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Progesterone prevents depression-like behavior in a model of Parkinson's disease induced by 6-hydroxydopamine in male rats

Sebastián Casas [a,1], Sebastián García [b,1], Ricardo Cabrera [a], Federico Nanfaro [b], Carla Escudero [a], Roberto Yunes [a,b,*]

[a] Instituto de Investigaciones Biomédicas (INBIOMED-IMBECU-CONICET), Universidad de Mendoza, Paseo Dr. Emilio Descotte 720, 5500, Mendoza, Argentina
[b] Área de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de Cuyo, Av. Libertador 80, Centro Universitario, 5500, Mendoza, Argentina

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ABSTRACT

Hemiparkinsonism induced by 6-hydroxydopamine (6-OHDA) injected in left corpus striatum is a recognized model of motor deficits in rats. Some reports concerning motor deficits indicate a favorable response to steroid administration in hemiparkinsonian animals. However, there is no much information regarding progesterone administration in relation to cognitive and affective dysfunctions. Here we could confirm earlier reports regarding a mild deficit of memory and a noticeable depressive-like behavior 4 weeks after injecting 6-OHDA. We also present some evidence that progesterone could be – when administered 7 days after the injection of 6-OHDA – a possible neuroprotector concerning both motor deficits as well as cognitive — memory- and depression-like behaviors. The affective deficit was reverted by administering the tricyclic antidepressant imipramine. Since Parkinson's disease is a conspicuous cause of psycho-organic decline in human beings, it would be important to be able of dealing early with non-motor indicators in order to use prospective neuroprotectors to prevent the progression of the disease.

1. Introduction

Parkinson's disease was first described by James Parkinson in 1817 (cited in Dauer and Przedborski, 2003). It is a relatively common and serious impairment of health in developing countries all around the world, affecting about 1% of the population over 55 years, with a mean age of onset of 60 years (Hayes et al., 2010). The brains of patients suffering from Parkinson's disease show a profound deficit in dopamine levels, because of the loss of neurons of the substantia nigra. Accordingly, authors considered the disease primarily as a disorder of movement (Dauer and Przedborski, 2003). However, there are important cognitive symptoms that precede the motor stage, collectively known as pre-motor phase (Savica et al., 2010; Tadaiesky et al., 2008). These symptoms are responsible, at least in part, for the extreme disability that accompanies the motor stages as the disease progresses (Dauer and Przedborski, 2003).

Pre-motor symptoms precede the motor phase by several years (Hayes et al., 2010). This period – characterized by constipation, hyposmia, sleep disorders, depression, among others – is not only an interesting target for early diagnosis and treatment of the disease but also a critical period to evaluate the elusive impact of neuroprotectors and/or neuroregenerators. Since progesterone has been postulated to be a neuroprotector (Bourque et al., 2009; De Nicola et al., 2009; Djebaili et al., 2004, 2005; Garay et al., 2009; Liu et al., 2010; Singh et al., 2010) we used this steroid to examine whether it could eventually protect our subjects from non-motor and motor components of the model. In order to do so, we decided to use a 6-hydroxydopamine (6-OHDA) toxin-based model of parkinsonism in rats (modified from Dauer and Przedborski, 2003). Several reports informed that unilateral 6-OHDA-lesioned rats are suitable for behavioral and biochemical evaluation of models of Parkinson's disease (Kondo et al., 2004; Ahmad et al., 2005; Saravanan et al., 2005). Additionally, there exists some literature regarding asymmetric Parkinson's disease in human beings, which supports the use of the proposed model (Rafal et al., 1989; Tessitore et al., 2010).

It is well known that progesterone – when used in 6-OHDA injected subjects – affects motor components as well as reproductive behaviors in female rats and hamsters (Hansen et al., 1991; Frye et al., 2010). Here we centered our interest around two common non-motor–non-reproductive-symptoms (Tadaiesky et al., 2008): 1) cognitive disorders in an appetitive model of memory (by using a novel object recognition test); and 2) depression-like behaviors (by using a forced swimming

* Corresponding author at: Instituto de Investigaciones Biomédicas, Universidad de Mendoza (INBIOMED-IMBECU-CONICET), Paseo Dr. Emilio Descotte 720, 5500, Mendoza, Argentina. Tel.: +54 261 4230127.
E-mail address: ryunes@lab.cricyt.edu.ar (R. Yunes).
[1] Both authors contributed equally to this work.

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test). Our results provide some interesting cues regarding what could eventually be a useful area of research in order to study non-motor stages in animal models, and the possible utility of using neuroactive steroids as neuroprotectors.

2. Materials and methods

2.1. Animals

We used male Sprague Dawley rats from our breeding colony. They were 60–120 days old at the beginning of the study, and their weight was 280–340 g. Experimental subjects were housed under controlled temperature (22 ± 2 °C) and lighting (12 hour light cycle beginning at 06.00 a.m.) conditions, with food and water made available ad libitum. Animals for these experiments were kept and handled according to the Guide for the Care and Use of Laboratory Animals of the National Research Council (National Academies, U.S.A., 8th edition, 2011). All efforts were made to minimize animal suffering.

2.2. Reagents

6-Hydroxydopamine hydrobromide, amphetamine, desipramine HCl, and progesterone were purchased from Sigma-Aldrich (St. Louis, MO, USA). Apomorphine hydrochloride was obtained from Research Biochemicals International (Natik, MA, USA). Chloral hydrate was purchased from Anedra (Buenos Aires, Argentina). Imipramine HCl was obtained from Farmacia Sevilla (Mendoza, Argentina).

2.3. Surgical procedures

In order to achieve unilateral lesions of the nigrostriatal system, rats received 6-OHDA injections into the left striatum. Animals were anesthetized with chloral hydrate (400 mg/kg, i.p.) and placed into a stereotaxic frame (David Kopf, USA). 6-OHDA was dissolved at a concentration of 2 μg/μl saline in 0.1% ascorbic acid. The lesion was performed by injecting the toxic with a Hamilton syringe at the following coordinates: AP: −1.2 mm; ML: ±1.1 mm; DV: −5.0 mm; TB at ±0 mm. The injection was conducted at a rate of 0.5 μl/min and the needle was left in place for another 5 min before it was slowly drawn back. To prevent uptake by noradrenergic neurons, animals were pretreated with desipramine (25 mg/kg, i.p.) 30–40 min before injection of 6-OHDA (Larramendy et al., 2008).

2.4. Experimental design and drug-induced behavioral tests

Behavioral records were all performed by an observer blinded to the experimental condition of the group as well as to any previous performance of the subjects in other behavioral tests. Procedures were performed according to the following outline: a) besides leaving some intact animals, adult rats were randomly selected in order to be surgically injected with the neurotoxic 6-OHDA, or received only a saline injection; b) seven days later the animals were randomly assigned to one of 4 experimental groups: 1) sham group: the animals were handled as in the other groups, but they were neither injected with 6-OHDA nor administered any experimental treatment at all; 2) progesterone control group: subjects in this group were administered only progesterone 4 mg/kg s.c. at noon for three consecutive days, according to Gonzalez et al. (2006); 3) hemiparkinsonian group: the subjects were injected with 6-OHDA in their left striatum during original surgery, and then received no additional treatments; and 4) hemiparkinsonian/progesterone group: as in the previous group, but here the subjects were administered progesterone 4 mg/kg s.c. at noon for three consecutive days, according to Gonzalez et al. (2006); c) two weeks after surgery all groups were tested for amphetamine-induced ipsilateral rotation according to the protocol described below; d) four weeks after surgery all groups were tested for apomorphine-induced contralateral rotation according to the protocol described below; e) finally, 2 days after testing contralateral rotation, the subjects were sequentially tested in the following behavioral tests: 2 days for the novel object recognition test (NORT) and 2 days for the forced swimming test (FST). The open field test was performed shortly before NORT and FST in order to avoid potential confounding variables. The behavioral tests are described below in detail (Sections 2.5, 2.6 and 2.7).

Each experimental group began with at least 12 animals. We dismissed animals not showing ipsilateral movements 2 weeks after injecting 6-OHDA or not showing contralateral movements 4 weeks after injecting 6-OHDA, according to the protocol described below. At least 8–10 animals were finally assigned to each group.

Amphetamine-induced rotation was measured at 2 week post-lesion. Rats received 1 mg/kg amphetamine i.p. (Larramendy et al., 2008), and were placed in individual plastic bowls with a diameter of 20 cm and attached via a specially adapted harness to an automated rotameter (Rotamex, Columbus Instruments, Columbus, OH). They were allowed to habituate to their dimly lit environment for 10 min before contralateral and ipsilateral turns – regarding the side of the lesion – were recorded over 90 min. Results were expressed as ipsilateral net turns/min (Galpern et al., 1996).

Apomorphine-induced rotation was tested at 4 weeks post-lesion. Apomorphine was injected s.c. at a dose of 2 mg/kg (Estrella et al., 2002) and rotation was monitored for 90 min using the same experimental set up as for amphetamine-induced rotation. Results were expressed as contralateral net turns/min.

2.5. Open field test

In order to assess the locomotive and exploratory activity of the animals – avoiding potentially confounding variables affecting the main memory results, i.e., the effect of fear, motivation and limitations regarding locomotive activity – we used an open field, according to Kaur et al. (2010), excepting for the fact that the floor of the box was painted black instead of white. The apparatus consisted of a wooden box 90.0 × 90.0 × 38.0 cm positioned in a dimly lit room. The floor was divided by 1 cm wide white lines into 25 squares 17.0 × 17.0 cm (16 peripheral squares and 9 central squares). Initially the animals were placed in the center of the box. For the following 10 min, the following measures were recorded with a computer according to a simplified ethogram: 1) ambulatory activity: all movements detected as displacement; 2) non-ambulatory activity: any activity performed by the animal while remains in the same place; 3) time spent by the animals adjacent to border squares or using center squares of the box during their displacement; 4) vertical activity: times the animal rise for at least 2 s on their rear feet in the air or against the walls. The ethogram was registered with the free software Etholog v2.0 (Ottoni, 2000).

2.6. Novel object recognition test

The apparatus consisted of a wooden box (70 × 45 × 30 cm) with a white acrylic floor. It was located in an isolated testing room that was dimly lit by constant indirect illumination from the main source, a 25 W light bulb suspended over the box. The objects utilized as familiar (previously experienced object) or unfamiliar (object not previously experienced, i.e. the novel one) were three copies of a pink truncated pyramid and a grayish-opaque candlestick — of approximately the same size, all of which were heavy enough to prevent displacement by the animals. Since rats are red color-blind, we compared grayscale values for both the pyramids and the candlestick, finding that the grayscale value for the pyramids was a composed red–green–blue (RGB) of 166 (the whole range extending from 0 to 255), while the corresponding value for the candlestick was R165:G169:B161, accounting for an average

value of RGB 165. From these values we concluded that the objects were: 1) quite comparable regarding their grayscale values; and 2) the present study dealt mainly with the shape of the objects and not their respective colors. The novel object recognition test was performed as described elsewhere (Nanfaro et al., 2010). Briefly, the animals were allowed to get used to the experimental room for at least 1 h. The day before training, each animal freely explored the apparatus with no objects for 2 min. A training session (T1) was followed by a test session (T2) 24 h later. During training session, animals were placed in the arena containing two identical objects (pink truncated pyramids). In the test session a familiar object was changed for an unfamiliar one (grayish opaque candlestick). Both training and test stages were 3 min each. The position of the objects (familiar and unfamiliar) and the extreme of the box used to place the objects were randomly exchanged for each experimental animal in order to avoid the use of potential confounding spatial clues. Exploration was defined as the orientation of animal's snout toward the object within a range of 2 cm or less from the object. Running around the object or sitting on it was not recorded as exploration. The objects and floor were carefully cleaned with ethanol (10%) after each individual trial to equate olfactory cues. The experiments were recorded with a camcorder digital camera JVC Everio GZ-MG330 (Japan) using a black and white recording mode in order to improve the register. The measures in the object recognition test were as follows: 1) total time spent by the subject exploring both objects during training (T1); 2) total time spent by the subject exploring just the novel object during T2; and 3) discrimination index, the difference between time spent exploring unfamiliar and familiar objects during T2.

2.7. Forced-swimming test

The procedure was previously described by Porsolt et al. (1978). Briefly, rats were placed in individual plexiglass cylinders (40 cm in height and 23 cm in diameter) containing water (water depth was 30 cm; temperature of the water 25 ± 1 °C). Two swimming sessions were conducted (an initial 15-min pre-test — day 1 followed 24 h later by a 5-min test — day 2). The total duration of immobility was manually scored continuously for a 5-min period. A rat was regarded as immobile when floating motionless or making only those movements necessary to keep its head above the water. Additionally, it was carefully registered the type of behavior (climbing attempts, swimming around the cylinder and diving) and the time spent by the subject animals in performing these behaviors. Animals were treated 30 min after training with an i.p. injection of imipramine HCl 10 mg/kg of body weight.

2.8. Statistical analysis

For the statistical analysis we utilized the software *StatView* for Windows (Abacus Concepts, Berkely, CA, USA). We performed the test of Shapiro–Wilks in order to prove whether or not our data came from a normally distributed population, which was precisely the case. We analyzed the discrimination index for object recognition, locomotive and exploratory behaviors by using a one-way ANOVA test followed by a Newman–Keuls *post-hoc* test. Pair comparisons were analyzed using the Student-*t* test. Data are expressed as the mean ± SEM. A value of $p<0.05$ was considered as statistically significant.

3. Results

The hemiparkinsonism induced by injection of 6-OHDA in the left striatum was experimentally assessed by checking the site of injection with a binocular microscope immediately after finishing the experiment (Fig. 1). Subjects injected outside of the target were dismissed of this work. Functional studies were performed in order to know whether we were using either healthy animals – controls – or animals treated with 6-OHDA. To evaluate those conditions we utilized an automatic rotameter according to published standards (Gonzalez et al., 2006). Two weeks after 6-OHDA administration we induced DA release after injecting amphetamine (Larramendy et al., 2008). Any animal failing to display ipsilateral movements regarding the site of injection was dismissed from the study. After 4 weeks of receiving the neurotoxin, remaining animals were tested again for their rotational behavior, but this time for movements contralateral to the site of injection, by administering apomorphine, a potent dopamine agonist (Frankel and Lees, 1990). Again, animals were dismissed if they failed in showing the expected rotational response. Animals were examined for spontaneous movements in week 4, establishing that there were no differences between control animals (sham operated) and controls injected with progesterone. In other words, progesterone did not show any deleterious effects per se. On the contrary, animals injected with 6-OHDA showed a statistically significant difference between contralateral (right) and ipsilateral (left) rotations, dominating right rotations. This result indicates clearly a diminished function of the left striatum (Fig. 2, panel A). Here is important to note that animals

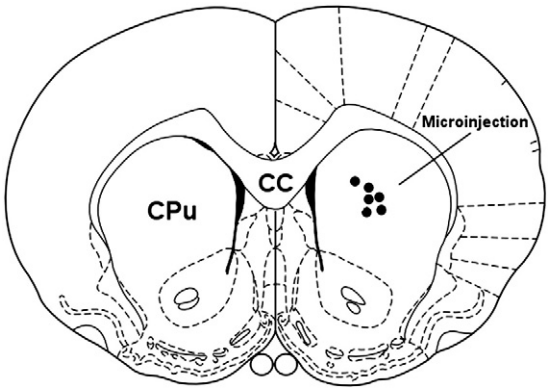

Fig. 1. Schematic representation of a brain coronary section showing the corpus striatum and the place where six illustrative microinjections were performed. Abbreviations: CC, corpus callosum; CPu, caudate putamen.

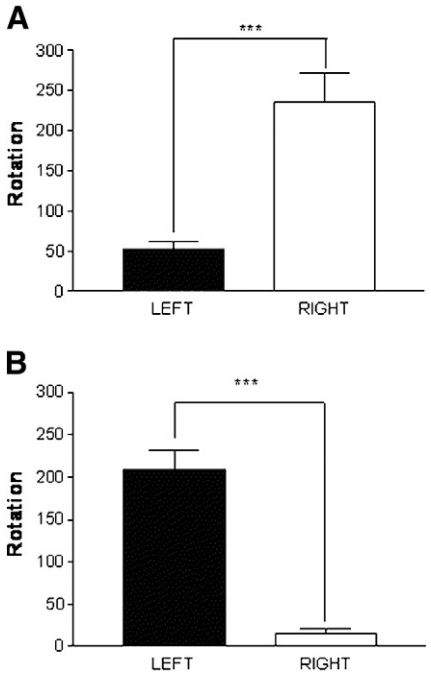

Fig. 2. Apomorphine-induced rotational test. Results are expressed as contralateral net turns/min. A) 6-OHDA injected animals; and B) 6-OHDA injected animals treated with progesterone. At least 8–10 animals were assigned to each group. *$p<0.001$.

treated with progesterone showed an opposite rotational behavior, now prevailing a left rotational behavior (Fig. 2, panel B).

To examine memory deficits we used an appetitive memory task known as novel object recognition (NORT). We selected this test because: 1) it is an appetitive test (Ennaceur and Delacour, 1988; Nanfaro et al., 2010), which means it applies to a group of natural occurring behaviors of rats in the wild, i.e. animals are naturally engaged by novel objects and their potential adaptive value (Dere and Huston, 2007); and 2) since it is an appetitive task, the test can be used repeatedly with the same animals by changing the objects. Our results showed no difference regarding the time spent by subjects exploring the two objects during the training phase (Fig. 3, panel A). When tested 24 h later, the 6-OHDA group showed a significant reduction of the time spent in exploring the novel object in relation to the group treated with progesterone (Fig. 3, panel B). This result is in line with several reports dealing with enhancing effects of progesterone on cognitive processes (for a review see Frye, 2009b). Also, it was indicative of a mild memory deficit, particularly so since there were no differences in any measure regarding the open-field test, i.e. there was no evidence of 6-OHDA animals being less motivated, more anxious or stiller than sham subjects. We cannot rule out the possibility of depression-like behaviors manifested as a lack of interest – anhedonia – regarding any object, novel or not, after a delay of 24 h. In fact, although it fell short of statistical significance, there was a clear tendency of 6-OHDA animals not treated with progesterone to spend less time exploring objects during the training phase. Interestingly, this apparent lack of motivation was undetected in the open field test, as mentioned above.

In order to further explore the possibility of dealing with anhedonic animals, we tested our subjects in a paradigm of depression-like behavior in rodents known as forced swimming test (Porsolt et al., 1978; Kulkarni and Dhir, 2007). Here, 6-OHDA animals without any treatment spent a significant more amount of time immotile during the first day of the test than in any other group, i.e. the animals did not actively fight against the stressful situation the test involves (Fig. 4). In order to confirm these results we treated our subjects with

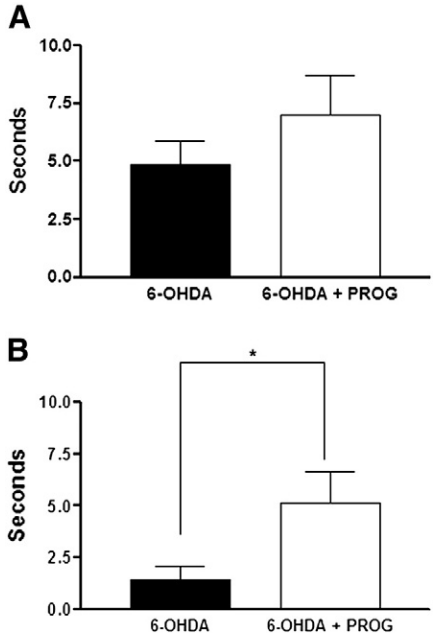

Fig. 3. Novel object recognition test performed on 6-OHDA injected animals. Animals without any further treatment are represented by black bars, and animals treated with progesterone (4 mg/kg s.c. — 3 doses — 1 week after being injected with 6-OHDA) are shown by white bars. A) total time spent by the animals exploring both objects during the training phase; B) total time spent by the animals exploring just the novel object. Results represent the mean ± SEM expressed in seconds during the test session. At least 8–10 animals were assigned to each group. *$p<0.05$.

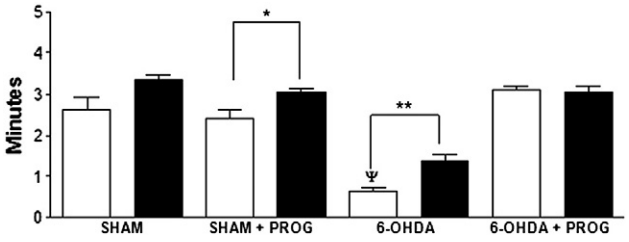

Fig. 4. Forced swimming test before (Day 1 = white bars) and after (Day 2 = black bars) treatment with imipramine HCl 10 mg/kg s.c. Bars show the time in minutes spent by animals trying to escape from the cylinder filled with water. Groups are as follows: sham animals (SHAM); sham plus progesterone treatment (SHAM + PROG); injected animals (6-OHDA); and 6-OHDA injected animals treated with progesterone (6-OHDA + PROG). Ψ $p<0.0001$ (shows the difference among the 6-OHDA group during training day against all the remaining training groups). At least 8–10 animals were assigned to each group. *$p<0.05$ (where it applies, shows differences between white and black bars).

imipramine, a tricyclic antidepressant that improve depression-like behaviors in rats in the forced swimming test (Kiloh and Ball, 1961). As expected, there was a statistically significant difference between day 1 (training) and 2 (test) phases, with an improvement of fight behaviors in rats previously showing depression-like behavior (Fig. 4, 6-OHDA). This result supports our point of view that 6-OHDA subjects were enduring a depression-like process, similar to what was previously reported by other groups (Branchi et al., 2008;Tadaiesky et al., 2008), and extensively reviewed by Frye (2009a).

4. Discussion

It is well known that there is a higher susceptibility for men regarding Parkinson's disease (Shulman, 2007). This fact suggests a neuroprotective role of sex steroids, protecting women not only from Parkinson's disease but also from several brain injuries (Grandbois et al., 2000). The most compelling evidence is the influence of estrogens – particularly 17β-estradiol – in preventing the disease (Callier et al., 2001; Bourque et al., 2009). Also, it has been reported that estrogens are particularly effective if neurons are healthy at the time of treatment (Chen et al., 2006). On the contrary, androgens did not protect against toxin-induced models of Parkinson's disease (Bourque et al., 2009). Progesterone has comparatively received less attention as a neuroprotective molecule, alone or in combination with estrogens. This is rather unusual since progesterone receptors are broadly expressed throughout the whole brain in several splice variants (for a review see Brinton et al., 2008). There are some reports showing beneficial effects of progesterone on brain functions, like neuroprotection, enhancement of cognitive capabilities and neurogenesis (Brinton et al., 2008), as well as sexual behavior, motivation, anxiety and response to drugs of abuse (Frye, 2007).

In the present study, there was a period of at least 3 weeks for progesterone to exert its beneficial role in preventing motor, cognitive and affective disorders (Figs. 2, 3 and 4). So, we cannot exclude any possibility regarding progesterone's mechanisms of action: regulation of gene expression, modulation of neurotransmitter systems – it has been proposed a possible indirect mechanism involving substantia nigra GABAergic neurons' excitability (Veliskova and Moshe, 2006) – activation of signaling cascades, or maybe all of them at the same time or differentially manifested along the elapsed time of the experiment. Notwithstanding, it is clear that progesterone is acting either as a neuroactive steroid and/or as a neurosteroid itself or via one or more of its 5α-reduced derivatives, i.e. dihydroprogesterone and tetrahydroprogesterone (allopregnanolone) (Baulieu, 1998; Brinton et al., 2008). It is worth noting that we administered progesterone coincidentally with the signs of early damage of dopaminergic terminals and cell bodies in the nigrostriatal pathway reported elsewhere (Tadaiesky et al., 2008). Recently, it has been proposed that an early stage of degeneration would be an appropriate time for neuroprotection by steroids since at that time

6-OHDA produces a loss of dendritic processes in cells of the substantia nigra (Bourque et al., 2009). It is possible to suggest that progesterone could support neurons by – among other things – protecting them against the loss of their dendritic processes.

Here we showed that hemiparkinsonian rats provide a robust model of work, both in terms of motor impairment and non-motor disorders. By using this model we showed that: 1) it was possible to prevent the rotational contralateral behavior induced by 6-OHDA by treating the subjects with progesterone 7 days after the lesion, suggesting a possible neuroprotective role for this steroid; 2) it was evident a mild memory deficit in an appetitive task involving experimental subjects not treated with progesterone; and 3) it was possible to revert a non-motor depression-like behavior in hemiparkinsonian animals by using progesterone as a neuroprotector. Currently we are trying to establish whether there is a potential relationship between neuroprotective actions of progesterone and enhanced organelles functions – particularly mitochondrial function – so neurons can better resist degenerative damage.

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