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Diphenyl diselenide induces anxiolytic-like and sedative effects on the chick social separation-stress behavior

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ABSTRACT

The purpose of this research was to investigate the anxiolytic-like effect of diphenyl diselenide [$(PhSe)_2$] on the chick social separation-stress behavior. Male chicks (six day-old) received, per oral route, a single administration of $(PhSe)_2$ at doses of 1, 10 and 50 mg/kg. Thirty minutes after treatment, chicks were submitted to the behavioral tests. The behavioral tests: number of separation-induced distress vocalizations and jumps, time of active wakefulness, time of standing/sitting motionless with eyes open, time of standing motionless with eyes closed and time of sleeping posture, during 10 min, were recorded. $(PhSe)_2$ at doses of 10 and 50 mg/kg reduced the number of vocalizations and jumps and the time of active wakefulness and increased the time of standing/sitting motionless with eyes open of chicks. The sleeping posture time was increased in animals treated with $(PhSe)_2$ at the dose of 50 mg/kg. In conclusion, treatment with $(PhSe)_2$, in a dose dependent-manner, caused anxiolytic-like and sedative effects in chicks.

Anxiety has been the most prevalent psychiatric disorder among the world population [31]. Anxiety disorders are common mental diseases of the central nervous system and contribute to ever increasing health problems worldwide. Anxiety disorders are present in a number of forms, although probably all are dependent upon a number of common neurological circuits [2]. Benzodiazepines have been used for the treatment of several anxiety forms, but these compounds have well-known side effects, such as sedation, muscle relaxation, amnesia and dependence [20,33]. For this reason, many researchers have evaluated new compounds with fewer undesirable effects.

Some compounds derived from selenium have been reported to possess several biological activities, including antimicrobial [13], antineoplastic [17] and anti-inflammatory [4]. Diphenyl diselenide $(PhSe)_2$ is an organoselenium compound which has pharmacological properties in rodents [15,16,18,19,23,25], such as antidepressant-like and anxiolytic-like [26].

Although some traditional models of anxiety in rodents have demonstrated predictive validity for screening antidepressants, they are not very economical, especially in terms of cost [1,3]. However, the chick separation-stress paradigm is a more cost-efficient animal model of anxiety in that, isolation induces an acute stress in chicks with an increase of spontaneous activity and vocalizations. Moreover, this model has been used for anxiolytic drug screening [7,10,32]. Hogg et al. [11] have demonstrated that changes related to anxiety or fearfulness in chicks produce changes in motor response, which may be mediated by modulation of the GABA–benzodiazepine function or of other neurotransmitters. In this way, the present study investigated if the treatment with $(PhSe)_2$ influences the isolation-induced stress responses in chicks.

$(PhSe)_2$ was prepared in our laboratory according to the method described in the literature [21]. Analyses of the ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectrum showed that $(PhSe)_2$ obtained presented analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of the compound (99.9%) was determined by GC/MS. All other chemicals were obtained from analytical grade. $(PhSe)_2$ was diluted in canola oil.

Male chicks (six day-old) from our own breeding colony were used. Animals were kept at a room temperature of $25 \pm 2\,^{\circ}C$, with free access to food and water. Animals were used according to the International Guiding Principles for Biomedical Research Involving Animals.

Chicks were divided into four groups of eight animals each. Animals belonging to group 1 received an oral administration of canola oil (10 ml/kg) by gavage. Chicks of groups 2, 3 and 4 received a single oral administration of $(PhSe)_2$ at doses of 1, 10 and 50 mg/kg, respectively. Thirty minutes after treatment with $(PhSe)_2$, chicks were submitted to behavioral tests.

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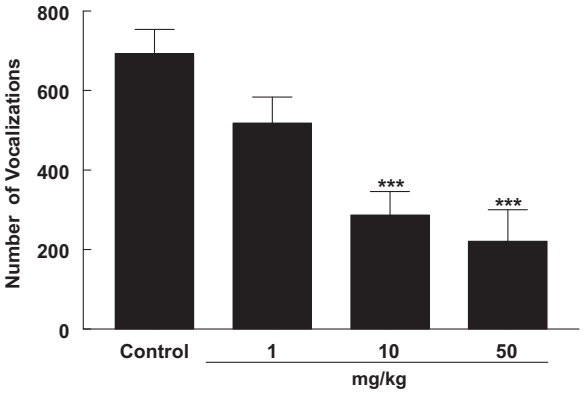

Fig. 1. Effect $(PhSe)_2$ on the number of separation-induced distress vocalizations during 10 min isolation chicks. Results are expressed as means ± S.E.M. of eight animals per group. (***) Denotes $p < 0.001$ as compared to the control group (one-way ANOVA/Duncan).

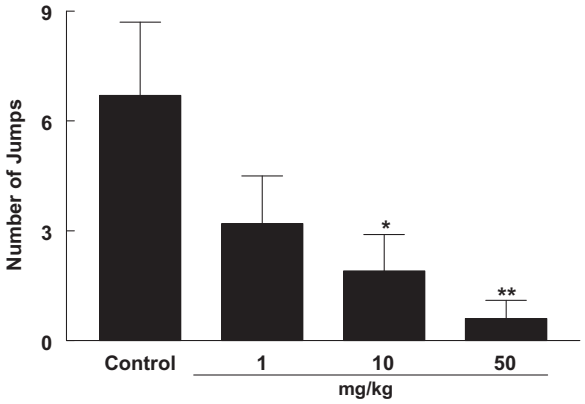

Fig. 2. Effect of $(PhSe)_2$ on the number of jump during 10 min isolation chicks. Results are expressed as means ± S.E.M. of eight animals per group. (*) Denotes $p < 0.05$ and (**) denotes $p < 0.01$ as compared to the control group (one-way ANOVA/Duncan).

On the day of the experiment, each chick was immediately placed separately in a no transparent open box (40 cm × 30 cm × 20 cm). Chicks were observed for 10 min (600 s) and during this period, they were deprived of feed and water. The number of separation-induced distress vocalizations (to index anxiety) and of jumps (to index motor response) was determined. Based on the method described by Van Luijtelaar et al. [29] chick behaviors were classified into four categories: active wakefulness; standing/sitting motionless with eyes open; standing motionless with eyes closed; sitting motionless with head drooped (sleeping posture). The number of separation-induced distress vocalizations (to index anxiety), the number of jumps (index of motor response) and the time that the animals remain in active wakefulness, standing/sitting motionless with eyes open, standing motionless with eyes closed or sitting motionless with head drooped (sleeping posture) were scored by an observer blind to the treatments the subjects received. The time of responses was measured by a stopwatch. All data, times and the number of responses, were calculated by the statistical program described below. All animals were returned to home cages following testing.

Data are expressed as means ± S.E.M. Statistical analysis was performed using a one-way ANOVA (different doses of $(PhSe)_2$) followed by the Duncan's test. Values of $p < 0.05$ were considered statistically significant.

Fig. 1 illustrates the effect of $(PhSe)_2$ treatment on the number of distress vocalization of chicks produced during 10 min of isolation. One-way ANOVA demonstrated a significant reduction in the number of distress vocalization [$F_{(3,26)} = 9.572$; $p < 0.0001$]. $(PhSe)_2$ at doses of 10 ($p < 0.0005$) and 50 mg/kg ($p < 0.0001$) significantly reduced the number of distress vocalization of chicks. Table 1 shows the effect of $(PhSe)_2$ treatment on behavioral categories during 10 min of observation period. One-way ANOVA showed a significant reduction in the time of active wakefulness [$F_{(3,26)} = 5.413$; $p < 0.004$] and a significant increase in the time of standing/sitting motionless with eyes open of chicks [$F_{(3,26)} = 4.153$; $p < 0.015$]. Treatment with $(PhSe)_2$, at doses of 10 ($p < 0.011$) and 50 mg/kg ($p < 0.006$), reduced the time of active wakefulness of chicks. The time of standing/sitting motionless with eyes open was increased in chicks treated with $(PhSe)_2$, at doses of 10 ($p < 0.036$) and 50 mg/kg ($p < 0.009$). One-way ANOVA yielded a significant reduction in the time for sitting motionless with head drooped (sleeping posture) [$F_{(3,26)} = 4.372$; $p < 0.012$]. The time for sitting motionless with head drooped (sleeping posture) was increased in chicks treated with the dose of 50 mg/kg $(PhSe)_2$ ($p < 0.009$). Fig. 2 demonstrates the effect of $(PhSe)_2$ treatment on the number of jumps during 10 min of isolation. One-way ANOVA showed a significant reduction in the number of jumps [$F_{(3,26)} = 3.254$; $p < 0.037$]. $(PhSe)_2$ at doses of 10 ($p < 0.031$) and 50 mg/kg ($p < 0.008$) significantly reduced the number of jumps of chicks. No alteration was observed for all behavioral parameters tested in animals treated with $(PhSe)_2$ at the dose of 1 mg/kg.

In this study, the anxiolytic-like effect of $(PhSe)_2$ was investigated in the chick social separation-stress behavior. Oral administration of $(PhSe)_2$ (10 and 50 mg/kg) attenuated spontaneous activity, the number of vocalizations and jumps of chicks. In addition, $(PhSe)_2$ at the dose of 50 mg/kg increased the time that chicks spent in sleeping posture.

The chick separation-stress paradigm is widely considered to be positively related to the antecedent anxiety state and to thereby represent a useful behavioral index of anxiety [10,32]. Results of the current study demonstrated the powerful effects of social separation-stress in chick behavior. The increase in the time spent for the posture of active wakefulness, in the number of jump and in the distress vocalizations was observed in isolated chicks. Our findings are consistent with previous studies that demonstrated similar alterations in these parameters [5,6,14]. It has been shown

Table 1
Effect of $(PhSe)_2$ on various behavioral categories of chicks during 10 min.

	$(PhSe)_2$ mg/kg			
	0	1	10	50
Active wakefulness[a]	387 ± 43	364 ± 49	195 ± 45*	173 ± 45**
Standing/sitting motionless with eyes open[a]	212 ± 43	235 ± 49	360 ± 41*	403 ± 39**
Standing motionless with eyes closed[a]	0 ± 0	0 ± 0	4.5 ± 4.6	1.4 ± 1.1
Sitting motionless with head drooped[a]	0 ± 0	0 ± 0	0 ± 0	21 ± 10**

Data are reported as means ± S.E.D.

[a] Results are expressed in a time unit seconds.

* Denotes $p < 0.05$ as compared to the control group

** Denotes $p < 0.01$ as compared to the control group (one-way ANOVA/Duncan).