

Received: 2003.10.16
Accepted: 2004.09.29
Published: 2005.04.01

Testosterone and aggressiveness

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Source of support: Self financing

Summary

Aggressiveness is an ancestral behavior common to all animal species. Its neurophysiological mechanisms are similar in all vertebrates. Males are generally more aggressive than females. In this review, aggressive behavior in rodents, monkeys, and man and the role of testosterone and brain serotonin levels have been considered. Interspecific aggressiveness in rats has been studied considering the mouse-killing behavior; the neonatal androgenization of females increases adult mouse-killing as does the administration of testosterone in adults. Intraspecific aggressiveness was studied by putting two or more male rats (or mice) in the same cage; the condition of subjection or dominance is influenced by testosterone.

In monkeys, testosterone is related to aggressiveness and dominance and, during the mating season, increases in testosterone levels and aggressive attitude are observed. In men, higher testosterone levels were obtained in perpetrators of violent crimes, in men from the army with antisocial behaviors, in subjects with impulsive behaviors, alcoholics and suicidals, in athletes using steroids, and during competitions. Aggressive and dominant behavior are distinguished. Testosterone influences both of these, even if man is usually inclined to affirm his power without causing physical damage. Testosterone receptors are mainly in some hypothalamic neurons, where it is aromatized into estrogens, which determine the increase in aggressiveness. A relation between testosterone levels and diencephalic serotonin has been shown: in fact, the lack of serotonin increases aggressive behaviors both in animals and man. Testosterone also increases ADH levels in the medial amygdala, lateral hypothalamus, and preoptical medial area, involved in aggressive behaviors.

key words: aggressiveness • testosterone • androgen • behavior • dominance • serotonin

Full-text PDF: http://www.MedSciMonit.com/pub/vol_11/no_4/4259.pdf

Word count: 5510

Tables: –

Figures: –

References: 137

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BACKGROUND

Aggressiveness is an ancestral behavior common to all animal species at least from fishes onwards, and it can be defined as the execution of an action, from menacing gestures to real attacks, against animals belonging to the same or different species. The neurophysiological and molecular mechanisms upon which aggressive behavior is based are probably similar in all vertebrates [1]. The main reasons for aggressive behavior are two: the instinct of individual preservation (i.e. predation to obtain food, defense behavior against a predator) and the instinct of species preservation (i.e. aggressiveness to conquer females). Depending on the motivation leading to the aggressive behavior, the actions which are carried out are peculiar to each species, which means that each species has precise and well-established nervous circuits which steadily respond depending on the motivation, at least qualitatively. This diversity might be determined by anatomic and/or functional adaptive processes of pre-existing ancestral neural circuits [1].

It is possible to distinguish 1) interspecific aggression, addressed to individuals of different species, generally motivated by the instinct of predation, and 2) intraspecific aggression, addressed to individuals of the same species, which can have different motivations (establishment of a hierarchy, copulation, defense of territory). This can be expressed by threats or real attacks, and can result in a dominant behavior or escape or submission.

In all vertebrate species, humans included, males are more distinctly aggressive than females. For this reason the interest of researchers has been addressed for a long time to the study of the effects of gonadic hormones on aggressive behavior. In 1849, Berthold was the first to show that castration in capons could inhibit sexual, aggressive, and singing behavior, and that subsequent testicle transplantation annuls such effects. In this way he established the experimental model for the ensuing studies on the behavioral effects of sexual hormones. The study of female aggressiveness is more complex and the results obtained until now are very contrasting. With regard to this, the only certain and valid data for all species of mammals is that aggression in the female increases in the presence of a newborn; maternal aggression, in fact, is the most commonly observed kind of aggression [2]. However, it is always necessary to consider that in the human species the differences in aggression between the two sexes might be due to social factors as well [1].

We shall consider here some data concerning the influence of testosterone on the aggressive behavior of some animal species and in humans, its action mechanism in the central nervous system (CNS), and in particular the effects of testosterone on brain serotonin levels [3,4], which were not taken into account, for instance, in the work of Mazur and Booth "Testosterone and Dominance in Men" [5].

OBSERVATIONS IN ANIMALS AND IN MAN

Interspecific aggressiveness in rats

The knowledge of interspecific aggression in the rat has been achieved through research performed on the mouse-killing behavior, a particular kind of aggressive behavior that can

be manifested in an adult rat (5–7 months) when an anesthetized mouse is placed in the same cage. Neonatal castration (within the 3rd day of life) of male rats reduces the percentage of animals reaching adult age compared with non-castrated brothers; also, the neonatal androgenization of female rats increases the percentage of adult mouse-killing animals compared with non-androgenized sisters [6]. Nevertheless, the presence of testosterone is of considerably important also in adult age; in fact, testosterone administration increases the percentage of mouse-killing animals, above all among those males who were castrated at birth, and the administration of ciproterone acetate (an antiandrogen) reduces it in healthy males and in females androgenized at birth [7]. It is interesting to note that the most testosterone-sensitive adult animals are those which were castrated at birth, and that androgenized females and healthy males are the most affected by ciproterone acetate administration.

Intraspecific aggression in rats

One of the main aims of the study on aggressive behavior in rodents is to determine the neurobehavioral factors which are the basis of human behavior. Intraspecific aggression can be evaluated mainly by analysis of the behavior of isolated males towards an intruder placed in the same cage. An important question is related to the effectiveness of the mouse model in providing valid information to understand the mechanisms (or at least some of them) of aggression in man. In fact, although rats and humans have more than 90% of their genes in common, the observed aggression in rats cannot always be compared to the violence shown by men, both in its kind and in its effects. For example, male rats attack females rarely, while among humans women are frequently targeted by male violence. Nevertheless, as we shall see, molecular mechanisms essential in explaining aggressiveness in rodents are also at the basis of human aggressiveness. In this way, mouse models provide valid information to understand the causes of human aggressiveness [1].

In the study of intraspecific aggressiveness it is interesting to observe both the effects of testosterone on aggressive behavior and the effects of interactions amongst animals on gonad function. Castration in males and androgenization in females, carried out during the neonatal period, lead to the same effects as the intraspecific aggressiveness (fighting) induced by electrical stimulation [8]. However, electrical stimulation of an animal is a behavior-altering factor, as it makes the animal more aggressive in an unnatural way. An intraspecific aggressiveness increase was obtained by using high doses of androgens chronically administered in healthy adult male rats [9].

When two male rats are placed in the same cage, a hierarchy is soon established because one of them tends to menace and attack the other, which, in turn, constantly assumes a defensive attitude. The dominant animal will always have supremacy attitudes compared with the other: for instance, the former will always take food first. Nevertheless, if two animals which have shown a dominant attitude to the detriment of other rats are placed in the same cage, it is possible that a hierarchy will not be established; in this case, both animals will constantly try to become dominant, neither will dare take food first and, together with this evident

chronic stress condition, this situation will lead to the two animals losing weight until one of them dies (Giammanco and La Guardia, unpublished observations).

Hierarchies are also formed when different animals are placed in a group. Subordinate males can be distinguished from dominant ones because they tend to assume defense attitudes constantly. Moreover, their life-spans are shorter than the dominants. Compared with isolated animals, those in groups show growth of the medulla adrenal gland and a reduction in thymus volume. These alterations are more evident in the subordinates, in whom, moreover, testosterone weight and preputial gland dimensions are smaller than in the dominants and in controls. The endocrine situation is different, as well: in subordinate animals, lower testosterone and higher prolactin and corticosterone levels can be observed; moreover, free corticosterone is even higher, because corticosterone-binding globulin levels are reduced [10,11].

Hierarchies established between male rats can be easily overturned by means of chronic administration of testosterone to the subordinates: animals that were observed losing in the competition are now winners; their testicles weight in relation to bodyweight is lower, as expected [12]. The dominance induced by testosterone administration is reversible if the animals that became dominant are fed with serotonergic drugs, which reduce aggressiveness, as we shall see later [13,14].

Intraspecific aggressiveness in mice

In mice (*Mus musculus*), perinatal castration also leads to a reduction of aggressiveness in adult age [15]. In male mice with whole gonads, chronic administration of propionate testosterone in adult age has few behavioral effects, these consisting of a reduction in the latency of menacing the opponent [16]. This observation can be explained considering that, in this case, the gonads of the animals are undamaged and the exogenous administration of testosterone is more efficient in males castrated at birth. This is in accordance with the results obtained during the prepubertal period in hamsters, which show higher intraspecific aggressiveness after chronic administration of high doses of androgens [17].

An interesting study was performed using mice selected for intraspecific aggressiveness (TA) and non-aggressiveness (TNA). TA females became aggressive as TA males do after neonatal androgenization and after 120 days, while non-androgenized TA females and TNA females were never aggressive. TNA males did not become aggressive even after neonatal androgenization and after 120 days [18]. These data show that androgens affect aggressive behavior only in the presence of a genetic background, which anyway is not enough in itself to manifest aggressiveness. Similar conclusions were achieved in another study where female mice, androgenized at birth and belonging to stocks selected for higher aggressiveness levels (SAL: short attack latency), increased their aggressiveness after castration and testosterone administration in adult age. This effect is observed to a lesser extent in similarly treated females belonging to stocks selected for lower aggressiveness levels (LAL: long attack latency). SAL females show higher aggressiveness even if, after castration, estradiol is administered [19]. Finally, Leydig

cells of fetuses of domestic mice selected for higher aggressiveness have an early secretory peak in comparison with cells belonging to fetuses of domestic mice selected for lower aggressiveness, and they likely secrete a higher quantity of testosterone [20].

Studies on monkeys

In male of *Macaca mulatta* monkeys, unstored, free testosterone levels in the cerebrospinal fluid are related to aggressiveness [21]. Furthermore, during the mating season an increase in cerebrospinal fluid and plasma testosterone levels and an increase in aggressive attitudes are observed [22]. A correlation between plasma testosterone levels and aggressiveness has been confirmed by Kalin [23] in males belonging to the same species. Another study showed that testosterone administration in *Macaca fascicularis* males, besides producing an increase in aggressiveness, produces also an increase in dominance attitudes, above all among already dominant [24]. At this point the question of differentiation between later aggressiveness and dominance arises, considering dominance as the attained social level; as this problem is much more evident in man, it will be treated in the next section.

A relation between plasma testosterone levels and dominance targeted to breeding was not found in a species of lemur, *Microcebus murinus*, in which dominance relationships are established at the beginning of every mating season. In this case, older males are always dominant, even though they show lower plasma testosterone levels and less aggressive attitudes [25]. According to some authors, in *Macaca fascicularis* males placed first separately and then in a group, the testosterone and cortisol levels obtained when they were separated did not correlate with the social level which they achieved when they were placed in a group [26]. In any event, in this study hormonal levels were not observed after interaction with other males, so it is not possible to establish whether some changes took place because of the new environmental situation.

Perinatal exposure to testosterone has an influence on adult behavior in monkeys as well. Young male monkeys generally take part in violent games more than females do. If testosterone is administered to mothers during pregnancy, daughters have male genitals and show behaviors similar to males. If testosterone administration is done later in the pregnancy, daughters' genitals are of a female kind, but the behavior is always of the male kind, thus showing that behavior attitudes are more sensitive to the presence of testosterone than to genital morphogenesis on its own [27]. Finally, considering self-destructive behavior as a kind of aggressiveness (self-aggression), interesting is also the observation of some authors who have found a reduction in such behavior in *Macaca mulatta* males after administration of ciproterone acetate, a steroid with antiandrogenic activity [28].

Testosterone and aggressiveness in adult men

For practical and ethical reasons, observations in man are limited to researching the correlation between plasma testosterone levels and aggressive behaviors in subjects with marked aggressive behaviors (including studies performed on prisoners), or to studying behavioral effects in subjects taking anabolic ster-

oids, generally in order to increase muscular mass. Significantly higher testosterone levels were obtained in prisoners guilty of violent crimes in comparison with those guilty of other crimes [29–31], and in prisoners who broke the prison rules more often than those with lower testosterone levels [32,33]. In a sample of 4,462 men from the American Army aged between 30 and 40, it was shown that plasma testosterone levels were related to different antisocial behaviors (difficulties on the job, nonobservance of the law, marriage failures, drug use, alcohol abuse, violent behaviors) which are indicators of rebellion and inclination to infringement of rules [34–37]. Criminals with troubled personalities (habitual criminals especially) have total and free plasma testosterone levels higher than schizophrenic criminals [38]. Subjects with a background of frequent impulsive behaviors, alcoholism, and attempts to commit suicide have high free testosterone levels in the cerebrospinal fluid [39,40]. A higher aggressiveness among alcoholics was directly related to plasma testosterone levels [41].

The administration of an antagonist of hypophysial Gonadotropin Release Hormone (GnRH) (a chemically reversible castration) reduces testosterone levels and aggressiveness in man [42]. Nevertheless, most of the above-mentioned studies concern clearly aggressive subjects and/or prisoners. In normal and free subjects, aggressiveness is evaluated by written tests, whose validity is sometimes doubtful. Therefore, in most of the studies a relation between aggressiveness and plasma testosterone levels has not been found [11,30–32,43–50]. In any event, it has not been possible to establish with certainty whether increased plasma testosterone levels are actually the cause of the increased aggressiveness in man, or whether they are an epiphenomenon or even a consequence.

Testosterone in perinatal period and aggressiveness

Studies on the influence of the presence of testosterone in the prenatal period on the behavior of the human species have obvious methodological limits. However, the most significant ones confirm altogether the results obtained in rodents and monkeys [51,52]. Moreover, a 3-month series of testosterone administration (to males) or estrogens (to females) at three different dosages, alternated with placebo administration, in hypogonadic adolescents increased the trend to impulsiveness and physical aggressiveness (nonverbal) both in males and females [53].

Exogenous androgens and aggressiveness in athletes

Athletes illicitly using anabolic steroids were largely observed to have behavioral changes consisting in an increase in aggressiveness [54–57] or changes in mood tone [58–60]. Nevertheless, these drugs are deliberately planned to minimize collateral effects, so their behavioral effects could be different from those of endogenous testosterone. Moreover, because they are generally taken in such strong, high doses, they can lead to a reduction in endogenous secretion of testosterone. For such reasons the results of these observations may not be very relevant [5].

Testosterone and dominance

In man, at least, it is necessary to distinguish between aggressive and dominant behavior. A subject is acting aggressive

sively if he has the evident aim to inflict physical injury to a member belonging to his own species. A subject is acting in a dominant way if his evident aim is to earn or to keep a high status (power, influence, privilege) over a member of the same species [5]. Rodents dominate typically in an aggressive way, but this does not happen amongst the main primates. Man is often inclined to affirm his power without any intention to cause physical harm: sports, political elections, various criticisms, and competition for career are just some examples in which man tries to dominate without attacking.

In fact, it seems that plasma testosterone levels are related not just to aggressiveness, but also to dominance behaviors, even non-aggressive ones. In 28 males who practiced judo, a positive relation between plasma testosterone levels and aggressiveness during fighting was pointed out [61]. A study on 14 university hockey-playing males aged between 18 and 23 pointed out a significant correlation between plasma testosterone levels and evaluation by the trainer of their aggressiveness [62]. Socially dominant and non-aggressive prisoners have quite high plasma testosterone levels, not so much different from those of aggressive prisoners; but in both, plasmatic testosterone levels were significantly higher than those of the non-aggressive or dominant group [63].

Social level and testosterone

During a challenge, plasma testosterone levels increase; moreover, they increase in the winner and decrease in the loser. It seems that a mutual influence between testosterone and dominance existed: not only does testosterone influence dominance, but also social level variations cause changes in plasma testosterone levels [5,64]. These data were assessed by different authors using male athletes of various individual sport disciplines as the experimental model. Plasma testosterone increases slightly before a competition [17], as if to make athletes more available to run risks [34]; it improves coordination, the conscious execution of movements, and concentration [67–69]. Moreover, for one or two hours after competition, the plasma testosterone levels of the winners are higher than those of the losers [65,70–72]. Such testosterone increase following a win is correlated with an improvement in mood tone in the subjects. If the increase in the mood tone is reduced because the subjects won by lucky circumstances rather than by their own efforts, or because they consider winning not so important, then the increase in testosterone is reduced or is totally lacking [70–74].

The above-mentioned results were obtained in the context of physically demanding sports. Other studies show the same behavior of plasma testosterone levels in males during ritual or at least nonphysical competitions, or after improving their social conditions. Examples are testosterone increases before games of chess [75] or in subjects who are verbally reacting to an insult [76]. Moreover, plasma testosterone levels are higher in chess tournament winners, as well [75], and among sport supporters, even though they are not taking part in the competitions. It was reported that in 1994, after the victory of Brazil against Italy during the football World Cup, testosterone significantly increased in those Brazilians who were watching the match on television, while it decreased in Italian supporters [77].

The effect of social conditions on plasmatic testosterone levels was also demonstrated in other studies. Abnormally low plasma testosterone levels were found amongst officer cadets during the first and most tiring weeks of military academy; later the levels returned to normal [30,31]. Amongst medicine students, plasma testosterone levels were high after their degree ceremony, such as was their mood tone [72].

The phylogenetic function of changes in plasma testosterone levels after a win or a defeat is unknown. It could be supposed that as winners can soon face other challenges, the high testosterone level prepares them for this event; also, the testosterone level reduction among losers could encourage withdrawal from other challenges, preventing in that way further injury.

Testosterone, aggressiveness, and dominance in women

The influence of testosterone on aggressiveness and on the inclination to dominate is much less evident in woman. In young criminal women, plasma testosterone levels were found higher than in other women of the same age [78]. Women sentenced for violent crimes had higher plasma testosterone levels than other women prisoners, but no differences were found between prisoners and free women. Among women who were whate in a high security prison, testosterone levels correlated with aggressive dominance, as among men. In elderly prisoners, testosterone levels decrease, and this causes a lower dominant aggressiveness [79]. In contrast, another study showed a negative relation between plasma testosterone levels and aggressiveness levels related to the examined women themselves [80]; nevertheless, in this case the method of surveying aggressiveness levels was even more questioned than in other works. Among women in a neurology clinic, significantly higher plasma testosterone levels were found than among the most aggressive women [81]; however, the examined subjects had different psychiatric diagnoses, so the comparison between the groups is doubtful.

Results on the relationship between testosterone and social condition are doubtful as well. Though it was reported that plasma testosterone levels increase with improvement in job position [82], in another study the social condition (as evaluated by colleagues) negatively correlated to plasma testosterone levels [83]. The incoherence amongst these results is likely due to the influence of other sexual hormones on aggressiveness. In fact, both estrogenic and suprarenal androgenic hormone effects have to be considered. It would be simplistic in women, much more than in men, to try to correlate aggressiveness and dominance just with plasma levels of the testosterone. The results of testosterone levels are also different from those of men in situations of competition. No increase in testosterone was found either before or after competition, whatever was its outcome [84,37]. These results suggest that the result of competition for testosterone is specific to men.

Testosterone in the prepuberal and peripuberal period

In the prepuberal and peripuberal age groups it is very difficult to correlate aggressive behavior with testosterone levels. In children, salivary testosterone levels correlate with aggressiveness in the context of social interactions (strong

aggressiveness), but not with aggressiveness during a game [85]. In prepuberal children (6–12 years old), plasma testosterone levels were found to correlate with dominance among schoolmates and success at school rather than with physical aggressiveness; on the contrary, the most violent children had the lowest testosterone levels, low school success, and were unpopular in their age group [86]. Aggressive children and those with antisocial behavior in the prepuberal period have higher levels of dehydroepiandrosterone (DHEAS), a suprarenal hormone with androgenic activity, but not of testosterone, compared with children of the same age having normal behaviors [87].

Considering these difficulties in interpretation, it is possible to explain the results of different authors who could not find any relation between plasma testosterone or any other androgen levels and aggressive behaviors in prepuberal and adolescent age [88–96]. Testosterone effects during puberty are likely limited mainly to the reorganization of the body structure: increases in dimensions and muscular mass, and the appearance of secondary sexual characters. Behavioral changes seem to be caused above all by environmental and social factors [5].

TESTOSTERONE'S ACTION MECHANISM IN THE CNS

The aromatization of testosterone into estrogens

Testosterone receptors are located in different brain areas, in particular in the medial preoptic area, in front of the hypothalamus. The medial preoptic area has a particular importance in sexual brain differentiation [97], as it shows anatomic and histological differences between males and females [98]. Testosterone acts in the CNS after its aromatization into estrogen [99]. More generally, the most active androgens in the CNS are those which are aromatizable [100]. In male mice, the aromatic activity of the hypothalamus (and then neural estrogen synthesis) during the embryonic and perinatal period is higher than in females; moreover, testosterone increases its activity [101].

The aromatic activity of the amygdala during the embryonic period also has an important role in the development of aggressiveness in the adult. In fetuses coming from aggressive mouse stocks, such activity is constant and higher than the activity of fetuses from non-aggressive stocks [102]. In an experimental model of adult female mice, androgenized at birth and belonging to stocks selected for higher (SAL: short attack latency) or lower (LAL: long attack latency) aggressiveness levels, an increase in aggressiveness after castration and administration of either testosterone or estradiol was found in the SAL stock [19]. It seems that the effects of both hormones were similar.

Some authors also supposed that estrogens are more efficient than testosterone in inducing aggressiveness, at least in mice. In fact, mice who were castrated and administered estrogens, testosterone, or dihydrotestosterone (non-aromatizable androgen) increased their aggressiveness. This outcome was attenuated by the administration of serotonergic drugs, which means that serotonergic drugs reduce aggressiveness with more difficulty (a combination of such drugs at high doses was needed) in animals receiving estrogens than those receiving testosterone (drugs combinations

were not necessary, or lower doses were enough). Even in animals administered with dihydrotestosterone, the individual drugs at low doses were enough [103–105].

Other interesting considerations come from studies performed on estrogen receptor knock-out mice. There are two such receptors in the CNS, alpha and beta. Alpha receptor knock-out mice (alphaERKO: alpha-Estrogen Receptor Knock-Out) are much less aggressive; moreover, the daily administration of testosterone in castrated alphaERKO mice is absolutely inefficient in inducing aggressiveness (unlike control animals). Therefore, testosterone is not efficient when it is converted into estrogen, which for its part has to interact with its alpha receptor [106]. BetaERKO adult mice showed no behavioral difference compared with controls, while the youngest were more aggressive than controls of the same age. This could make one think that the role of the beta receptor for estrogens is to mediate an inhibitory effect on aggressive behavior, which is evident only in youth [107].

Effects of testosterone on cerebral levels of serotonin

Serotonin (5HT) is a neurotransmitter synthesized by neurons from the aminoacid tryptophane. Lack of 5HT increases aggressive behavior both in experimental animals and in man. About half of adult rats which do not show interspecific aggressiveness towards a mouse, become aggressive (and some also kill mice) after only four days if they are submitted to a diet lacking in tryptophane [4]. A 5- to 6-month diet almost lacking in tryptophane leads to the mouse-killing behavior in nearly half of non-killer rats, while a subsequent return to a normal diet makes this behavior regress in about half of the mouse-killers. Intraperitoneal administration of 5-hydroxytryptophane (an intermediate product of 5HT biosynthesis) causes the disappearance of the mouse-killing behavior in another percentage of killer rats and delays the mouse-killing response in others [3].

In rats, the interruption of serotonergic pathways of the proencephalon makes aggressive attacks more likely to occur [108]. The role of 5HT in inhibiting aggressiveness in rodents is demonstrated by pharmacological studies, as well, through the administration of receptor agonists [103,109,110] or 5HT re-uptake inhibitor agonists [111,112]. Knocked-out mice for the gene encoding the serotonergic receptor 5HT1B show a shorter latency and a higher intensity in attacking an intruder placed in their own cage [113]. Studies performed on undomesticated and free *Macaca mulatta* monkeys showed how low levels of 5-hydroxyindolacetic acid (5HIAA, a catabolite of 5HT, whose high levels are considered an index of high activity in serotonergic neurons) obtained from cerebrospinal fluid (monkeys were captured in order to take a sample of cerebrospinal fluid and then were set free) were related to a higher inclination to move away from the group they belonged to and to face extreme risks, such as fighting with other, older and stronger, males. The consequence was that the surviving percentage of these animals was lower than those with high fluid levels of 5HIAA [21,114,115]. There are many studies assessing the inhibitory role of 5HT on aggressive behavior in man as well. Low cerebrospinal fluid 5HIAA levels are correlated with aggressive and antisocial inclinations [116,117]. The administration of 5HT agonist drugs (fluoxetine) reduces the aggressiveness levels [118].

As aggressive behavior is influenced by cerebral 5HT levels, it is right to wonder whether testosterone influences these functions by changing cerebral 5HT levels. Actually, testosterone affects the metabolism of diencephalic 5HT. In fact, in male rats, the chronic administration of testosterone reduces 5HT and 5HIAA levels in the hippocampus [14]. The androgenization of female rats causes a reduction in 5HT levels in the amygdala [119]. Castration increases both diencephalic 5HT levels and hypothalamic and hippocampal 5HIAA levels [120,121], the latter effect being abolished by testosterone or estrogen administration [122]. Moreover, male animals treated with anti-GnRH antibodies (which causes an immunological castration) leads to an increase in hypothalamic 5HT [123].

The presence of testosterone in the prenatal period affects the distribution of serotonergic fibers in the medial pre-optic nucleus. It also leads to masculinization of the architectural traits of that nucleus [98].

The inhibition of the aromatase enzyme, which converts testosterone into its active form, during neonatal age causes in adult males both a feminine sexual behavior and a lack of dimorphism of the metabolism of extrahypothalamic 5HT, which was, in contrast, found in control animals [124]. Moreover, in females which were administered intraventricular testosterone in neonatal age, 5HT turnover in the striatum and in the limbic system was similar to that of control males [125].

An inverse relation between testosterone and cerebral 5HT was also assessed by behavioral studies. Rats that became dominant after treatment with testosterone are inclined to lose their dominance if they are treated with serotonergic drugs; this effect is avoided by antiserotonergic drugs administration [14]. In monkeys, offensive and/or impulsive aggressiveness is correlated with low serotonergic activity, high plasma testosterone, and low cortisol levels [23].

However, in monkeys and in man a certain difference between aggressiveness and impulsiveness has been demonstrated. In monkeys, the free testosterone levels in cerebrospinal fluid are correlated with aggressiveness, but not with impulsiveness, 5HIAA levels in the cerebrospinal fluid being inversely correlated with impulsiveness and wild aggressiveness, but not with all kinds of aggressiveness. However, high testosterone levels in the cerebrospinal fluid of subjects with low 5HIAA cerebrospinal fluid levels further increase aggressiveness [21,114]. In subjects with personality disorders, a reduction in serotonergic function (established through a functional test) is inversely correlated with impulsiveness, while plasma testosterone levels are directly correlated with the frequency of aggressive actions [126].

The effects of testosterone on vasopressin cerebral levels

Vasopressin (or antidiuretic hormone: ADH) is synthesized by hypothalamus and neurons of other cerebral areas and it is known to control the osmotic balance of the organism. Recently, excess hypothalamic ADH has also been ascribed a role in aggressive behavior, dominance, and memory. Apart from the hypothalamic supraoptic and paraventricular nucleus, ADH is also produced by the neurons of the proprius nucleus of the stria terminalis, by the medial amygdala nu-

cleus, by the hippocampus, and by the diagonal Broca's band [127]. In the monkey, vasopressinergic receptors were found in the prefrontal, pyriform, and cingulum cortex, in the amygdala, in the lateral septum, in the hypothalamus, and in the cerebral stalk [128]. Briefly, compared with less aggressive animals, those more aggressive show higher ADH levels in the lateral hypothalamus [129] and lower levels in the lateral septum [130,131]. The administration of ADH in the lateral hypothalamus of the hamster decreases the latency of attack against an intruder. This effect is prevented by the administration of a drug increasing serotonergic neuron activity (fluoxetine). This prompts the hypothesis of a correlation with ADH-5HT, at least in the lateral hypothalamus [129,132]. In man, cerebrospinal fluid levels of ADH are correlated with aggressiveness episodes also towards other individuals, at least in subjects with personality disorders [133]. ADH has an important role in mechanisms related to dominance attitudes; hamsters, rendered subdued during puberty, have a reduction in ADH levels in the anterior hypothalamus, which is a site involved in the regulation of aggressive behavior in this species [134].

The action of testosterone in the CNS was also correlated with ADH. Some authors pointed out that males have more ADH-releasing neurons and that androgens increase ADH and its receptor levels in some cerebral areas involved in aggressive behavior (the medial amygdala, lateral hypothalamus, and medial preoptic area), at least in rodents [127,135,136]. In hamsters, androstendione and testosterone administration prevents ADH level reduction induced by castration in the nucleus proprius of the stria terminalis and in the middle medial amygdala [137]. The action of testosterone on the CNS is likely based both on 5HT level reduction and on the increase in vasopressinergic system activity. Correlations between 5HT and ADH have also been assessed [129,132].

CONCLUSIONS

Testosterone is a determinant for the onset of aggressive behavior in animals and in man. This assertion, drawn from empirical observations, has been confirmed by several experimental studies performed in animals and man. Testosterone receptors in the CNS are located above all in neurons belonging to the hypothalamic nucleus, which is involved in aggressive behavior. After testosterone links to its receptor it is aromatized into estrogens within the neurons. The estrogens determine the increase in aggressiveness in animals. In order to show aggressive behavior in adult age, the presence of adequate testosterone quantities in the fetal period in primates and in the prenatal period in other animals is essential; the aromatization of testosterone into estrogens in this period of life steers the brain in a masculine direction, not only from an endocrinological, but also a behavioral point of view. The effect of testosterone is correlated with the influence that it exerts on some neurotransmitters and neuromodulator levels, as well as on their own receptors. In particular, an inverse relation between plasma and cerebrospinal fluid testosterone levels and brain 5HT levels exists, as a lack of brain 5HT leads to an increase in aggression in all the considered species.

It is necessary, however, to apply common sense when extrapolating the convincing experimental data from animal to man. In the case of the latter, it is indeed also necessary

to take into account the environmental, social, and cultural factors which can attenuate or increase the influences of biological factors.

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