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Physical and neurobehavioral development of rat offspring after maternal exposure to *Valeriana officinalis* during gestation

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The exposure to agents acting on GABA-A system during gestation in rats can produce behavioral alterations in their descendants in the adult life. This work was designed to evaluate the effects of the exposure to *Valeriana officinalis* L. during gestation on the development of the offspring and on their anxiety state and memory in the adult stage. Pregnant rats were randomly distributed into four groups (n = 10): control (1 ml distilled water) and three valerian-treated groups with the doses T-500 (500 mg/kg/day), T-1000 (1000 mg/kg/day) and T-2000 (2000 mg/kg/day). After birth, maternal behavior was evaluated and the physical and reflexological development of the offspring was assessed. The anxiety and memory were evaluated at 90 days of age. Maternal behavior was not affected by treatment with valerian. The offspring exhibited some alterations on the day of appearance of physical signs, which did not affect the adult life, whereas similar days of appearance of the reflexes were observed among the groups. No significant difference was detected in the offspring in the anxiety and memory tests. Therefore, no alterations in the neonatal and neurobehavioral development of rats exposed to valerian during intrauterine life were found in the present work.

Key words: Valerian, pregnancy, gamma-amino butyric acid (GABA), neonatal development, anxiety, memory.

INTRODUCTION

The concept of “natural” has contributed a great deal to the increased employment of medicinal plants to treat our ailments in the last decade, since they became a synonym for healthy products (Mengue et al., 2001). Many studies have already evaluated the effectiveness of phytotherapies, but little has been done so far to investigate the teratogenic

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effect and the effects on the adult life of offspring exposed to drugs during intrauterine life *Valeriana officinalis* L. (Valerianaceae), a species used in the past as folk medicine, has moderate sedative activity, being indicated in the treatment of sleep disorders, anxiety and sleep disorders induced by anxiety (Miyasaka et al., 2006). Studies regarding the toxicity of Valerian have demonstrated that one of its main constituents, namely, valtrate, strongly inhibits DNA synthesis in rat hepatic cell cultures (Bounthanh et al., 1983). In addition, Hui-Lian and colaborators (2003) evidenced the *in vitro* genotoxicity of the valerian dichlorometanolic extract in human cell cultures. *In vivo* studies developed by Yao et al. (2007) did not reveal any increase in the incidence of fetal internal and external malformations and of adverse effects on fertility after the eight-day-oral administration of 2.79 g/kg/day of Valerian extract to pregnant rats. However, Tuffik et al. (1994) reported that high doses of valepotriate (a chemical constituent found in Valerian) can delay ossification.

Nowadays, this species is considered an important raw material for the manufacture of remedies in contemporary medicine. It is suggested that the pharmacological effects of valerian extract and valerenic acid are mediated by modulation of receptor gamma-amino butyric acid (GABA) A function (Benke et al., 2009; Murphy et al., 2010).

During gestation, the hematoencephalic barrier is not fully developed, allowing the transit of substances through the placenta to the fetal organism and brain (Jonhoson, 1980). Possible interaction with receptors, such as GABA receptors, may occur, and in some cases, the alterations in these receptors may persist in the adult life. Therefore, drugs that exert anxiolytic, antidepressant and anticonvulsant roles, among others, may reach the fetus brain (Yang et al., 2010). Corroborating this assumption, many authors have demonstrated changes in the level of anxiety in animals exposed to benzodiazepines during neonatal life (Schroeder et al., 1997).

Therefore, the use of Valerian during gestation could be a promising alternative for the benzodiazepines. This study analyses the influence of prenatal exposure to valerian in the physical and reflexological development of the offspring and its effects on the animals' memory and anxiety in the adult life.

MATERIALS AND METHODS

The methodology of this work was approved by the Ethical Committee on Animal Experimentation (protocol number 019/2011 – CEEA, Federal University of Juiz de Fora, MG, Brazil), which follows the international principles in ethics for animal experimentation

Drug

The dry extract of valerian was supplied by ORTOFARMA® Company, where the physicochemical quality analysis was carried out, and imported by QUIMER® company (registration No. 002/2009). The dry extract was suspended in deionized water and kept from the light. It was then preserved in a vacuum desiccator to avoid humidity.

Animals

Forty female Wistar rats (*Rattus norvegicus* BERCKENHOUT, 1769), 90 days old and with regular estral cycle, were obtained from the vivarirum of the Reproductive Biology Center at the Federal University of Juiz de Fora. The females were placed in cages with male rats for mating at the proportion of two females and one male per cage. The presence of spermatozoa in the vaginal smear indicated successful mating and considered as day one of gestation (DG1) (Beaudoin, 1985).

Pregnant rats were housed individually in cages and randomly divided into four groups (n = 10): three treated and one control that received, by gavage and once daily, 500 mg/kg body weight/day of valerian (T-500), 1000 mg/kg body weight/day of valerian (T-1000), 2000 mg/kg body weight/day of valerian (T-2000), and distilled water, respectively (Al-majed et al., 2006). The dose of 500 mg/kg calculated for the rat was based on the dose recommended for humans, while the two other doses were two and four times higher than the lower dose, as indicated by toxicological protocols. Treatment began on the 12th day of gestation and ended on the 19th day that corresponded to the most vulnerable period for brain development (Vorhees et al., 1990). The animals were kept under standard laboratory conditions, with a controlled temperature of 22 ± 2°C, and a 12-h light/dark photoperiod, with the light period beginning at 06:00 h.

Maternal evaluation

During treatment, the rats were weighed and observed for 30 min for detection of clinical signs of toxicity, such as ambulation, posture, piloerection, diarrhea and stereotypical movements. At the beginning of treatment, the animals received a controlled amount of rat chow pellets (40 g/day/animal) and water *ad libitum*. Food consumption was estimated by the weight difference between the amount of pellets placed in the cages and what was left in the next day. Maternal behavior, such as nursing, cannibalism, pup liking, pup retrieval and nesting were examined (Chiavegatto et al., 1997).

Offspring evaluation

Twenty pregnant rats (5 rats per group, 3 treated and one control) were randomly selected and, after birth, the number of pups and the number of males and females born to each litter were registered. Afterwards, the litter size was standardized to 8 pups/litter. The day of birth was considered the first postnatal day (PND1). In order to avoid the handling of pups and stress, the animals were counted, separated by sex and weighed 24 h after birth and on the 4, 10, 15, 20 and 25th postnatal day (Bailey et al., 2009).

For the evaluation of neonatal development, 4 males were chosen from each litter, and for the behavioral assessment of the pups in the adult life, three males from each litter were selected. The animals were identified by specific marking criteria established by the vivarium of the Reproductive Biology Center.

At 90 days of age (PND 90), the behavioral tests were carried out using 10 animals from each treatment group for the memory tests and 20 animals for the anxiety tests. In the memory tests, the same animals were used in the object recognition test and in the inhibitory avoidance test, while in the anxiety protocols, different animals were

used in the hole-board and elevated plus maze tests to avoid that the stressful situation, leading to an increased anxiety status, of one test interferes with the result of the other test.

Physical development

The signs of physical development examined were: eye opening, ear unfolding, appearance of lanugo and hair, superior and inferior incisors eruption, vaginal aperture and testes descent. The day of first appearance of these features was registered and for even structures, it was registered the first day of appearance of either one (Chiavegatto et al., 1997; Dorce et al,. 2009; Oliveira et al., 2011).

Data were expressed in animal frequency per day of appearance of each physical development sign.

Reflexological development

The following tests were carried out: grasping reflex (holding of a paper clip with the forelimbs), righting reflex (return to normal ventral position after lying on its back), cliff avoidance (animal movement away from the cliff), and negative geotaxis (90° turn after being placed facing down the incline of 45° from the horizontal). The tests were performed daily from PND1 until the day of appearance, with duration of 15 s each (Chiavegatto et al., 1997; Dorce et al., 2009; Oliveira et al., 2011).

Elevated plus maze test

The elevated plus-maze apparatus consisted of two open arms and two closed arms (50 cm long) with walls of 30 cm high elevated 60 cm above the floor. To investigate anxiety of the animals, each rat was placed at the center of the maze facing one of the open arms and the time spent (in seconds) on the open and closed arms were recorded for 5 min. Entry into an arm was defined as the animal having crossed with all four paws, the dividing line between the central area and the arm (Pellow et al., 1985). The variable used as an indicator of anxiety was the time (percentage) the animal spent in the open arms (% tOP): (time spent in the open arms divided by time spent in the open and closed arms) × 100. The use of % tOP instead of the measurement of time spent in the open arms alone has the advantage of taking into account an important intervenient variable which is the locomotor activity of the animal (Rodgers and Dalvi, 1997).

Hole-board test

The hole-board apparatus consisted of a square box like, whose walls are made of clear acrylic sheet (50 × 50 × 30 cm) containing 16 equidistant holes of 2 cm in diameter. Each rat was placed at the center of the hole-board facing away from the observer and the number of head dips was counted for 5 min by photocells placed below the surface of the hole (Rodriguez et al., 1987). After each trial, the hole-board was carefully cleaned with 70% isopropyl alcohol.

Object recognition test

This test was carried out in a medium density fiberboard (MDF) arena (60 × 40 cm) containing anti-slip glass flooring and surrounded by 30 cm high-walls. Before the test, each animal was allowed to explore the arena freely for 5 min. On the next day, the animals were placed again in the arena with two identical white cylinders (A_1 and A_2) positioned at two adjacent corners and submitted to a 5-min training section. In the long-term memory test carried out for 5 min 24 h after the training section, the objects A_1 and A_2 were replaced by another white cylinder (A_3, used in order to avoid olfactory recognition of the objects) and a black cylinder (B). The time spent by the animal exploring the objects A_3 (T_A) and B (T_B) was monitored for calculation of the discrimination index [$T_B/(T_A + T_B)$]. In case the animal remembered the object A_3, the calculated index was expected to be above 50%. Sniffing or touching the object with the snout or paws was considered exploratory behavior. The experimental procedure was based on the methodology developed by Bevins and Besheer (2006).

Inhibitory avoidance test

The inhibitory avoidance box consists of a four-walled acrylic arena (height 21 cm) and floor (20.5 × 22 cm) made of stainless steel bars 1 mm in diameter and 1 cm apart from each other) suitable for application of shock. The animals were placed on a metal plate (length 22.5 cm, width 7cm, and height 2.5 cm) set adjacently to one of the apparatus' side walls. In the training section, the animals received a shock (intensity 0.5 mA) for 2 s, immediately after leaving the metal plate. The long-term memory test took place 24 h after the training section. In this section, shock was not applied and latency time for the rat to leave the metal plate with the four paws was registered. After taking more 3 min to leave the plate, the animal was withdrawn from the apparatus and returned to the cage. After each trial, the avoidance box was cleaned with 70% isopropyl alcohol. The experimental procedure employed in this study was based on the literature data (Vinade et al., 2004).

Statistical analysis

The data obtained from the physical and reflexological tests were presented according to the frequency of pups that exhibited developmental signs in each day and were grouped in three categories: 1: Frequency similar to control group; 2: Frequency prior (anterior) to that exhibited by control group; 3: Frequency posterior to that exhibited by control group.

The results were analyzed using the Chi-square test and differences were considered significant when $p \leq 0.01$ (to avoid the effect of multiple comparisons). In the elevated plus-maze, hole-board and object recognition tests, one-way analysis of variance (ANOVA) was used when normality and homoscedasticity assumptions were unbiased. Otherwise, the Kruskal-Wallis test was used. For the inhibitory avoidance, Kruskal-Wallis test was employed. Data were expressed by mean ± standard deviation. The tests were performed using SPSS software, version 20.

RESULTS

Maternal variables

No clinical signs of maternal toxicity such as ambulation, posture, piloerection, dayrrhea and stereotypical movements were observed. Maternal behavior regarding general activity, nursing, cannibalism, pup liking, pup retrieval and nesting was similar among the groups. No significant different was observed in food consumption and body weight in treated animals when compared with controls ones (data not shown).

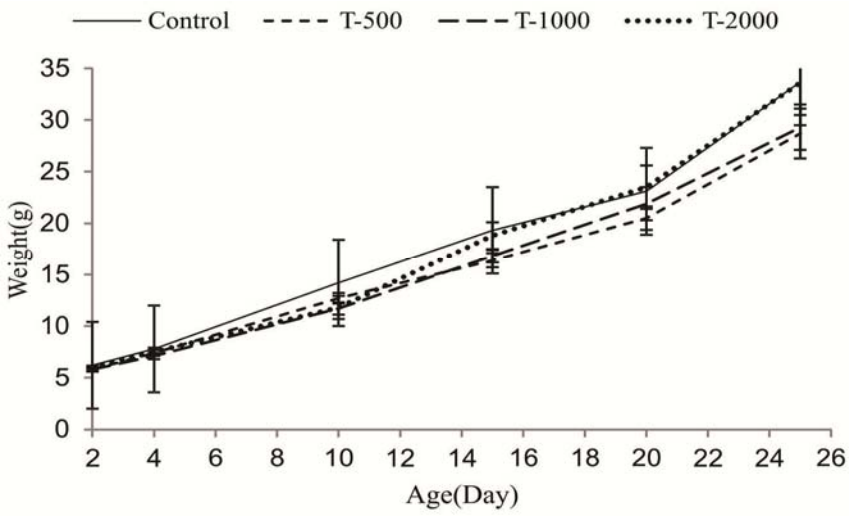

Figure 1. Body weight of male pups from 24 h after birth (day 2) until the 25 postnatal day. Control (n=40), 500 mg/kg (n=40), 1000 mg/kg (n=40), 2000 mg/kg (n=40).
No statistically significant difference was present. Error bar represents standard error.

Offspring development

The weight of pups was not significantly different between treated and control animals (Figure 1).

Physical development

The data of appearance of physical signs such as eye opening, ear unfolding, superior incisor eruption and testes descent was similar among the male groups (Table 1); however, the following parameters were significantly different between treated and control groups: inferior incisor eruption-control and treated T-2000 ($p=0.006$), appearance of lanugo-control and treated T-500 ($p=0.003$), and appearance of hair-control and treated T-500 ($p<0.001$), and control and treated T-1000 ($p=0.006$).

Reflexological development

The data of appearance of the reflexes in male pups did not differ among the groups (Table 2).

Elevated plus maze

The parameter analyzed in this test was the percentage of time spent in open arms (% tOA). The Kruskal-Wallis test did not show any significant difference between the groups ($p=0.48$). The descriptive statistics data of the groups are demonstrated as shown in Table 3.

Hole-board test

According to Kruskal-Wallis test, the number of head-dipping analyzed was not significantly different between the groups ($p=0.58$) (Table 4).

Object recognition test

The parameter object recognition was evaluated through the discrimination index of objects in 24 h-intervals between sections. According to ANOVA, there was no significant difference between the groups ($p=0.73$). The descriptive statistics data of the groups are demonstrated as shown in Table 5.

Inhibitory avoidance test

In this test, the latency time (time the animals spent to leave the platform) was not significantly different between the groups, as evidenced by the Kruskal-Wallis test ($p=0.82$). The descriptive statistics data of the groups are demonstrated as shown in Table 6.

DISCUSSION

During developmental process, a substance is referred to as toxic when there are adverse effects on the offspring development without producing maternal toxicity (Farrar and Blumer, 1991). Experimental studies consider body weight loss, reduced water and food consumption, clinical

Table 1. Physical development of male pups from control or valerian-treated mothers during pregnancy (500, 1000 or 2000 mg/kg).

Physical sign	Control n=23	T-500 n=20	T-1000 n=23	T-2000 n=18
Ear unfolding				
Prior	26.0 (6)	30.0 (6)	13. 0 (3)	66.0 (12)
Day 5	69.5 (16)	70.0 (14)	82.6 (19)	34.0 (6)
Posterior	04.5 (1)	00.0 (0)	04.4 (1)	00.0 (0)
Inferior incisor eruption				
Prior	04.4 (1)	00.0 (0)	00.0 (0)	00.0 (0)*
Day 11	47.8 (11)	45.0 (9)	13.0 (3)	05.5 (1)
Posterior	47.8 (11)	55.0 (11)	87.0 (20)	94.5 (17)
Superior incisor eruption				
Prior	04.5 (1)	00.0 (0)	00.0 (0)	0.00 (0)
Day 9	56.5 (13)	55.0 (11)	43.5 (10)	61.1 (11)
Posterior	39.0 (9)	45.0 (9)	56.5 (13)	38.9 (7)
Appearence of lanugo				
Prior	39.1 (9)	10.0 (2)*	34.8 (8)	72.2 (13)
Day 4	60.9 (14)	35.0 (7)	30.4 (7)	27.8 (5)
Posterior	00.0 (0)	55.0 (11)	34.8 (8)	00.0 (0)
Appearance of hair				
Prior	30.4 (7)	15.0 (3)*	26.0 (6)*	39.0 (7)
Day 8	69.6 (16)	45.0 (9)	52.0 (12)	61.0 (11)
Posterior	00.0 (0)	40.0 (8)	22.0 (5)	00.0 (0)
Eye opening				
Prior	26.0 (6)	50.0 (10)	08.7 (2)	16.7 (3)
Day 17	56.5 (13)	35.0 (7)	65.2 (15)	38.9 (7)
Posterior	17.5 (4)	15.0 (3)	26.1 (6)	44.4 (8)
Testes descent				
Prior	0.00 (0)	0.00 (0)	22.7 (5)	00.0 (0)
Day 20	35.3 (6)	10.6 (2)	04.5 (1)	16.7 (3)
Posterior	64.7 (11)	89.4 (17)	72.8 (16)	83.3 (15)

The results are represented in percentage followed by the corresponding number of males that have exhibited physical development in the three categories: prior, similar day to control, and posterior. *Significant difference between control and treated groups.

signs of toxicity and mortality as primary maternal toxic signs (Castro, 2004). According to these parameters, in this study, the exposure to valerian during gestation did not exert any toxic effect on the mothers.

After birth, maternal behavior is crucial to the survival of the offspring as it can influence the quality of the offspring development in different life stages (Poindron, 2005). Alterations in the maternal metabolism caused by diseases, stress or toxicity may interfere with the offspring development (Sodersten and Eneroth, 1984; Champagne et al., 2003) to the extent that the cognitive development of the rat offspring can be compromised by factors that affect the mother-son relationship (Renard et al., 2005). For example, rats deprived of their mothers in neonatal life, when investigated in the adult life, exhibited increase fear and anxiety in response to a stressor agent (Renard et al., 2005; Renard et al., 2007). Exposure to valerian did not change the nursing, pup liking, pup retrieval and nesting behavior nor did it provoke cannibalism. Moreover, the body weight of the pups from treated mothers did not differ from that of the control group. Together, these data indicate that the pups were properly nursed and

Table 2. Reflexological development of male pups from control or valerian-treated mothers during pregnancy (500, 1000 or 2000 mg/kg).

Reflex	Control	T-500	T-1000	T-2000
	n=23	n=20	n=23	n=18
Grasping				
Prior	00.0 (0)	00.0 (0)	00.0 (0)	00.0 (0)
Day 2	69.5 (16)	80.0 (16)	56.5 (13)	72.0 (13)
Posterior	30.5 (7)	20.0 (4)	43.5 (10)	28.0 (5)
Righting				
Prior	00.0 (0)	00.0 (0)	00.0 (0)	00.0 (0)
Day 2	87.0 (20)	90.0 (18)	83.0 (19)	89.0 (16)
Posterior	13.0 (3)	10.0 (2)	17.0 (4)	11.0 (2)
Cliff avoidance				
Prior	34.8 (8)	20.0 (4)	17.4 (4)	22.2 (4)
Day 7	34.8 (8)	15.0 (3)	47.8 (11)	33.3 (6)
Posterior	30.4 (7)	65.0 (13)	34.8 (8)	44.5 (8)
Negative geotaxis				
Prior	26.0 (6)	15.0 (3)	30.4 (7)	33.3 (6)
Day 6	26.0 (6)	25.0 (5)	17.4 (4)	11.2 (2)
Posterior	48.0 (11)	60.0 (12)	52.2 (12)	55.5 (10)

The results are represented in percentage followed by the corresponding number of males that have exhibited physical development in the three categories: prior, similar day to control, and posterior. *Significant difference between control and treated groups.

Table 3. Descriptive statistics data of groups of male pups from control or valerian-treated mothers during pregnancy (500, 1000 or 2000 mg/kg) in the elevated plus maze.

Group	n	(% tOA)
Control	10	22.93±4.5 (21.5)
T-500	10	20.30±5.4 (16.2)
T-1000	10	21.21±5.5 (15.5)
T-2000	10	39.62±9.8 (43.0)

Results expressed in mean ± standard error (median).

Table 4. Descriptive statistics data of groups of male pups from control or valerian-treated mothers during pregnancy (500, 1000 or 2000 mg/kg) in the hole-board.

Group	n	Hole-board
Control	10	50.7±2.7 (52.5)
T-500	10	45.4±3.8 (44.5)
T-1000	10	47.3±4.1 (47.5)
T-2000	10	44.0±4.5 (40.0)

Results expressed in mean ± standard error (median).

Table 5. Descriptive statistics data of groups of male pups from control or valerian-treated mothers during pregnancy (500, 1000 or 2000 mg/kg) in the object recognition test.

Group	n	Discrimination index
Control	10	58.63±8.8 (58.11)
T-500	10	49.82±5.1 (50.00)
T-1000	10	49.38±8.1 (54.92)
T-2000	10	54.31±2.4 (55.71)

Results expressed in mean ± standard error (median).

Table 6. Descriptive statistics data of groups of male pupsfrom control or valerian-treated mothers during pregnancy (500, 1000 or 2000 mg/kg) in the inhibitory avoidance test.

Group	n	Latency
Control	10	153.0±18.0 (180.0)
T-500	10	151.3±16.4 (180.0)
T-1000	10	129.5±22.4 (180.0)
T-2000	10	147.7±21.0 (180.0)

Results expressed in mean ± standard error (median).

had adequate maternal care and physical development, suggesting that maternal exposure to valerian did not reduce the quality and quantity of milk and did not cause long-term maternal behavior alterations that prevented the care of the pups.

In the physical development, the appearance of lanugo and hair, and inferior incisor eruption were affected by the treatment; however, in the adult life, none of the animals exhibited important morphological alterations as a result of these altered characteristics.

It has been proposed that the pharmacological effects of valerian extract and valerenic acid are mediated by modulation of the GABA-A receptors function (Benke et al., 2009). Studies carried out in rodents have shown that exposure to drugs that act on the GABA-A system during prenatal or neonatal life can interfere with the reflexological development. For instance, exposure to diazepam, a GABA-A receptor binding agent, caused delayed response to fear and negative geotaxis (Nicosia et al., 2003), motor deficit and reduced energetic metabolism in posture and body balance control regions that could be related to impediment of locomotor activity (Schroeder et al., 1995). However, in this study, no differences in the date of appearance of the reflexological responses were observed in the offspring from treated mothers when compared with the control group.

Anxiety and memory are also related to modulation of GABA receptors. The GABAergic transmission inhibits the initial acquisition of fear memory and possibly its consolidation (Kim et al., 2007), and also reduces anxiety (Nutt, 2001). It is known that alterations in the GABA system

during development can persist during the adult life. The GABA neurotransmitter is one of the first to appear during brain development (Fiszman et al., 1993) and modulate the proliferation of non-differentiated cells and neuroblasts, and cellular differentiation (Emerit et al., 1992; Nguyen et al., 2001). In the brain of developing mammals, GABA exerts an excitatory effect, depolarizing the membrane and increasing the level of intracellular calcium (Cherubini et al., 1991) in contrast to the hyperpolarizing action in the mature brain. Owens et al., (1996) suggested that the excitatory effect can influence the initial neocortical development events, such as neurogenesis and synaptogenesis, through the transduction paths of calcium-dependent signals.

Schroeder et al. (1997) have demonstrated that exposure of nursing mothers to diazepam resulted in reduced level of anxiety in the offspring during the adult life and did not interfere with learning and memory. In this study, no alterations were detected in memory of offspring whose mothers were treated with valerian during the most susceptible period of the developing nervous system; however, the valerian extract, which, as specified earlier, acts by GABA system, did not influence the anxiety state.

Data obtained from the literature do not make any reference to the passage of valerian through the placenta; nevertheless, Tuffik et al. (1994) reported that prenatal exposure to valepotriates caused delayed ossification in the offspring, suggesting its passage through the placenta. Differently, in this work, the administration of valerian to pregnant rats did not interfere with postnatal development, anxiety state, learning and memory of the offspring. According Yao et al. (2007), the administration of Valerian extract to pregnant rats did not reveal any increase in the incidence of fetal internal and external malformations and of adverse effects on fertility.

According to Tucker (1995) and Nicosia et al. (2003), developmental alterations occur only with high doses of benzodiazepines, whereas here, the highest dose of valerian used (2000 mg/kg), that is, the highest dose recommended in toxicological assays, was unable to cause developmental alterations in the offspring or in the anxiety state or in the process of memory, suggesting a moderate effect of valerian. It is known that there are various subtypes of GABA-A receptors which vary in function and pharmacology (Olsen and Sierghat, 2009). Therefore, the difference reported in the results found in the literature with respect to intrauterine exposure to benzodiazepines and the results obtained in this study regarding intrauterine exposure to valerian could be due to the interaction of these two psychopharmacs to different subtypes of GABA-A receptors.

Conclusions

The results suggest that maternal exposure to the aqueous extract of *V. officinalis* did not alter the physical, reflexological and behavioral development of rats. Also, it was not possible to verify if this situation was due to the valerian constituents' failure to cross the placental barrier or to the possibility that the extract is innocuous to the fetuses.

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Conflict of Interests

The author(s) have not declared any conflict of interests.

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