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Neuroprotective and Antinociceptive Activity of Two New Derivatives of Deoxypeganine Alkaloid

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Abstract

Deoxypeganine alkaloid isolated from *Peganum harmala* L. is well known as a reversible acetylcholinesterase inhibitor. Further investigations showed its effectiveness in treatment of drug and nicotinic addictions and alcoholism, Alzheimer dementia, clinic depression, schizophrenia and chronic fatigue, poisoning by psychotrops. In the present investigation we revealed the neuroprotective activity of deoxypeganine and two its amino derivatives on two animal models. In the first series of experiments deoxypeganine and its derivatives were injected to mice intraperitoneally, in 15 minutes nicotine-base introduced subcutaneously, in 30 minutes the animals were placed in the central compartment of 12-compartement maze, and their exploratory activity effectiveness monitored. In the second series of experiments we used atropine sulfate instead of nicotine. The test proceeding was the same. Both amino derivatives were more potent in mice cognitive functions improvement than deoxypeganine and galantamine that indicates the necessity of their further investigation. Experiments in analgesic activity assessment in acetic writhing and hot plate tests have shown the lack of antinociceptive responses to pain in the centrally mediated analgesia (hot plate) test for deoxypeganine and its derivatives, while galantamine shown relatively high analgesia. In the acetic writhing test deoxypeganine and its derivatives were potent, but in a less extent than galantamine. Relatively high analgesic effect of galantamine may possibly be attributed to the involvement of "hypophysis - glucocorticoids" axis. Anti-inflammatory effects of all investigated derivatives in formalin rat test were low, although their ability to shorten the recovery period in inflammation attracts the special attention and needs further investigation.

Keywords

Deoxypeganine, 6-Aminodeoxypeganine, 6,8-Diaminodeoxypeganine, Cognitive Functions, Analgesic, Anti-Inflammatory

1. Introduction

Deoxypeganine (DOP) alkaloid isolated from *Peganum harmala* L. (Turkish rue) is well known as a reversible acetylcholinesterase inhibitor [1]. The pharmacological actions of DOP had been intensively investigated in the Institute of the Chemistry of Plant Substances, Uzbek Sciences Academy (ICPS) in 1980-90s, and the substance has been registered as an AChE inhibitor drug in the Former Soviet Union. There are further data in literature regarding its effectiveness in treatment of drug and nicotinic addictions and alcoholism [2], [3], [4], Alzheimer dementia [5], clinic depression [6], schizophrenia and chronic fatigue [7], poisoning by psychotrops [8]. Thus, pharmacological study of new deoxypeganine derivatives may reveal more potential agents with combined useful properties for therapy of the abovementioned disorders.

The objective of this research was to reveal the neuroprotective and antinociceptive activity of hydrochlorides of DOP and two its amino derivatives in compare to conventional drug galantamine hydrobromide.

2. Main Content

2.1. Reagents

Hydrochlorides of 6-aminodeoxypeganine and 6,8-diaminodeoxypeganine have been provided by Organic Synthesis Department of ICPS. Galantamine hydrobromide (GAL) and deoxypeganine hydrochloride were commercial pharmacopeia products produced by the Institute of the Chemistry of Plant Substances (Uzbekistan).

2.2. Animals

The experiment protocols involving use of animals for the study was approved by the Institutional Ethical Commission in accordance with the GLP guidelines issued by the Head Department for Quality Control of Drugs and Medical Technique, Public Health Ministry of the Republic of Uzbekistan.

Healthy albino rats of either sex weighing 150-200 g and mice weighing 22-32 g were taken to study. Animals were acclimatized by keeping them in animal house. They were housed individually in polypropylene cages containing sawdust as bedding material and maintained under room temperature. The animals were fed with standard diet and water.

Each investigated group contained 6 animals.

2.3. Investigation of Neuroprotective Activity

In the first series of experiments DOP and its derivatives (5 mg/kg), GAL (5 mg/kg) were injected to mice intraperitoneally, in 15 minutes nicotine-base introduced subcutaneously (0.5 mg/kg), in 30 minutes the animals were placed in the central compartment of 12-compartement maze, and their exploratory activity monitored. The following indicators had been evaluated: total time of mouse moving and investigating the maze compartments; numbers of mouse repeat visiting of each compartment (effectiveness of exploratory activity).

In the second series of experiments we used atropine sulfate 0.1 mg/kg instead of nicotine. The test proceeding was the same.

2.4. Investigation of Analgesic Activity

Analgesic activity of the investigated substances was evaluated in acetic writhing and hot plate tests.

In the acetic acid induced writhing test [9] the investigated substances were introduced to mice subcutaneously in 1/10 LD_{50} dose for 30 minutes before the acetic acid injection. The control group was treated by distilled water in the same conditions.

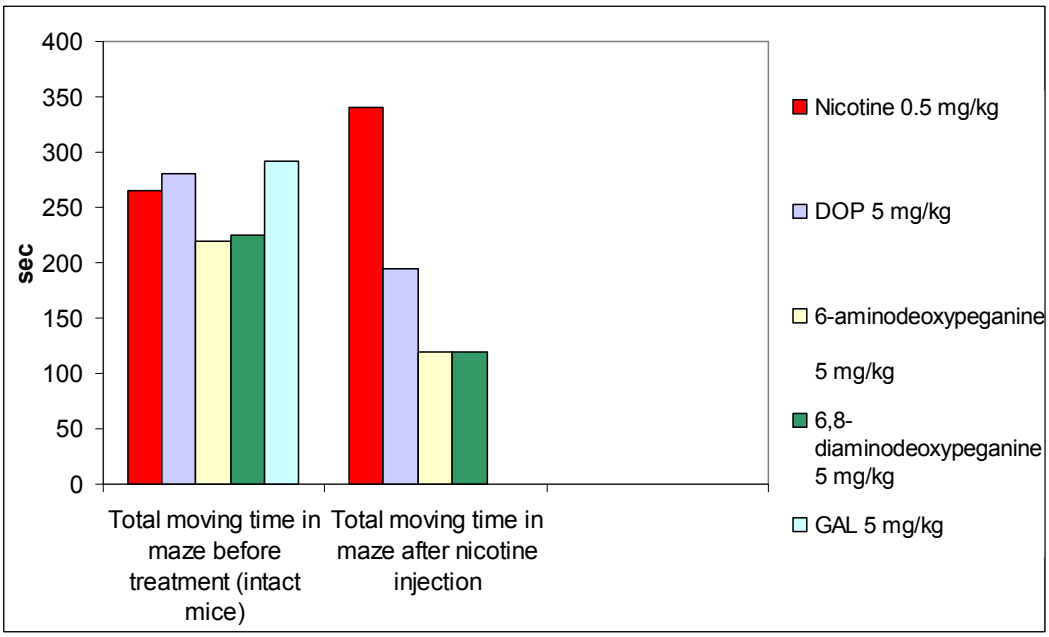
In the hot plate test [9] the investigated substances were introduced to mice subcutaneously in a dose 5 mg/kg, after 15 minutes the animals are placed on the hot plate (56^{o}C) and the observations were recorded and at the time interval of 30, 60, 90 and 120 minutes till the appearance of the first discomfort sign – paw licking.

2.5. Investigation of Anti-Inflammatory Activity

Anti-inflammatory activity had been evaluated in formalin rat test [10]. Investigated substances were injected subcutaneously for 30 minutes before 1% formalin introduction to the paws of rats. The control group was treated by distilled water in the same conditions.

3. Results

The positive central cholinergic receptors agonists influence on teaching processes is well known [11]. But, nicotine being nAChRs agonist, in dose 0.5 mg/kg displayed abnormal influence on mice exploratory activity in maze: it broken the mnestic function of animals and decreased the effectiveness of exploratory activity [12]. This abnormal effect of nicotine is suggested due to its affecting on associative zones of the cerebral cortex, in particular perirhinal cortex [11]. This model is very appropriate to screen substances having nootropic activity attributed to N-cholinergic processes, without preliminary longtime development of conditioned reflexes. In our experiments we evaluated the influence of DOP and its mentioned derivatives on amnestic effects of nicotine. Results are represented in the Fig. 1.



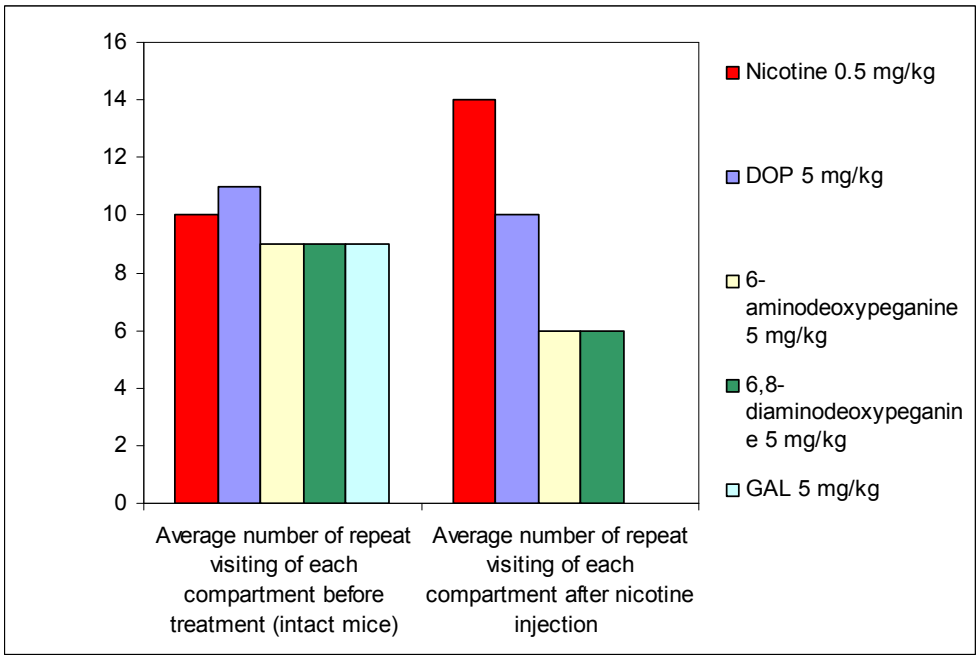


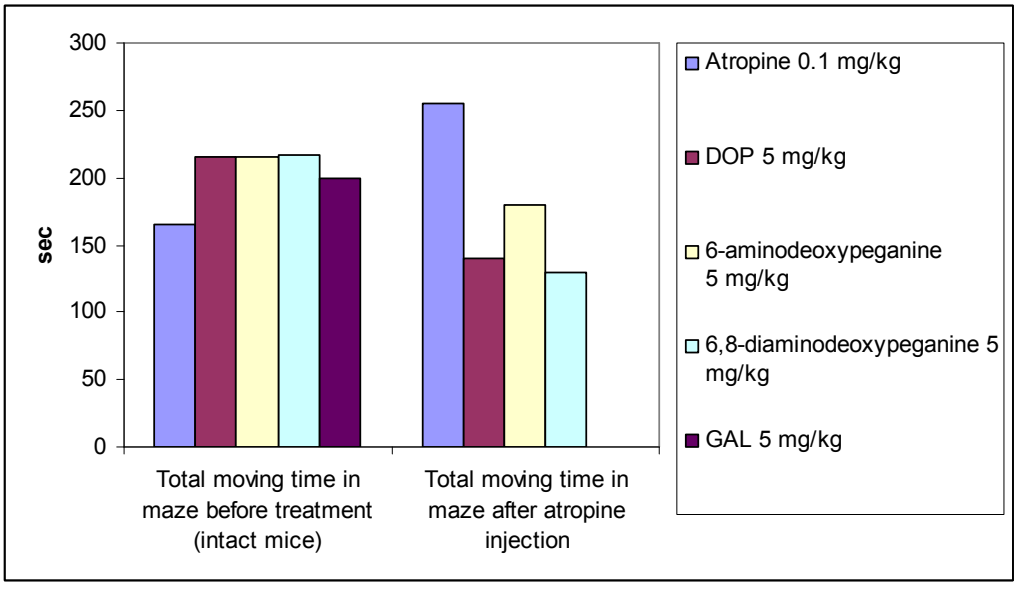
Fig. 1. *Effect of the investigated substances on cognitive functions of mice disturbed by nicotine (GAL effect after nicotine injection not determined).*

It was founded that all investigated substances, excepting GAL, decrease the total moving time of mice in maze after nicotine injection. We were not able to evaluate GAL effects in the investigated dose because of potentiating of nicotine toxic effects that led to animal convulsions. DOP and its derivatives substantially decreased all investigated parameters. DOP was less potent on this model than its derivatives.

Investigation of the substances effect on cognitive functions disturbance in mice caused by atropine shown that atropine substantially increases both a total moving time in maze and number of repeat visiting of each compartment by mice. Preliminary introduction of the investigated substances, excepting GAL, prevented this effect of atropine. GAL potentiated the effects of atropine and caused tremor and failure of mice exploratory activity. Being introduced to mice in a less dose (2.5 mg/kg) it doesn't cause tremor, but destroyed the exploratory activity (Fig. 2).

Analgesic activity of the substances in acetic acid induced writhing test is listed in the table 1. The results demonstrated the significant analgesic activity in range GAL>6-aminodeoxypeganine hydrochloride>DOP>6,8-diaminodeoxypeganine hydrochloride.

Hot plate test is useful in the elucidating the centrally mediated antinociceptive responses. In this test the DOP and its derivatives in a dose 5 mg/kg didn't display antinociceptive responses, while GAL in dose 2 mg/kg increased the pain threshold of mice in one hour for 1.6 times in compare to the control.



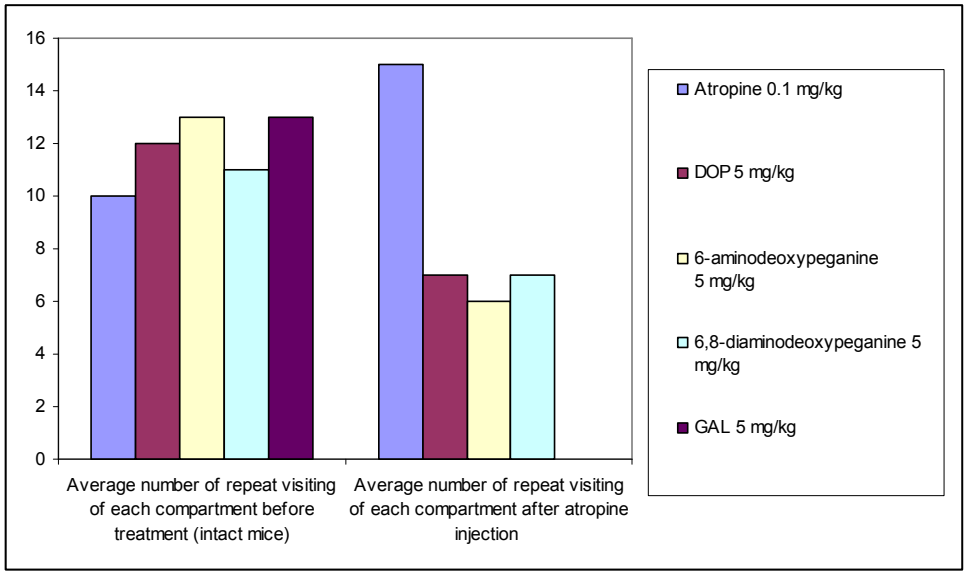


Fig. 2. *Effect of the investigated substances on cognitive functions of mice disturbed by atropine (GAL effects after atropine injection not determined).*

Table 1. *Inhibition of acetic acid induced writhing in mice.*

Substance	Dose, mg/kg	Average number of writhes in 20 min	Inhibition (%)	P
Distilled water (control)	0.2 ml	59±2,1	-	-
GAL	1.5	10±0,9	83	< 0,01
DOP	6.0	24±1,8	59	< 0,01
6-aminodeoxypeganine hydrochloride	10.0	19±1,4	68	< 0,01
6,8-diaminodeoxypeganine hydrochloride	10.0	27±1,5	54	0,01

Table 2. *Anti-inflammatory effect of the investigated substances on formalin rat model.*

Substance	Dose, mg/kg	Average volume of paw, ml		Anti- inflammatory effect, %
		Intact	In 3 hours after formalin injection	
Control	-	0.6	1.36	-
GAL	1.5	0.6	1.2	28
DOP	6.0	0.7	1.43	18
6-aminodeoxypeganine hydrochloride	10.0	0.66	1.26	28
6,8-diaminodeoxypeganine hydrochloride	10.0	0.63	1.22	26

Results in investigation of inflammatory effects of the investigated substances shown that the preliminary injection of all substances in doses equal to 1/10 LD_{50} before formalin introduction slightly decreases the edema (Table 2). But further observation during two weeks shown that the investigated DOP derivatives make shorten the total time of recovery (7-8 days) in compare to the control group (10-11 days).

Cholinergic-enhancing drugs are the current therapy for Alzheimer diseases [13]. Pharmacological properties of DOP make it more favorable than other reversible AChE inhibitors like GAL and eserine in treatment of cognitive disorders and drug addiction. Moreover, it is less toxic than GAL. Desoxypeganine significantly inhibited MAO and butyrylcholine esterase *in vitro* in contrast to GAL and eserine, and in our own observations on mice it decreased the "group toxicity" of benzedrine and triptamine, and in high doses depressed the mice head nods caused by 5-OTP. In addition, starting from the dose of 1 mg/kg it prolonged the duration of tremor called by nicotine and arecoline displaying it's targeting both to M- and N-cholinoreceptors. Our experiments in evaluation of the neuroprotective properties of DOP on two animal models proved its high effectiveness and safety. Both DOP amino derivatives were more potent in mice cognitive functions improvement than DOP and GAL that indicates the importance of further investigation of DOP derivatives.

Acute pain is said to be one of the discomfort reasons worsening people life. Studies have demonstrated the involvement of multiple targets, such as receptors of neurotransmitters, into analgesia. A large body of evidence suggests a role for serotonin in pain modulation. Some studies have shown analgesic effect of serotonin in descending serotoninergic pathway, while others one had been demonstrated the activation of nociceptors in the periphery [14]. It has been founded that DOP inhibits MAO-A selectively [6], and it may possibly affect on pain sensation. But our experiments in analgesic activity assessment have shown the failure of antinociceptive responses to pain in the centrally mediated analgesia test both

for DOP and its derivatives, while GAL shown relatively high analgesia. In the acetic writhing test DOP and its derivatives were potent, but in a less extent than GAL. Relatively high analgesic effect of GAL may possibly be attributed to the involvement of "hypophysis - glucocorticoids" axis in its analgesic action. Anti-inflammatory effects of all investigated derivatives were low, although their ability to shorten the recovery period in inflammation attracts the special attention and needs in further study.

4. Conclusion

In the present investigation we revealed the neuroprotective activity of deoxypeganine and two its amino derivatives on two animal models. Both amino derivatives were more potent in mice cognitive functions improvement than deoxypeganine and galantamine that indicates the necessity of their further investigation. Experiments in analgesic activity assessment have shown the lack of antinociceptive responses to pain in the centrally mediated analgesia test for deoxypeganine and its derivatives, while galantamine shown relatively high analgesia. In the acetic writhing test deoxypeganine and its derivatives were potent, but in a less extent than galantamine. Relatively high analgesic effect of galantamine may possibly be attributed to the involvement of "hypophysis - glucocorticoids" axis. Anti-inflammatory effects of all investigated derivatives were low, although their ability to shorten the recovery period in inflammation attracts the special attention and needs further investigation.

Thus, the present study shows the perspectives of further DOP derivatives investigations for searching more potent agents for therapy of cognitive disorders.

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