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Behavioral and hormonal changes after continuous testosterone administration in adult females of capuchin monkeys (Sapajus Libidinosus)

Alterações comportamentais e hormonais após a administração contínua de testosterona em fêmeas adultas de macacos-prego (Sapajus Libidinosus)

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Abstract

Although the role of estradiol in female sexual behavior is well documented, some studies have suggested a joint action of this steroid with testosterone in modulating female sexual behavior. Therefore, the objective of this study was to evaluate the effects of testosterone administration on the behavioral and hormonal aspects of female capuchin monkeys (Sapajus libidinosus). 12 adult female capuchin monkeys kept at the Primatology Center of the University of Brasília were used. The study was divided into three phases, that is, 1st phase: baseline (24 days); 2nd phase: testosterone treatment (63 days) and 3rd phase: Placebo (63 days), totaling 150 consecutive days. The sexual and non-sexual behavior of the monkeys was monitored throughout the phases using the Focal Animal Method. For hormonal analyses, 15 blood samples were collected from each female every 10 days. An increase in the frequency of expression of sexual behavior ($p<0.05$) and serum levels of testosterone and DHT ($p<0.05$) was observed during testosterone treatment. Thus, this study points to a positive effect of exogenous testosterone in modulating the sexual behavior of female capuchin monkeys. The results of this study may contribute to a better understanding of continued testosterone use in humans and may be useful in assessing the risks of chronic testosterone use.

Keywords: Testosterone; Sexual Behavior; Physiological Changes; Primates.

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Resumo

Embora o papel do estradiol no comportamento sexual feminino esteja bem documentado, alguns estudos têm sugerido uma ação conjunta deste esteroide com testosterona na modulação do comportamento sexual feminino. Portanto, o objetivo deste estudo foi avaliar os efeitos da administração de testosterona nos aspectos comportamentais e hormonais de fêmeas de macacos-prego (Sapajus libidinosus). Foram utilizados 12 macacos-prego femeas adultos mantidos no Centro de Primatologia da Universidade de Brasília. O estudo foi dividido em três fases, ou seja, 1ª fase: basal (24 dias); 2ª fase: tratamento com testosterona (63 dias) e 3ª fase: Placebo (63 dias), totalizando 150 dias consecutivos. O comportamento sexual e não-sexual dos macacos foi monitorado ao longo das fases pelo Método Animal Focal. Para análises hormonais, foram coletadas 15 amostras de sangue de cada fêmea a cada 10 dias. Observou-se aumento na frequência de expressão do comportamento sexual ($p<0,05$), nos níveis séricos de testosterona e DHT ($p<0,05$) durante o tratamento com testosterona. Assim, este estudo aponta para um efeito positivo da testosterona exógena na modulação do comportamento sexual de fêmeas de macacos-prego. Os resultados deste estudo podem contribuir para uma melhor compreensão do uso continuado de testosterona em humanos e podem ser úteis na avaliação dos riscos do uso crônico de testosterona.

Palavras-chave: Testosterona; Comportamento Sexual; Alterações Fisiológicas; Primatas.

INTRODUCTION

Capuchin monkeys exhibit a vast behavioral repertoire used in the communication of individuals, which is essential for hazard warning, hierarchical dominance status, and indicators of the reproductive period (Fragaszy *et al*. 2004). In the reproductive context, female capuchins signal alpha males the period of ovulation, since, during the preovulatory stage, they display a variety of sexual behaviors such as eyebrow raise, mutual gaze, head cocking, grin, and massaging of the breasts, genitals, and armpits (Carosi *et al*., 2005). It is worth mentioning that female capuchin monkeys are a unique neotropical species with a menstrual cycle, that is, an ovarian cycle, very similar to humans and other Old World primates (Domingues *et al*., 2007). The average cycle time of this monkey is ±19 days, divided into two distinct phases: the follicular phase (first phase) and the luteal phase (second phase).

The phases of the menstrual cycle of female capuchin monkeys are also characterized by different levels of sex steroids. Estrogens, especially estradiol are present during the follicular phase, and progesterone in the luteal phase (Nagle *et al*. 1979). Estradiol also modulates sexual behavior in these monkeys, since there is a positive correlation between increased levels of the steroid and the display of sexual behavior that occurs in the phase that precedes ovulation, i.e. the follicular phase of the menstrual cycle (Carosi *et al*., 2002; Carnegie *et al*., 2005; Carosi *et al*., 2005), this result is the same observed in other primates (Shideler *et al*., 2001; O'Neill *et al*., 2004; Roney and Simmons, 2013).

Although the role of estradiol in the sexual behavior of the female primate is well documented, studies have demonstrated that estradiol collaborates with testosterone in the modulation of the sexual behavior of females, including in humans (Braunstein *et al*., 2005; Nelson *et al*., 2005). In women, there is an increase in androgen levels in the preovulatory phase, which precedes ovulation (Maner and McNulty, 2013), normally, during this phase women are more attractive (Trouton *et al*., 2012) (Roney and Simmons, 2013). and receptive to mates. Thus, both testosterone and estrogen have an important role in the expression of human sexual behavior.

Considering the physiological similarities of the menstrual cycle of monkeys in comparison to women, our study aimed to monitor throughout the menstrual cycle the sexual and non-sexual behavior of female capuchin monkeys after continuous use of testosterone. We hypothesize that testosterone acts in the modulation of the sexual behavior of these primates. Yet, the objective of this study was to analyze the effects of exogenous testosterone use in serum levels of estradiol, estrone, DHT (dihydrotestosterone), and testosterone. However, for the latter objective, the hypothesis is that the administration of testosterone does not promote changes in estradiol, estrone, DHT, and testosterone levels, whereas the route of administration, i.e. intranasal is fast-acting and without hepatic metabolism (Banks *et al*., 2009), Even in non-human primates, since the use of intranasal testosterone affected physiological parameters of blood coagulation (Rodrigues et al., 2019). Therefore, management action intravenously preferably has effects on the central nervous system.

Importantly, this study was the first to address the role of testosterone in the menstrual cycle of Neotropical female monkeys. Although Tavares *et al*., (2007) examined the effect of acute administration of testosterone on the sexual behavior of female capuchin monkeys this study lasted only 10 days, which does not cover the period, representing the effect on the menstrual cycle. Thus, the results of this study have the intention to contribute to a better understanding of the possible hormonal modulators of sexual behavior throughout the menstrual cycle of these females.

MATERIALS AND METHODS

Ethical aspects

The current study was approved by the Committee for Ethical Animal Research from the Faculty of Medicine at the University of Brasilia (UnB) (UnBdoc 101375/2011). Every ethical aspect associated with animal research established by the Brazilian College of Animal Experimentation was strictly followed during this study.

Subjects and Local Studying

For this study, 12 female capuchin monkeys (*Sapajus libidinosus*) aged 12 years on average were used. These were maintained in trios composed of two females and one adult male, used only as behavioral companions. Every subject used in this study was kept at the Primatology Centre of the University of Brasilia (CP-UnB), according to the norms of the Brazilian Institute of Environment (IBAMA – register number 1/53/1999/00006-2).

At the CP-UnB, animals are kept in cages in the middle of the Brazilian Savannah, with natural luminosity, temperature, and humidity. Each cage measures 4m X 2m X 3m (depth, width, height). A nest box is found in each cage to serve as shelter for the animals, besides ropes and swings as a form of environmental enrichment. This experiment did not alter the diet and daily care of the animals. Veterinarians also constantly evaluated them.

Administration of testosterone and placebo.

Mattern Pharmaceuticals AG (Stans, Switzerland) provided the testosterone (Noseafix®) and placebo. Each female was given 0.10ml of the viscous gel, on each nostril, which corresponds to a dose of 0.24mg of testosterone. Females were given testosterone or the placebo three times a week in fixed intervals (Mondays, Wednesdays, and Fridays), once a day, every morning, in 1ml syringes without needles. These administrations lasted three consecutive menstrual cycles.

Blood samples

To analyze the physiological data, blood samples were collected. For this purpose, animals were separated from their group and taken to the biomedical procedure room, where they were anesthetized and had their blood collected. Anesthesia was done by inhalation of isoflurane with the aid of anesthetic equipment (Vetcase® Brasmed). After making sure that physiological parameters such as cardiac and respiratory frequencies indicated sedation, a volume of 8 to 10ml of blood was collected via venipuncture (femoral vein) for each female. The order of capture for the females was the same throughout the experiment and the blood samples were taken always in the morning, between 8:00 am and 12:00 pm. The total time of this procedure was between 5 and 20 minutes depending on each animal.

Throughout the study, 15 blood samples were taken from each female, one sample every 10 days. This procedure was strictly followed to obtain blood samples from the two phases of the menstrual cycle: follicular phase (mid-cycle) and luteal phase (end of cycle).

The blood was kept in tubes and transported to SABIN Laboratory, where the following parameters were measured: female sexual steroids (estradiol and estrone), male dihydrotestosterone (DHT), and testosterone.

Study Design

As presented in Figure 1, the current study lasted for 150 consecutive days, divided into 03 phases: 1st phase: baseline (BL) 21 days: no treatment and two blood samples; 2nd phase: testosterone (TT) 63 days: thirty administrations of gel composed of testosterone and six blood

samples; and last phase 3rd phase: placebo (Plac.) 63 days: administration of placebo gel, and six blood samples. Throughout all experimental phases, sexual and non-sexual behavior of females was monitored.

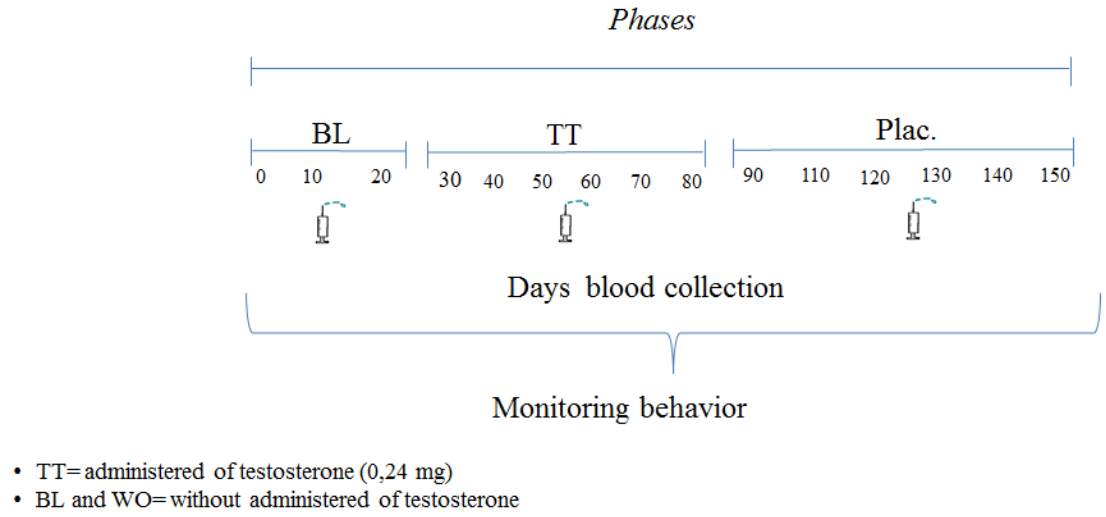

Figure 01- Experimental design with BL phases (Baseline); TT (administration of testosterone) and Plac. (Vehicle administration), day of blood collection and behavior monitoring of female capuchin monkeys (n=12).

Analysis of behavioral aspects

Monitoring of sexual behavior was done throughout every experimental phase. Each female was observed for 20 minutes per day, being one 10-minute observation in the morning (8:00 am to 12:00 pm) and another one in the afternoon (2:00 pm to 5:00 pm). The method used was instantaneous recording with 15-second intervals. The following sexual behaviors were noted: eyebrow raise, breast massage, axial massage, genitalia massage, grin, mutual look, and head cocking. All behaviors are defined and described in the current literature (Carosi and Visalberghi, 2002, Carosi *et al*., 2005 Carnegie *et al*., 2005). Etholog (2.25) was used to register these behaviors freely available from the University of São Paulo (USP).

Analysis of statistical data

To evaluate the effects of chronic use of testosterone, the average and standard error (±SE) of each physiological and behavioral parameter was calculated. Since female sexual behaviour in the mornings did not differ from the one in the afternoon, the data were concatenated.

Both physiological and behavioral data were analyzed via the Multivariate Analyses of Variance (MANOVA). When significant results were obtained, analyses were followed by the Tukey Post Hoc Test. Every statistical result was obtained via the statistical software SPSS ® version 20. Averages were considered significantly different when p≤0,05.

RESULTS

The results show that the chronic use of testosterone can influence the physiological and behavioral parameters of female capuchin monkeys. There is an increase in testosterone levels ($F_{2, 156}$=13,54; p<0,001) during the TT phase, and DHT ($F_{2, 156}$=4,35; p<0,002) during both TT and Plac phases (Figura 02). None of the other physiological parameters studied, namely, estradiol ($F_{2, 156}$=0,34; p=0,71) and estrone ($F_{2, 156}$=0,74; p=0,74) showed changes between experimental phases (see Figure 2).

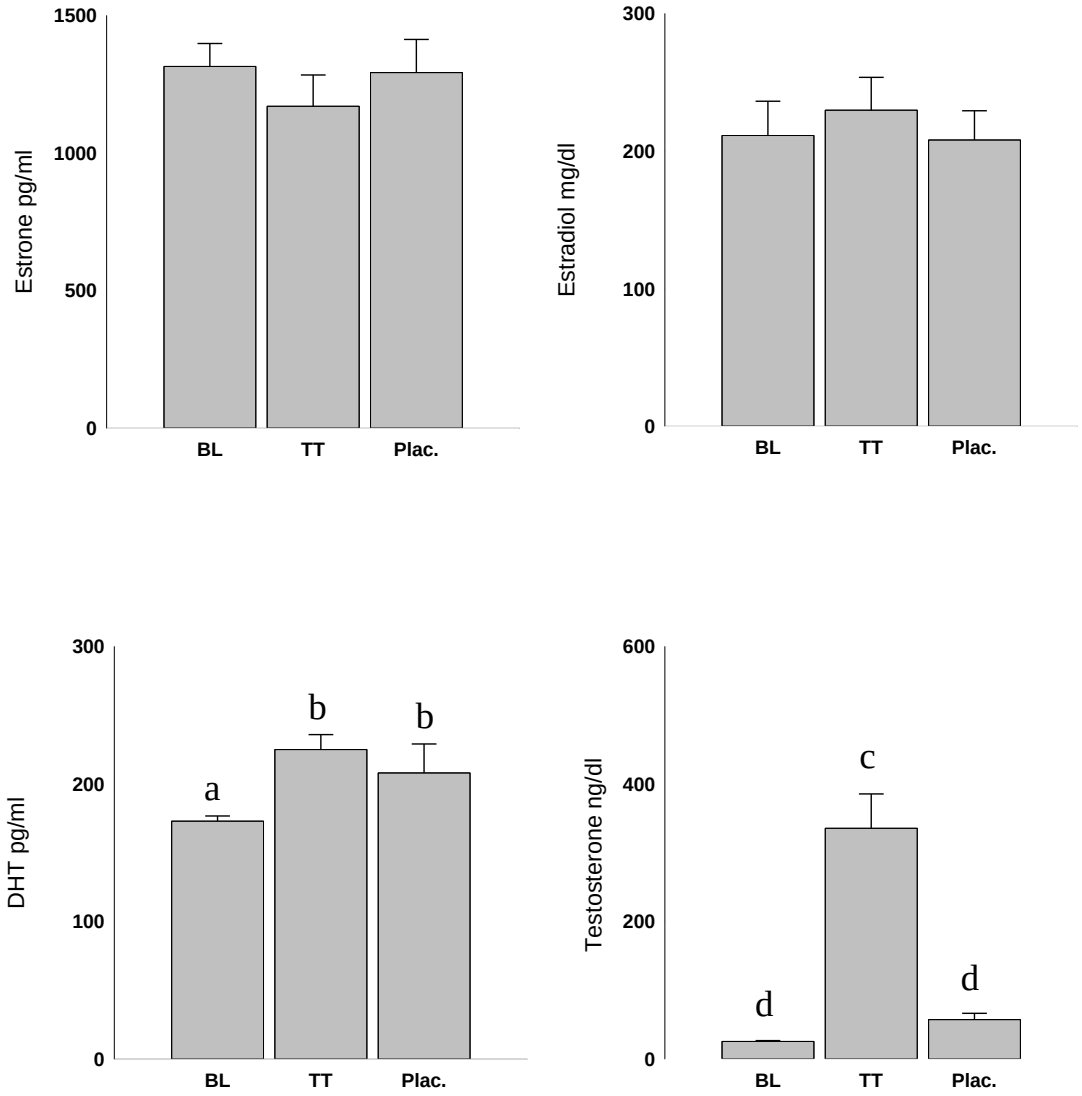

Figure 02 - Mean (±EPM) levels of estrone (pg/ml), estradiol (mg/dl), DHT (pg/ml) and testosterone ng/dl phases BL (baseline), TT (testosterone administration), and Placebo. (placebo administration) in female capuchin monkey (*Sapjus libidinosus*) (n= 12) [a] p<0,05 BL *vs* [b] p<0,05 TT and Plac.; [c] p<0,05 TT *vs* [d]BL and Plac. (p<0.05).

In Table 01 we can see that in phase (TT) no increase in these sexual behaviors: eyebrow raise ($F_{2, 156}$= 10,13; p<0,001); ($F_{2, 156}$= 2,22; p<0,05), mutual gaze ($F_{2, 156}$= 9,53; p<0,001) and grin ($F_{2, 156}$= 5,15; p<0,007). However, genitália massage ($F_{2, 156}$= 1,04; p=0,35), axial massage ($F_{2, 156}$= 2,19; p=0,11), and head cocking ($F_{2, 156}$= 1,45; p=0,23) tended to increase in the TT phase but were not significantly different. Even as, the non-sexual grooming behavior ($F_{2, 156}$= 0,87; p=0,41); stereotypies ($F_{2, 156}$= 0,99; p=0,37) and agonistic ($F_{2, 156}$= 0,65; p=0,52) they did not change in the experimental stages.

Table 01 - Mean (±EPM) of the frequencies of sexual behaviors (eyebrow raise; breast massage; genitalia massage; axial massage; mutual gaze; grin; head cocking and duration (in seconds) of non-social behaviors (grooming, stereotypes, and agonistic) observed in female capuchin monkeys along the experimental BL (baseline), TT (testosterone administration) and Placebo. (placebo administration) in female capuchin monkey (*Sapjus libidinosus*) (n=12) [a] p<0,05 TT vs LB.

Behaviors	*Phases*			*Value (p)*
	Bl	**TT**	**Plac.**	
Eyebrow raise	0,1 ±3	2,0 ±2 [a]	0,6 ±2	p<0,05
Breast massage	0,3 ±0,2	7,1 ±0,1 [a]	5,5 ±0,1	p<0,05
Mutual gaze	3,4 ±0,3	12,4 ±2 [a]	6,4 ±2	p<0,05
Grin	0,1 ±0,3	23,1±2 [a]	11,1 ±2	p<0,05
Genitalia massage	1,3 ±1	3,4 ±1	1,3 ±1	p>0,05
Axial massage	0,1 ±0,9	1,9 ±0,6	0,6 ±0,5	p>0,05
Head cocking	0,3 ±1	4,0 ±1	1,8 ±0,4	p>0,05
Grooming	43,6 ±28	66,4 ±19	58,4 ±29	p>0,05
Stereotypies	156 ±67	264 ±47	261 ±49	p>0,05
Agonistic	27 ±16	33 ±19	43 ±19	p>0,05

DISCUSSION

The results of this study point to a positive effect of testosterone on the sexual behavior of female capuchin monkeys the frequency of expression of sexual behavior after administration of testosterone was noted. However, non-sexual behavior in females did not suffer changes during the experimental phases. Our results were like those observed by Tavares *et al.* (2007), but the dose used by these authors was double that of ours, respectively, (0,48 mg) e (0,24 mg). In this context, we can aver that the dose used was sufficient to cause changes in the sexual behavior of these primates, consequently, our hypothesis was achieved, ie, testosterone promotes behavioral changes.

The results in capuchin monkeys are corroborated in other animal models, for example, changes in sexual behavior in wistar rats that received exogenous administration of testosterone were also observed. After administration of testosterone rats began to exhibit an increase of sexual behavior such as an increase in lordosis or body positioning for mating (Jones *et al*. 2012). A similar case was observed in women who reported an increase of desire and sexual satisfaction during the use of testosterone (Davis and Braunstein, 2012; Fooladi *et al*., 2014).

In women, the exogenous administration of testosterone-induced neurophysiological changes in neural regions, for example, in the limbic system, related to sexual behavior (Davis and Braunstein, 2012), it was also noted an increased sex desire, well-being, and sexual satisfaction (Davis and Braunstein, 2012; Fooladi *et al*. 2014). Possibly, same as was observed in women, the exogenous administration of testosterone in capuchin monkeys and rats also activates neural regions that are responsible for sexual behavior.

In females, usually, sexual motivation is attributed to the female sex steroids, primarily estradiol, as already mentioned in the introduction. However, testosterone also plays an important role in the physiology of the menstrual cycle, since it acts in the follicles (Wang *et al*. 2001), stimulating early stages of follicular growth (Vendola *et al*. 1998; Ryan *et al.* 2003). They also amplify the effect of estrogens (Weil *et al*. 1999). Therefore, it is possible to infer that testosterone has joint action with estrogens in the modulation of the sexual behavior of mammals since the ovarian cycle of female vertebrates is evolutionarily similar. Some studies have shown that testosterone also acts in sexual behavior, for example, in female fish (Munakata and Kobayashi, 2010); birds (Ketterson *et al*. 2005); rats (Jones *et al*. 2102) and in women (Van Anders *et al*. 2011).

In females, testosterone plays a key role in the steroidogenesis of estrogens, through the action of aromatase converting in estradiol (Davis and Worsley, 2013). However, there were no increases in estradiol and estrone levels after testosterone treatment, even though the results showed elevated levels of testosterone and DHT in capuchin female monkeys.

We hypothesized that male and female sex steroids would not change after testosterone treatment, because the route of administration used in our study (intranasal) directly affects the central nervous system. This route is used to reduce peripheral side effects, because of how fast it can act and that it does not suffer hepatic metabolism (Talegaonkar and Mishra, 2004). However, the results of this study demonstrate the contrary, that intranasal administration of testosterone promotes changes in the levels of androgens since there have been significant increases in these sex steroids.

In humans, excess testosterone brings side effects such as acne, oily skin, infertility, breast changes, muscle hypertrophy, and increased blood glucose levels (Pace, 2015). The occurrence of tumors (Bachmann, 1999), and cardiovascular risk. (Guo *et al*. 2015) and the redistribution of adipose tissue has been documented (Li *et al*., 2015). It is important to comment that loss of hair was observed among the capuchin monkeys, possibly, because of treatment with testosterone, since this loss was noted during phase TT (administration of testosterone). Perhaps the testosterone dosage must still be adjusted or even reduced, thus making necessary new studies to establish the appropriate dose for the test species in question. In this respect, the results of this study may

contribute to a better understanding of the continued use of testosterone in humans in a very similar animal model. Therefore, these results can be useful in evaluating the serious risks of chronic testosterone use.

We must emphasize that the results of our study are the first to demonstrate that testosterone plays an important role in modulating the sexual behavior of capuchin female monkeys. Therefore, it is possible to say that estradiol alone does not modulate the sexual behavior of this species, since there was no increase in estradiol levels in the treatment phase with testosterone, even though changes in the behavioral profile of female monkeys were observed. The changes coincided with the rise of testosterone and DHT, therefore, androgens, mainly testosterone, can act on modulating the sexual behavior of capuchin monkeys.

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CONFLICT OF INTERESTS

No conflict of interest.

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