entirely. Table 1 summarizes the total time spent in particular patterns. In Session 1, there are significant differences in floor sniffing [$H = 22.4$, $p < 0.001$], grooming [$H = 18.4$, $p < 0.001$] and immobility [$H = 8.9$, $p = 0.03$]. Irrespective of TMT dose given a significant increase of the time spent in floor sniffing, and on the contrary, a significant decrease of the time spent in grooming is evident. Rats given the highest TMT dose spend significantly less time in immobility as compared with the other groups. In Session 2, significant differences were found in floor sniffing [$H = 25.2$, $p < 0.001$], grooming [$H = 31.6$, $p < 0.001$] and immobility [$H = 16.0$, $p = 0.001$]. Rats given the highest TMT dose spend significantly more time in floor sniffing, less time in immobility, and no grooming was observed. In both sessions no differences among the groups were found for air sniffing, hole sniffing and rearing.

Experiment 2: As summarized in Fig. 2 there are significant group differences in the total number of registered patterns in Session 1 [H =29.7, $p < 0.001$] and Session 2 [$H = 30.8$, $p < 0.001$]. In both sessions, there is a conclusive evidence for significant difference between TMT group and five other groups. AL+TMT treated animals, irrespective of AL doses, did not differ from the controls and those given AL alone. The overall analysis of the total time spent in individual patterns (see Table 2) during Session 1 revealed a significant difference in floor sniffing [$H = 26.4$, $p < 0.001$], groom-

Table 1. Total time (s) spent in individual behavioral patterns following a single trimethyltin (TMT) administration to male rats (Experiment 1).

		Behavioral patterns:					
Session 1		**Floor sniffing**	**Air sniffing**	**Hole sniffing**	**Rearing**	**Grooming**	**Immobility**
	Group						
	Control	51.1±4.4	32.1±2.7	45.0±5.8	30.7±2.5	27.6±4.4	113.5±7.1
	TMT 2.5	127.1±7.0*	24.9±3.0	35.8±3.0	23.5±2.2	7.5±2.4*	81.2±7.4
	TMT 5.0	117.4±8.1*	30.6±4.4	37.4±3.4	25.7±5.2	6.5±2.4*	82.4±12.9
	TMT 7.5	138.6±11.7*	29.2±5.5	35.2±6.9	25.7±7.5	3.7±1.7*	67.6±11.8*
	H =	22.4	2.8	2.6	6.1	18.4	8.8
	p	< 0.001	= 0.43	= 0.45	= 0.11	< 0,001	= 0.03
Session 2							
	Group						
	Control	40.7±4.0	28.5±2.5	38.0±4.6	24.0±1.3	54.1±3.6	114.7±5.6
	TMT 2,5	63.9±8.7	23.1±3.8	38.0±9.1	22.0±3.4	26.4±4.0	126.6±11.4
	TMT 5.0	70.3±9.9	28.8±3.4	27.1±3.0	26.1±3.5	9.4±4.6*	138.3±14.3
	TMT 7.5	146.7±8.8*+x	40.5±7.8	31.8±3.9	22.9±2.9	0.0±0.0	58.1±11.5
	H =	25.2	5.2	4.5	1.8	31.6	16.0
	p	< 0.001	= 0.16	= 0.21	= 0.61	< 0.001	= 0.001

TMT dose is expressed as mg/kg b.w.
Session 1 performed 21 days after TMT administration; Session 2 performed 28 days after TMT administration. Given average values ± SEM (n = 10). Statistical analysis: Kruskal-Wallis one-way analysis of variance by ranks (H =) followed by Tukay´s method, $p < 0.05$: * vs control group, x vs TMT 2.5 group, + vs TMT 5.0 group

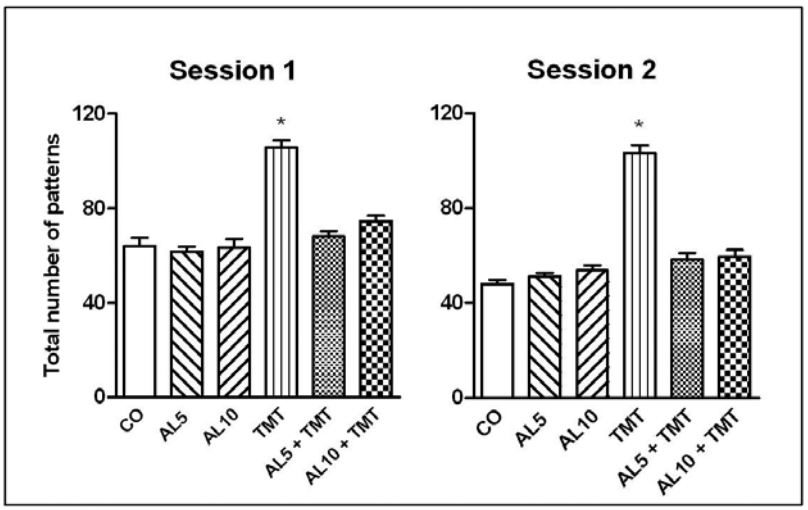

Fig.2. Effect of alaptide (AL) on trimethyltin (TMT) produced deficits in spontaneous behavior of adult male rats (Experiment 2). The total number of all registered patterns expressed as the mean ± SEM (n = 9). AL was administered for 10 days before and 10 days after TMT insult. Session 1 = testing on Day 21, Session 2 = testing on Day 28 after TMT insult. CO = control group; AL5 = alaptide 5 mg/kg b.w., AL10 = alaptide 10 mg/kg b.w.; TMT = trimethyltin 7.5 mg/kg b.w. Statistical significance for the total number of patterns is shown above a given column; $p < 0.05$: * vs all other groups.

ing [$H = 27.5$, $p < 0.001$] and immobility [$H = 23.4$, $p < 0.001$]. More conspicuous group differences in the time spent were found in Session 2. Except for rearing there were differences in floor sniffing [$H = 26.4$, $p < 0.001$], air sniffing [$H = 19.8$, $p = 0.001$], hole sniffing [$H = 20.6$, $p = 0.001$], grooming [$H = 26.5$, $p < 0.001$] and immobility [$H = 25.5$, $p < 0.001$]. Again, TMT treated group differed significantly from five other groups. No differences were found among the controls, both AL+TMT treated groups and both AL treated groups. Except for grooming no difference was found in the efficiency of both AL doses.

DISCUSSION

The finding on the effect of TMT (Experiment 1) is in agreement with previous studies describing a time course and dose dependency of hyperactivity following acute administration (Earley *et al.* 1990; Earley *et al.* 1992; Hagan *et al.* 1988; Johnston *et al.* 1984; Moser, 1996; Ruppert *et al.* 1982). In adult male rats, the highest TMT dose (7.5 mg/kg) produced conspicuous changes in spontaneous behavior persisting at least for four weeks. This time the total number of exhibited patterns reached approximately twofold level of the con-

Table 2. Total time (s) spent in individual behavioral patterns following a single TMT administration and chronic pre- + post-alaptide (AL) treatment in male rats (Experiment 2).

		Behavioral patterns:					
Session 1		**Floor sniffing**	**Air sniffing**	**Hole sniffing**	**Rearing**	**Grooming**	**Immobility**
	Group						
	Control	73.2±5.1	23.6±3.6	42.2±8.7	28.3±4.2	25.3±3.2	107.3±10.5
	TMT 7.5	133.1±10.5*	41.0±8.5	43.1±6.6	18.8±7.6	3.2±0.7*	60.8±7.2*
	TMT+AL5	70.8±6.8^{+}	27.2±4.1	26.4±2.4	19.2±2.0	27.9±4.6^{+}	128.4±7.0^{+}
	TMT+AL10	63.2±6.0^{+}	29.2±3.0	22.8±1.6	26.7±3.2	29.7±7.2^{+}	128.4±13.7^{+}
	AL5	50.7±7.3^{+}	43.7±6.3	34.2±5.5	22.4±2.2	92.6±2.2^{+}	136.4±9.0^{+}
	AL10	55.3±4.9^{+}	27.7±3.2	25.9±3.5	19.8±1.5	36.2±5.6^{+x}	135.1±7.9^{+}
	H =	26.4	8.6	9.1	9.2	27.5	33.2
	p	< 0.001	= 0.13	= 0.11	= 0.10	< 0.001	< 0.001
Session 2							
	Group						
	Control	34.1±4.0	16.6±1.9	26.1±5.2	17.9±2.5	52.9±5.0	152.4±5.2
	TMT 7.5	143.6±6.0*	37.1±5.8*	36.1±2.1*	14.6±1.4	4.8±2.0*	61.7±8.2*
	TMT+AL5	45.7±4.7^{+}	18.6±1.7^{+}	18.7±1.6^{+}	14.0±1.1	62.9±6.2^{+}	140.2±4.2^{+}
	TMT+AL10	45.1±3.9^{+}	22.9±3.0^{+}	18.7±2.1^{+}	14.7±1.8	65.3±6.6^{+}	133.3±8.5^{+}
	AL5	87.4±4.5^{+}	25.4±2.8	22.8±3.3^{+}	16.0±1.5	52.8±3.9^{+}	145.6±3.6^{+}
	AL10	36.9±3.5^{+}	20.6±2.4^{+}	15.4±1.6^{+}	12.6±0.7	66.7±7.6^{+}	144.6±5.6^{+}
	H =	26.4	19.8	20.6	2.3	26.5	25.5
	p	< 0.001	= 0.001	< 0.001	= 0.81	< 0.001	< 0.001

TMT and AL doses are expressed as mg/kg b.w.

Session 1 performed 21 days after TMT administration; Session 2 performed 28 days after TMT administration. Given average values + SEM (n = 9). Statistical analysis: Kruskal-Wallis one-way analysis of variance by ranks "(H =) followed by Tukay´s method, $p < 0.05$: * vs control group, $^{+}$ vs TMT 7.5 group, ^{x} vs AL5 group"

trols. While the time spent in air sniffing, hole sniffing and rearing did not differ from the controls, the time spent in floor sniffing increased significantly. On the contrary, TMT treated animals spend little time in the immobility and exhibited almost no grooming. Although certain deficits were also observed in animals given the medium TMT dose (5 mg/kg) in Session 1, they disappeared one week later. The lowest TMT dose was entirely ineffective. In fact, the animals given the highest TMT dose varied rapidly locomotor-exploratory patterns so that they were not able to preserve a definite behavioral (motivational) state for a longer period of time. Typically, floor sniffing was shortly interrupted with other patterns except for grooming and immobility. In general, TMT impaired the structure and timing of spontaneous behavior in male rats when tested in the open-field arena. This is a fundamental contribution of the present study. The deterioration of spontaneous behavior in rats given the highest TMT dose was more conspicuous in Experiment 2. Not only sniffing but also air sniffing and hole sniffing were significantly increased as compared with the controls.

An explicit beneficial influence of AL on the spontaneous behavior of TMT treated animals was sufficiently proved in Experiment 2. There was no fundamental difference in the total number of exhibited patterns as well as in the time spent in particular patterns among the controls, both AL groups and both AL+TMT groups. Compared to the TMT group, a distinct reduction of the time spent in floor sniffing, air sniffing, hole sniffing and rearing, and on the contrary, a significant increase of the time spent in grooming and resting (immobility) was measured in both AL+TMT groups. Beneficial effects of AL on the structure and timing of spontaneous behavior outlasted for a number of days, even without additional AL treatment. Based on these results, AL treatment interfered with deleterious effects of TMT and forestalled behavioral changes. It has been proposed that AL exerts a long-lasting effect due to the prolonged presence in the organism (Krejčí *et al*. 1986). Thus, spontaneous behavior and its mechanisms seem to be resistant to the TMT insult in animals treated sufficiently long with AL. It remains to be solved if it was the pre- or post-AL treatment which exerted the beneficial effect. In our previous study (Hliňák & Krejčí,

2005) pre- but not post-treatment with nootropic substance oxiracetam prevented social recognition deficits produced with TMT in rats.

Regarding the most different beneficial efficiency of AL such as improvements of cognitive performance in rodents (Hliňák & Krejčí, 1991; Hliňák & Krejčí, 1992; Hliňák *et al*. 1996; Krejčí *et al*. 1981; Krejčí *et al*. 1986) and suppression of aggressive contacts in grouped mice (Šulcová & Krejčí 1991), the dipeptide apparently takes part in a number of physiological processes related to the behavioral outcome. As to the spontaneous behavior, AL prevented deficits produced TMT (the present study) and ameliorated behavioral consequences of $NaNO_2$ hypoxia (Hliňák *et al*. 1990). Support for the favorable properties of synthetic dipeptides comes from studies showing that N-phenylacetyl-L-prolylglycine ethyl ester (GVS-11) converting in the body to the bioactive cyclo-prolylglycine has antiamnesic activity (Gudasheva *et al*. 1996; Gudasheva *et al*. 1997). There is a possibility that dipeptide AL can be designated as a substance having "neuroprotective" character.

Unfortunately, exact mechanisms of AL effect are not clear so far. AL is readily absorbed from the gastrointestinal tract and penetrates the blood-brain barrier, the maximum concentration in the brain being reached within one hour and thereafter the level slowly decreases (Lapka, 1991; Rádl *et al*. 1990). AL moderately influences some of the dopamine neuronal systems (Krejčí *et al*. 1986; Lebedev *et al*. 2000; Nedvídkova *et al*. 1994; Valchář *et al*. 1985), however there is no evidence for a direct action of AL on the dopamine receptors.

Since TMT produces deficits in the serotonergic, dopaminergic, GABA-ergic, cholinergic and glutamatergic systems (Earley *et al*. 1990; Keilhoff *et al*. 1991; Koczyk & Jablonska, 1998; O'Connell *et al*. 1994a), the effect of AL might be mediated by influencing different neurotransmitter systems. It has been proved that behavioral and cognitive TMT-produced deficits were attenuated and/or reversed by the compounds of various origin and structure like codergine, captopril, tacrine, JO 1784 and dextromethorphan (Earley *et al*. 1989; Manning-Sayi & Leonard 1989; Maurice *et al*. 1999; O'Connell *et al*. 1994b; O'Connell *et al*. 1996; Shin *et al*. 2007). Another possible explanation is that AL protected appropriate brain structures against TMT damage stemming from an increased formation of reactive oxygen species including hydroxyl radicals (Ali *et al*. 1992).

The fact that AL and its analogues are poorly soluble in the water has important clinical implications for development of these compounds. An increase of the solubility of prospective spirocyclic dipeptides can be done by means of synthesis of N-prolonged peptides as pro-drugs. A crucial step seems to be constructing linear precursors with active amine acid sequences that would be enzymatically hydrolyzed and undergo cyclization to form the spirocyclic dipeptide in the organism (Kasafirek *et al*. 1992a; Kasafirek *et al*. 1992b). We can anticipate that the observed behavioral effects of the neuropeptide AL derivative could be related to the well established role of the parent hormone oxytocin and vasopressin on cognitive functions in the mammalian brain.

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