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Neonatal antiandrogens and organization of behavioral sex differences in the rat (*Rattus norvegicus*)

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ABSTRACT. *Neonatal antiandrogens and organization of behavioral sex differences in the rat* (Rattus norvegicus).- The role of androgens in the masculinization and later activation of socio-sexual behavior, was studied in the following experimental groups of Wistar rats: control males (MAL); peripubertally castrated males (GON); peripubertally castrated males supplied with testosterone propionate in adulthood (GTP); and males postnatally injected with cyproterone acetate, gonadectomized and supplied with testosterone propionate (CGTP). The observed decrease of sexual performance in animals neonatally treated with cyproterone acetate (CPA) should be a consequence of the reduced neonatal binding of testosterone (T) or 5αdihydrotestosterone (DHT) to androgen receptors provoked by the antiandrogen. On the contrary, animals treated with CPA showed higher levels of sexual motivation (sniff, partner grooming, anogenital sniff and mount); neonatal CPA seems to increase the sensibility to testosterone in adulthood, perhaps potentiating the aromatization of androgens by blocking its direct actions. Finally, the reduced frequency and latency of the studied patterns in castrated rats suggest that the presence of T in adulthood is necessary for the activation of socio-sexual and mating behavior. However, testosterone propionate (TP) supplementation in gonadectomized animals did not completely recover the behavior of the control males, suggesting that T probably can play an organizational effect upon certain patterns during puberty.

KEY WORDS. Cyproterone acetate, Testosterone propionate, Socio-sexual behavior, Sexual motivation and performance, Sexual maturation, Rats

Introduction

To explain two different steps of androgenic actions, during a perinatal critical period or during adulthood, the concept of organization / activation, has been developed. Initially, it was applied to the differentiation of the sexual behavior of guinea pigs (Phoenix et al., 1959). Nowadays this biphasic concept is broadly used in many species, and not only in relation to sexual behavior. The exposure to androgens during a short perinatal critical period, masculinizes and defeminizes the neural areas involved in the control of the sexual behavior. Later, during adulthood, sexual steroids can activate these areas, triggering mating behavior by the rat in response to any relevant stimuli (Sachs & Meisel, 1988; Van Der Schoot & Kooy, 1988).

Two metabolic routes might mediate the androgenic actions. The intracellular aromatization of androgens into estrogens, i.e., estradiol (E2), has been the main mechanism suggested (Naftolin & MacLusky, 1984), although androgens by themselves, testosterone (T) or their 5α–reduced

metabolite dihydrotestosterone (DHT), also seem to be involved. Moreover, intraneuronal aromatization of androgens into estrogens and the actions of androgens by themselves do not seem to have the same role in the masculinization and defeminization of sexual behavior.

Concerning defeminization of sexual behavior, the inability of adult rats to show estrous-like behavior in response to E2 and progesterone (P) seems to be a direct consequence of the perinatal exposure to T and / or E2. Many studies suggest that aromatization might be the main way for this process that normally occurs in the male rat (Naftolin & MacLusky, 1984; Van Der Schoot & Kooy, 1988).

In relation to masculine sexual behavior, the distinction between motivation and performance, i.e., appetitive and consummatory aspects, must be made (Sachs & Meisel, 1988). Considering that the capacity of the female to display mounts is enhanced when they are located near a male fetus during the uterine development (Clemens et al., 1978), it could be possible suggested that the development of showing a male motivated behavior when T is present in adulthood occurs basically in the prenatal step of the critical period. Male levels of mounting behavior might be more related to the sensitivity of the central nervous system (CNS) to androgens when they are given in adulthood, than to the masculine genital development (Olsen, 1985).

On the other hand, the development of male-like patterns of intromission and ejaculation is abolished in neonatally gonadectomized males (Södersten & Hansen, 1978; Van Der Schoot, 1980). It is maintained, at least in part, by neonatal treatment with EB (Södersten & Hansen, 1978) or non-aromatizable androgens (Van Der Schoot, 1980; Olsen, 1985), and completely with testosterone propionate (Booth, 1977; Södersten & Hansen, 1978; Thomas et al, 1980) or with a combination of estrogens and non-aromatizable androgens (Booth, 1977; Van Der Schoot, 1980). Moreover, the high correlation between genital and behavioral masculinization must be considered (Sachs & Meisel, 1988). The effects of perinatal androgens upon sexual performance during adulthood might be mediated by genital development, necessary for a complete copulation, or by the masculinization of the sensitivity of central nervous system. In any case, when T acts to masculinize sexual behavior, its aromatization to estrogens as well as the direct participation of androgens (T or DHT) seems to be necessary. (Booth, 1977; Södersten & Hansen, 1978, Van Der Schoot, 1980; Olsen, 1985).

In the study of the actions of androgens by themselves, antiandrogenic agents, like cyproterone acetate (CPA) or flutamide (FLU), have sometimes been employed. CPA is a synthetic steroid hydroxyprogesterone by-product, which is believed to work as a competitive antagonist upon androgen receptors (Neumann, 1977). Prenatal administration of CPA (Neumann & Elger, 1965; Nadler, 1969, Ward & Renz, 1972) or FLU (Clemens et al., 1978) disrupts masculinization of sexual behavior in males and females and modifies androgen-induced somatic differentiation in the male rat. Furthemore, neonatal treatment with CPA prevents genital and behavioral masculinization in the male rat (Neumann & Kramer, 1967).

The aim of this work is to study the effects of neonatal treatment with CPA in the masculinization and later activation of socio-sexual behavior of the rat. For this study, several patterns of socio-sexual behavior (sexual attraction) and mating behavior displayed in a group of male adult rats have been independently analyzed, with the intention of recognizing the effect of antiandrogen on each behavioral pattern.

Methods

Outbred male Wistar rats (*Rattus norvegicus*)

from our own colony, bred and maintained under a reversed red-light cycle of 12 hours of light and other standard conditions (Hernández et al., 1991), were used in this study. Surgical and pharmacological manipulations were made to establish the following experimental profiles, each consisting of two groups of six animals: 1) control males (MAL); 2) males gonadectomized at 40 days (GON); 3) males gonadectomized at 40 days and supplied with TP in adulthood (GTP); and 4) males neonatally treated with CPA, then treated like GTP males (CGTP).

Subjects received, during the first five days postpartum, daily sc. injections of 0.1 ml vehicle consisting of 95 parts of maize germ oil and 5 parts of benzyl benzoate (MAL, GON, GTP) or 1 mg of CPA suspended in the same volume of vehicle (CGTP). All the animals were submitted to surgical operation under ether anesthesia, the controls (MAL) being sham-gonadectomized. In both cases of TP supplementation (GTP and CGTP), adult animals were sc. injected during 10 consecutive days with 1 mg TP in 0.1 ml maize germ oil per day. Thirty days after finishing the behavioral trials, when it was assumed that the exogenous TP disappeared, the animals were killed, and the plasmatic testosterone levels were measured by RIA (Furuyama et al., 1972). The sensivity of the assay (Testo-CTK, Sorin) was 2.3±1.2 pg and the intra assay and inter assay coefficient of variation were 6.4 % and 10.2% respectively.

During adulthood, at 90-100 days old, videotaped behavioral tests of 30 min. were performed, in homogeneous groups of 6 animals. A female brought into estrous by a sequential treatment with 10µg estradiol benzoate (EB) 28 h. before test and 1 mg progesterone (P) 4 h. before the test (Beck, 1974) was introduced.

Each test was recorded using a VHS Color Video Tape Recorder NV-180 (Robert Bosch GmbH) connected to a Bauer VCE 412 Color Video Camera (Robert Bosch GmbH) with a built-in electronic timer. The camera was mounted vertically, 1 m from the floor of the testing cage (body measuring 62x62x33 cm). Tests were performed under white light, needed for the recording, by positioning the cage approximately 190 cm under a 100-watt tungsten bulb (Hernández & Cerezo, 1990).

Behavioral tests were analyzed in terms of frequency of two kinds of patterns: 1) socio-sexual patterns, also present in nonsexual context; and 2) mating patterns, more specific of the copulatory behavior. As each animal had been provided with dark tint marks in the back, scores of individual identifiable males were possible.

The recorded socio-sexual patterns were (Hernández & Cerezo, 1990): sniff (SN), including sniffs at the head, body or limbs of a female; partner grooming (PG), defined as licks and nibbles to the fur of the female, especially at neck and shoulders, usually leaning upon it with one or both forelegs; and genital sniff (GS), comprising sniffs or licks at the anogenital area of the female.

The recorded mating patterns were (Clark, 1993): mount (MO), mount with pelvic thrusting but without behavioral signs of intromission; intromission (IN), mount and deep pelvic thrusting, generally associated with penile intromission; and ejaculation (EJ), intromission resulting in ejaculation, characterized by the reflexive clasping of the female, often followed by the male falling off the female to the side.

With regard to mating behavior, the following time periods were also calculated for the first series of mating behavior: contact latency (CL), the period between the introduction of the female and the first MO or IN by the male; ejaculatory latency (EL), the period between the first MO or IN and the first EJ or the end of the test, when the EJ is not present and the resulting measure is not lower than the lowest latency for a real EJ; and post ejaculatory interval (PEI): the period between the first EJ and the first MO or IN of the following series of copulations,

measured only when both of the delimiters are present.

Behavioral data were recorded and subsequently statistically analyzed on a Tandon LT/386 computer, by means of two programs, developed in our department. A comparison between the groups was performed by means of the Wilcoxon Test by pairs (the U Mann-Whitney Test) after the Kruskal-Wallis one-way analysis of variance, in each case according to the procedure described in the following section.

Results

1) Testosterone levels

The following mean blood levels of testosterone, in pg/ml, were determined by RIA: 2307.83 for control males; 98.36 for GON males; 83.72 for GTP males; and 63.9 for CGTP males. The

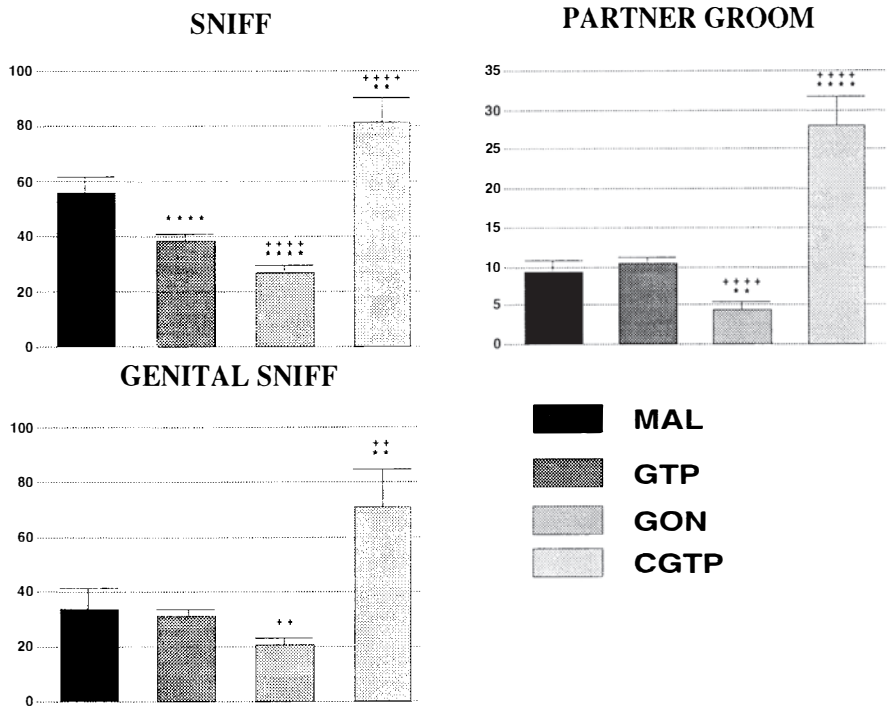

FIGURE 1. Frequencies of sniff, partner groom and genital sniff in the four experimental groups. The following symbols indicate statistically significant differences: 1) with MAL: * p<0.1, ** p<0.05, *** p<0.01 and **** p< 0.001; 2) with GTP: + p<0.1, ++ p<0.05, +++ p<0.01 and ++++ p< 0.001.

[Frecuencias de olfateo corporal, aseo de pareja y olfateo genital en los cuatro grupos experimentales. Los siguientes símbolos indican los niveles designificación estadística: 1) Diferencias respecto a los MAL: * p<0.1, ** p<0.05, *** p<0.01 and **** p< 0.001; 2) Diferencias respecto a los GTP: + p<0.1, ++ p<0.05, +++ p<0.01 and ++++ p< 0.001.]

comparison among the four groups by a one-way ANOVA showed a Fisher F of 72.798 and consequently, a very significant difference ($p<0.0001$). A multiple range analysis with confidence intervals of 95% suggested that control males were the only group responsible for these differences; the other three groups did not present significant differences among them.

2) Socio-sexual behavior

The three socio-sexual patterns observed in this study have been represented in figure 1. Significant differences were obtained in the Kruskal-Wallis tests for SN ($H=32.39$ $p<0.01$), PG ($H=28.76$ $p<0.001$) and GS ($H=8.51$ $p<0.05$). Consequently, all the different pairs of groups were subjected to Wilcoxon Test by pairs (U Mann-Whitney Test) for the three patterns, to find out at which moment the presence of androgens is most important.When the effect of gonadectomy at puberty was analyzed, a decrease in the frequency of the three patterns after surgery was observed. Significant differences between gonadectomized (GON) and control males (MAL)

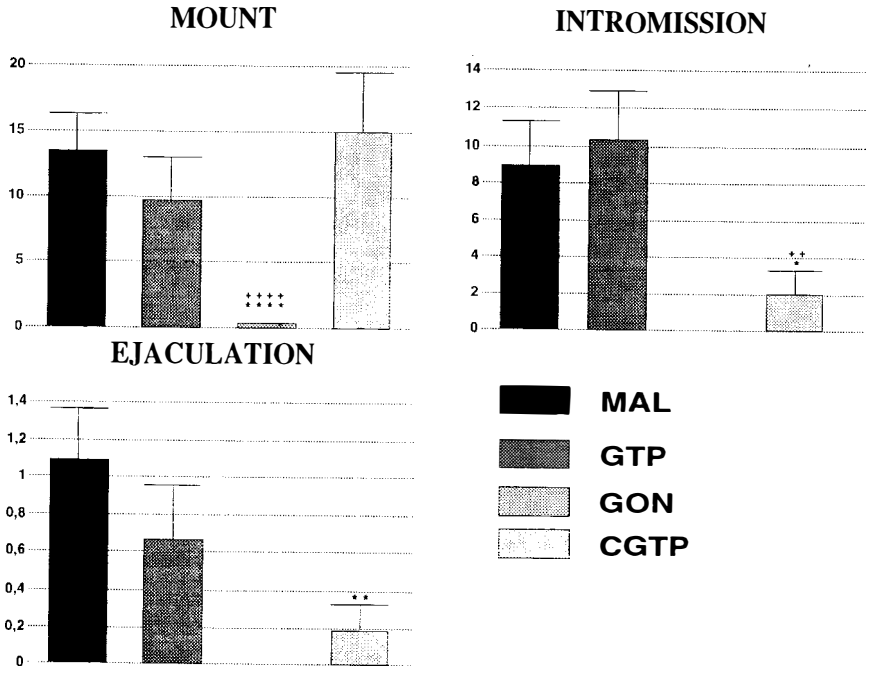

FIGURE 2. Total frequencies of mount, intromission and ejaculation during the 30 min. test. The following symbols indicate statistically significant differences: 1) with MAL: * $p<0.1$, ** $p<0.05$, *** $p<0.01$ and **** $p< 0.001$; 2) with GTP: + $p<0.1$, ++ $p<0.05$, +++ $p<0.01$ and ++++ $p< 0.001$.

[Frecuencias totales de monta, intromisión y eyaculación durante los 30 min. de la prueba. Los siguientes símbolos indican los niveles de significación estadística: 1) Diferencias respecto a los MAL: * $p<0.1$, ** $p<0.05$, *** $p<0.01$ and **** $p< 0.001$; 2) Diferencias respecto a los GTP: + $p<0.1$, ++ $p<0.05$, +++ $p<0.01$ and ++++ $p< 0.001$.]

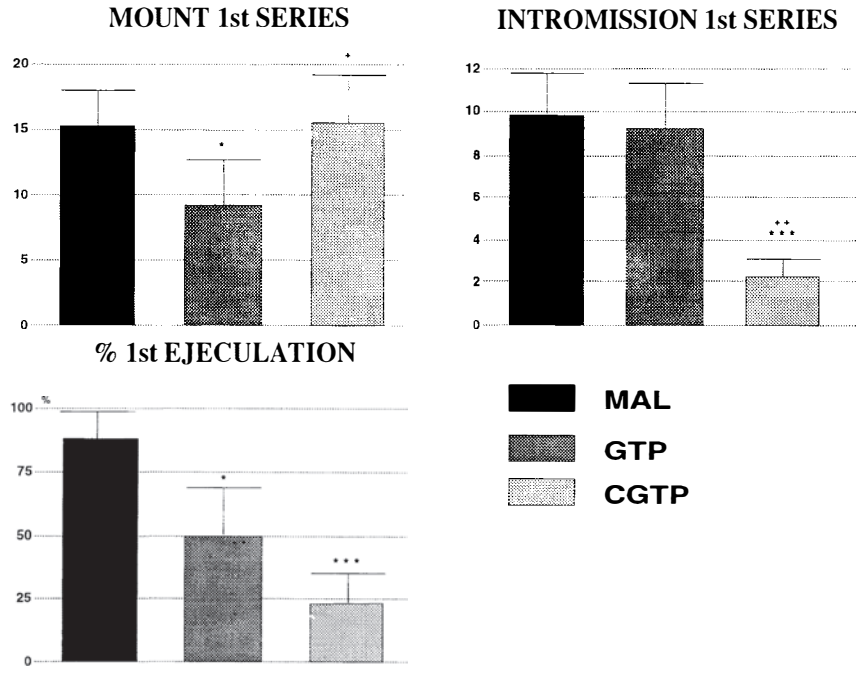

FIGURE 3. Frequencies of mount, intromission and ejaculation in the first mating behavior series. The following symbols indicate statistically significant differences: 1) with MAL: * p<0.1, ** p<0.05, *** p<0.01 and **** p< 0.001; 2) with GTP: + p<0.1, ++ p<0.05, +++ p<0.01 and ++++ p< 0.001.

[Frecuencias totales de monta, intromisión y eyaculación en la primera serie de conducta copulatoria. Los siguientes símbolos indican los niveles de significación estadística: 1) Diferencias respecto a los MAL: * p<0.1, ** p<0.05, *** p<0.01 and **** p< 0.001; 2) Diferencias respecto a los GTP: + p<0.1, ++ p<0.05, +++ p<0.01 and ++++ p< 0.001.]

were found in SN (U=131, p<0.001) and PG (U=104, p<0.05), but not in GS (U=93.5, N.S.). This role of the presence of T in adulthood was corroborated when GON males were compared to the animals supplied with TP in adulthood (GTP). The first showed significantly reduced fiequencies of SN (U=126.5, p<0.001), PG (U=129.5, p<0.001), and GS (U=108, p<0.025). With this trend, statistical analysis showed that GTP males reached the frequencies of control males, for PG (U=78, N.S.), GS (U=75.5, N.S.), although not for SN, significantly higher in control males (U=125, p<0.001).

Finally, the effect of neonatal treatment with CPA was analyzed in relation to the role that androgens play during development. With respect to controls, CGTP animals showed higher levels in SN (U=102.5, p<0.025), PG (U=126.5, p<0.001) and GN (U=97.5, p<0.05). Compared with GTP males, the results were almost the same, showing CGTP males with higher levels in SN (U=132, p<0.001), PG (U=129.5, p<0.001) and

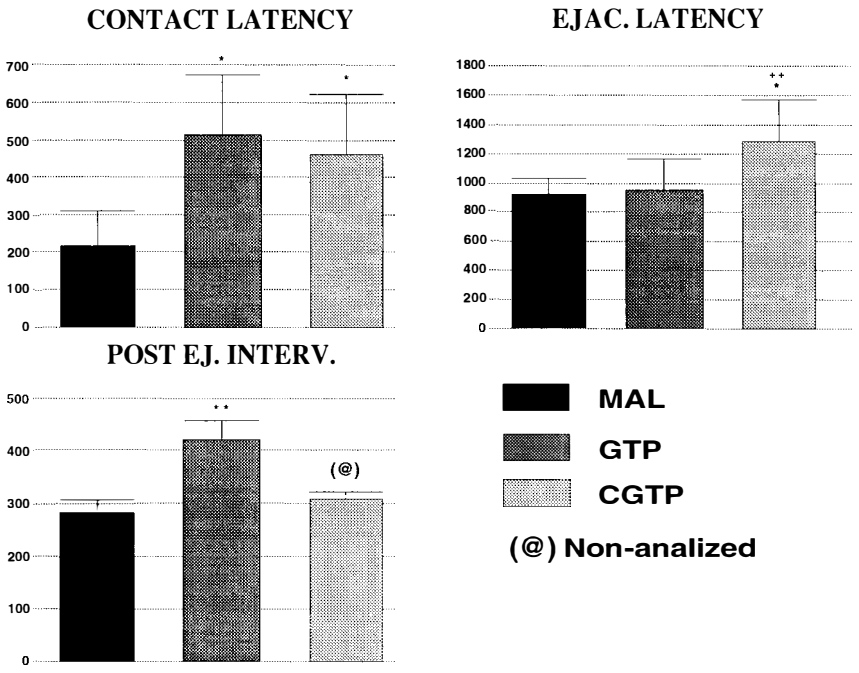

FIGURE 4. Time periods in the first mating behavior series. The following symbols indicate statistically significant differences: 1) with MAL: * p<0.1, ** p<0.05, *** p<0.01 and **** p< 0.001; 2) with GTP: + p<0.1, ++ p<0.05, +++ p<0.01 and ++++ p< 0.001.

[Periodos de tiempo en la primera serie de conducta copulatoria. Los siguientes símbolos indican los niveles de significación estadística: 1) Diferencias respecto a los MAL: * p<0.1, ** p<0.05, *** p<0.01 and **** p< 0.001; 2) Diferencias respecto a los GTP: + p<0.1, ++ p<0.05, +++ p<0.01 and ++++ p< 0.001.]

GS (U=97, p<0.05)

3) Total mating behavior

The total frequency of each copulatory item during the 30 minutes test can be seen in figure 2. Analyzed by the Kruskall-Wallis Test, it results in significant differences for MO (H=15.95, p<0.005), IN (H=14.21, p<0.005) and EJ (H=12.36, p<0.01). For the three measured items, group GON showed such low levels as the absence of IN and EJ as well as a total number of 2 MO for the 12 animals. This group has not been included in the following pair comparisons.

The pair comparisons between the other groups have been performed. GTP animals reached frequencies not significantly different from control males, for MO (U=83, N.S.), IN (U=80, N.S.) and EJ (U=88.5, N.S.). On the other hand, CGTP animals showed the same frequency of MO as control (U=70, N.S.) and GTP males (U=77, N.S.), but a different frequency of other patterns. Its frequency of IN is significantly lower than

frequencies in control (U=91, p<0.1) and GTP animals (U=96, p<0.05). Frequency of EJ in CGTP animals is lower than in control males (U=98.5 p<0.05), and is not significantly different from GTP animals (U=84.5)

4) Copulatory items in the first mating behavior series

A first behavioral series since the initiation of the test was analyzed for the three groups with androgens. The condition for finishing this series was: 1) the first MO or IN after the first EJ; or 2) the end of the test, when the previous one was not present. As only sexually active animals were compared, the number for each group was: n=8 for MAL, n=10 for GTP and n=9 for GTP.

The numbers of MO and IN, as well as the percentage of animals that reach EJ before finishing the series, has been represented in figure 3. GTP males presented lower frequencies than controls, significantly different for MO (U=59, p<0.1) and EJ (U=59.5, p<0.1), although not for IN (U=45, N.S.). CGTP animals showed a significantly higher frequency of MO than GTP males (U=62.5 p<0.1) but the same as controls (U=39, N.S.) as well as significantly lower frequency of IN than control (U=63.5, p<0.01) and GTP males (U=72.5, p<0.05). The percentage of CGTP animals that ejaculated was the lowest, being significantly different from controls (U=65.5, p<0.01) but not from GTP animals (U=60.5, N.S.).In figure 4 three periods of time have been represented: CL as well as EL and PEI only for the animals that satisfy the conditions defined in the methods. Therefore, only MAL, GTP and CGTP groups have a large enough number of data to be statistically significant.

The times were increased in the treated groups compared to MAL, but the differences were not always significant. CL was significantly smaller in control males than in GTP (U=59, p<0.1) and CGTP animals (U=51.5, p<0.1), but there was no significant difference between both (U=47, N.S.). The increase in EL was significant in CGTP versus MAL (U=52, p<0.05) and versus GTP (U=58, p<0.1), while the later ones had no significant difference (U=34, N.S.). Finally, there were significant differences for PEI in the case analyzed, being lower in control than in GTP males (U=26, p<0.05).

Discussion

The neonatal presence of CPA produces a decrease in the frequency of intromission and ejaculation, as well as a prolongation of the ejaculatory latency (i.e. a decreased copulatory behavior) that might be explained by the obstruction on the binding of T or DHT to androgen receptors (AR) in the genitalia or in the CNS during the first days of life. Our work confirms that early androgens are needed for a masculine performance of sexual behavior in response to these hormones during adulthood. However, the role that androgens play during development upon the different motor skills of sexual behavior and other aspects of sexuality is not the same.

In relation to intromission, a similar treatment with 2 mg of CPA postnatally (Neumann & Kramer, 1967) or prenatally (Neumann & Elger, 1965; Nadler, 1969) applied in the male rat also produces a reduced level of this pattern, accompained by the alteration of the penile morphology. Therefore, the action of T or DHT upon the AR would be required during the sexual differentiation for full genital development and for the display of normal levels of intromission. This genital and behavioral development is observed when exogenous androgens, as well as estrogens, are present during the neonatal critical period (Booth, 1977; Hart, 1977; Södersten & Hansen, 1978; Van Der Schoot,

1980; Olsen, 1985).

The decrease in ejaculatory response, that is not only consequence of the genital development (Booth, 1977; Hart, 1977, Södersten & Hansen, 1978, Van Der Schoot, 1980; Olsen, 1985), suggests the participation of early androgens by themselves in the masculinization of copulatory behavior, as recent works with non-aromatizable androgens have shown (Van Der Schoot, 1980; Olsen, 1985), although estrogens are also implicated in this process (Booth, 1977; Hart, 1977).

In relation to socio-sexual behavior, animals treated with CPA show higher frequencies of sniffing, partner grooming and genital sniff than control males, and a slight increase in mount frequency. The decreased ability of these animals to show a normal mating pattern is joined precisely with an increase in the time employed in socio-sexual patterns. If these animals have normal levels of masculine sexual motivation and if they employ the same amount of total time in sexual behavior, the increase in the frequency of the same patterns could be due to the decrease in others (i.e. intromision and ejaculation). This suggests that masculinization of sex motivated behaviors like mount does not depend on the neonatal presence of androgens. Several studies using female rats suggest that the development of both behavioral signs of masculine sexual motivation and capacity of mounting in adulthood, requires prenatal gonadal hormones. In this sense, when the treatment with CPA is prenatal, a reduced number of mounts has been observed in female rats (Ward & Renz, 1972). However, the longer contact latency showed by the CPA treated males in our study (CGTP) in comparison with control males would indicate the extension of this masculinizing process during the first days of postnatal life.

The second focus of our work is the activation of sexual behavior by the gonadal hormones present in adulthood. The decreased frequency of sniffing, partner grooming and genital sniff observed in the gonadectomized animals, seems to suggest that these patterns are androgen dependent in adulthood. This is according to the generally accepted role that androgens play in the activation of social behavior during adulthood (Beatty, 1979). However, most of the data concerning this kind of patterns have been recorded in a nonsexual context. In a previous work about intermale social relations (Hernández & Cerezo, 1990) we could show that the presence of androgens in adulthood activates the underlying substratum of some social attraction patterns, but not others, i.e., genital sniff. Therefore, what we call socio-sexual patterns here would have more specific features of sexual recognition than expected by their mere description.

In male rat mating behavior, the presence of T in adulthood seems to be essential in eliciting mount, intromission and ejaculation. The absence of the last two as well as an insignificant number of mounts have been demostrated with castrated animals. As a consequence, we agree with other authors that have shown how male sexual behavior gradually declines until disappearing completely after castration (Damasa et al., 1977; Broere et al., 1985). However, it has also been described that mounting behavior does not completely depend on androgens and it may occasionally happen in castrated male rats (Van Der Schoot & Kooy, 1988). It is even possible to suggest that there are qualitative differences between gonadectomized animals and animals with either exogenous or endogenous androgens.

Another important question observed in our work is the ability of exogenous androgens to compensate gonadectomy. In relation to socio-sexual patterns and mating patterns, when the whole test is considered TP supplied animals almost reproduce the control situation. On the contrary, when the first of a series of copulatory behavior is analyzed, a noteworthy pattern of differences is observed (see figure 3), without such a radical compensation of gonadectomy by TP supplementation as the whole time data suggest. In spite of exogenous androgens,

animals gonadectomized at puberty are different from control males. The former group shows a lower frequency of mount and fewer animals that finish the first copulatory series ejaculating, as well as a longer contact latency and postejaculatory interval. Compensation of sexual behavioral deficits that occur in long-term castrated rats has been described (Damasa et al., 1977) 1-2 weeks after the T administration that produces around 1 ng/ml T in blood, although the blood level in intact rats is close to 2 ng/ml. The same authors indicate that supraphysiological levels (3-5 ng/ml) do not alter sexual behavioral characteristics.

In our present work, the dramatic reduction of T levels in the three groups of gonadectomized animals, measured after a sufficient period of time without exogenous application of steroids, confirms that any endogenous source of androgens interferes with the exogenous TP. Since we have measured, in previous works, that the TP dose we used elevated the levels of T in blood to around 4 ng/ml, our results do not seem to be explained in relation to the difficulty of eliminating the effects of the long term castration. On the contrary, the moment of the gonadectomy might be more important, taking into account that T might play a organizational effect upon certain behavioral patterns during puberty (Brand & Slob, 1988).

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Resumen

Neonatal antiandrogens and organization of behavioral sex differences in the rat (Rattus norvegicus).

El presente trabajo tiene por objetivo contribuir al estudio del papel de los andrógenos en la masculinización y posterior activación de la conducta socio-sexual. Para ello hemos hemos formado los siguientes grupos experimentales de ratas Wistar: machos control (MAL); machos gonadectomizados en época peripubertal (GON); machos gonadectomizados en época peripubertal y suplementados con propionato de testosterona en época adulta (GTP); y machos postnatalmente inyectados con acetato de ciproterona, gonadectomizados en época peripubertal y suplementados con propionato de testosterona en época adulta (CGTP).

Hemos encontrado un significativo descenso en el despliegue de conducta sexual en los animales tratados neonatalmente con acetato de ciproterona, que parece indicar un bloqueo total o parcial de los procesos de masculinización de los órganos genitales o del sistema nervioso central. En nuestra opinión, dicho bloqueo podría ser debido a la reducción de la unión de testosterona (T) or 5αdihidrotestosterona (DHT) a los receotores de andrógenos provocada por la presencia neonatal del antiandrógeno. Al mismo tiempo, los animales que recibieron ese tratamiento mostraron elevados niveles de motivatión sexual, como indican las frecuencias de olfateo corporal, aseo de pareja, olfateo anogenital y monta. En este caso, la presencia neonatal de acetato de ciproterona parece incrementar la sensibilidad a la testosterona en el adulto, quizás potenciando la aromatización de andrógenos como consecuencia del bloqueo de sus acciones directas.

Con respecto a los animales gonadectomizados, la reducción tanto en la frecuencia como en la

latencia de las pautas estudiadas, sugiere que la presencia de T en época adulta es necessaria para la activación de la conducta socio-sexual y copulatoria. Sin embargo, la suplementación con propionato de testosterona en los animales gonadectomizados no produce una recuperación completa de los niveles de conducta propios de los machos controles. Esto sugiere que durante la pubertad, la testosterona podría jugar un papel organizador de ciertas pautas de conducta.

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