REVIEW ARTICLE

The Role of Testosterone in Aggression

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ABSTRACT This review article explores the evidence that testosterone is significantly correlated with certain forms of aggression in a number of animals, although firm evidence is lacking for humans. Studies have revealed that structures within the limbic system are particularly involved in the elicitation of aggression and are sexually dimorphic. Testosterone can exert its effects in one of two ways: either on androgen receptors after conversion to 5-alpha-dihydrotestosterone or on estrogen receptors after aromatization to estradiol. It can act via genomic mechanisms to induce production of proteins or via non-genomic mechanisms to modulate neural activity. Androgen and estrogen receptors are also found along neurotransmitter pathways. As such, testosterone is able to modulate levels of various neurotransmitters that show evidence of mediating effects on aggressive behaviour. In addition, recent evidence suggests that these neurotransmitters are involved in processes such as olfaction and arousal and suggestions have been put forward explaining how testosterone may modulate these processes. However there is a critical time period early in life, usually within the first few days after birth, during which testosterone exposure is essential to elicit aggression in adulthood. It is thought that testosterone and its metabolites sensitize an androgen-responsive system, while estrogenic metabolites establish the capacity to fight in response to estrogenic stimulation later in life. Despite this, testosterone is only one of a myriad of factors that influence aggression and the effects of previous experience and environmental stimuli have at times been found to correlate more strongly.

INTRODUCTION

Changes in the concentration of hormones can have profound effects on mood and behaviour in humans. Variation in hormone levels have been implicated in some psychiatric disorders such as depression. For example, 50-75% of patients with major depression show hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis characterised by excess secretion of cortisol (1,2).

Aggressive behaviour in society is a serious social problem. Between 1998-1999, the number of violent offences in England and Wales rose by 6.3%, the majority of which was violence against the person (83%) (3). Although aggression is affected by various influences, there is evidence to suggest that certain biological factors may modulate aggressive behaviour.

This paper reviews the evidence supporting the role of testosterone as a biological factor affecting aggressive behaviour. Human studies have so far demonstrated a relationship between measures of testosterone in adolescent males and aggression (4) with similar results found in women (5). However, results from human studies have also been subjective (6-9) since results are based on psychological questionnaires and observation. For example, girls with a condition called congenital adrenal hyperplasia, in which androgens are secreted in large amounts, have been shown to act in a more rough-and-tumble way during childhood which was thought to correlate with aggression (10).

In contrast, strong evidence for the role of testosterone in influencing aggression is available from

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animal studies. It is believed that testosterone mediates these effects during two separate periods in life. The first period is the 'critical time period', usually the first few days after birth during which sensitization of certain neural circuits is thought to occur. The second period occurs in adulthood perhaps through modulation of neurotransmitter pathways and is thought to depend on the earlier sensitization.

This paper briefly reviews the evidence suggesting that testosterone modulates aggression in both males and females and is followed by a detailed discussion on the evidence which may shed light on the mechanisms involved. As such this paper focuses on effects during the critical time period shortly after birth and also later in adulthood, and also considers the brain regions thought to be involved in the androgen and estrogen responsive pathways. Relevant details regarding neurotransmitter pathways and other factors possibly involved are included to support the evidence.

EVIDENCE FOR A ROLE OF TESTOSTERONE IN AGGRESSION

The term aggression has been defined as "a response that delivers noxious stimuli to another person" (11). In animals, however, there are various forms of aggression classified into predatory, intermale, fear-induced, irritable, territorial, maternal and instrumental (12). Androgens have been found to affect only certain forms, for example, intermale aggression which can be illustrated by the resident-intruder test. In contrast, predatory aggression is entirely independent of androgens (13). Therefore only the forms of aggression that have been found to have a link with testosterone facilitation will be discussed.

The classical hormone removal and replacement experiment approach has shown a definite link between testosterone and aggression in animals. In general, castration leads to a decrease in aggression whilst replacement of testosterone restores the behaviour. However differences in the effects induced by testosterone have become apparent between males and females. Different regions in the brain modulate different hormone-dependent aggression (14) and females require longer exposure to androgens after ovariectomy to induce male-like behaviour (15).

Male aggression

In 1849 Berthold described behavioural changes in cockerels after castration and how these were reversed after the testes were replaced. Similarly it has been shown that aggression in castrated rats was restored to its previous levels by androgen replacement (16). More recently, intermale aggressive behaviour in rats induced by electrical stimulation of the hypothalamus was enhanced by androgens (13). Studies in rats, mice, monkeys and humans show that competitive or intermale aggression increases at puberty, whereas it is reduced by castration and increased by testosterone injection (13,16-22).

Female aggression

Aggression in females, like in males, appears to be facilitated by testosterone in a dose-dependent manner (16). In one study, ovariectomized female rats were given daily injections of testosterone, estradiol or a placebo. It was found that testosterone increased aggressiveness, measured by the frequency of fighting, whereas estradiol or a placebo had little effect (23).

In general, female aggression patterns were similar to those seen in males, i.e. ovariectomy without hormone replacement decreased interfemale fighting and replacement of gonadal testosterone stimulated it (24). However, according to the authors, the presence of testosterone was not sufficient to 'activate' the aggression. Instead, the missing essential factor was likely to be an experiential event, for example, competition. Therefore it is possible that hormones are required for its persistence but are not sufficient to activate the neural circuitry required for aggression.

HOW DOES TESTOSTERONE CAUSE AGGRESSION?

Testosterone acts as a prohormone which when converted into 5-alpha-dihydrotestosterone (5α-DHT) acts on androgen receptors or when converted into estradiol by the enzyme aromatase, acts on estrogen receptors (Figure 1). There is overwhelming evidence that most of the effects of testosterone in mediating aggression occur after aromatization (33). For example, testosterone induced aggression is concurrent with an elevated level of aromatization and nuclear estrogen receptor activity in the hypothalamic/preoptic area. Treatment with an aromatase inhibitor blocked this aggression and lowered nuclear activated estrogen receptors (34,35). Furthermore the intensity of aggressive behaviour was directly correlated with the aromatase activity ($p < 0.02$) in the posterior hypothalamus (34).

Testosterone also has effects that are manifested early in life. The neonatal organising actions of testosterone are achieved by stimulating cell growth and differentiation in the preoptic area, ventromedial hypothalamus and amygdala, and dendritic branching in the preoptic area and the hypothalamus (35). For example, authors have suggested that testosterone increases the size of the granule cell layer in the dentate gyrus (origin of hippocampal mossy fibres) and that these effects occur during a 'critical time period' (36,37).

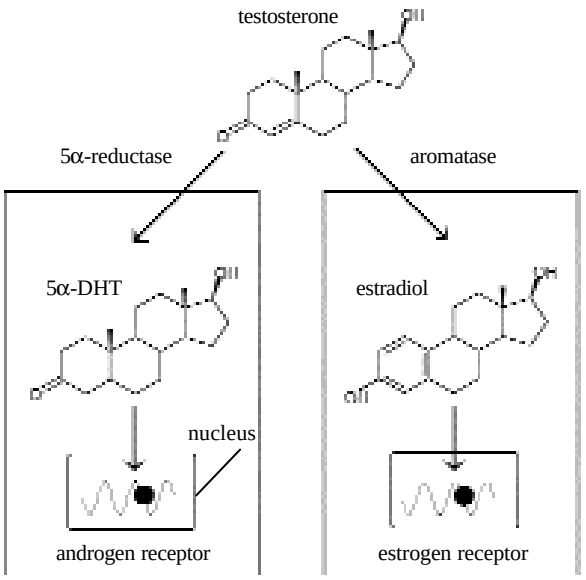

Figure 1. The chemical structures of testosterone and its derivatives are shown. Testosterone is converted into 5α-DHT by the enzyme 5α-reductase to then act on androgen receptors. Alternatively, aromatase can convert testosterone into estradiol which acts on estrogen receptors.

Critical time period

The idea that there is a critical time period during which testosterone acts on the brain to sensitize certain neural circuits has received a great deal of attention and testosterone is now considered to have a definite role in the establishment of aggressive behaviour in adulthood (38-40). Furthermore, it appears that while testosterone modifies aggression, it does so only within a range that has been genetically programmed (41).

In mice, male castration at birth decreased levels of fighting even in the presence of large amounts of testosterone propionate as adults. However, if the castration took place at ten days of age, the difference in fighting levels compared to controls was much less pronounced (39). Similar findings were found in females (16). It was concluded that androgen stimulation of the mouse before ten days of age causes differentiation of a neural system for aggression which is sensitive to androgens in adulthood. This agrees with others' findings (42,43) that castration on day 0 followed shortly by a single injection of testosterone results in a relatively normal adult male with respect to fighting behaviour.

Recently it has been proposed that in males during the first few days after birth, testosterone and its metabolites sensitize an androgen-responsive system while estrogenic metabolites organize an estrogen-responsive pathway (44). In general the organising effect is primarily done by testosterone and its ability to be aromatized, and can influence either androgen- or estrogen-sensitive circuits (45). For example, administration of testosterone or methyltrienolone (R1881), a potent nonaromatizable androgen, on day one of life caused aggression which was brought on in response to androgens but not estrogens in adulthood (46). In contrast, if estrogenic metabolites were present early, then in adulthood this changed with both testosterone or estrogen able to affect aggressive behaviour in males (46).

In females, there is also an androgen-sensitive pathway, although a greater exposure to androgens is required to induce male-like fighting behaviour. Evidence to support this comes from the finding that 400 μg of testosterone propionate will effectively organise female aggression at 0-2 hours after birth but it will not at two days of age. However if 600 μg is given at this later stage, the treatment is effective (47). Furthermore, adult females are completely insensitive to the aggression-promoting effects of estrogens seen in males.

Therefore there appears to be a sensitive period when the differentiation of aggression with hormones is most likely, i.e shortly after birth, but the period can be extended by increasing the hormone dosage. Furthermore the results indicate that hypothalamic and associated brain mechanisms become less sensitive to exogenous androgen with time after castration (39), most likely due to decreased sensitivity of the receptors with age (48). There is, however, some conflicting evidence to suggest that the critical time period is not essential to elicit aggression in adulthood. For example, males castrated on day 0 were found to show aggression in adulthood in response to testosterone however larger doses and often a longer duration of treatment was required (16).

Recently it has been speculated that changes also occur *in utero*: the testosterone secretory capacity of Leydig cells in the testes of mice changes differentially during intrauterine development in males of the aggressive and non-aggressive selection lines (49). The peak secretory capacity is reached at day 17 of gestation for the males of the aggressive selection line while the peak for the non-aggressive line is reached on the first neonatal day. Similarly female mice fought significantly sooner following the initiation of testosterone treatment in adult life if they were exposed to it between the 13^{th} and 18^{th} day of fetal development (50). Similar results were obtained by others (51,52). Coincidently, the brain aromatase activity changes during development as well (53-55); for example, at day 1, aggressive males show higher aromatase activity in the amygdala than in the hypothalamus, whereas in less aggressive strains the activity did not differ (54).

The effects of testosterone in adulthood

While the primary action of steroid hormones is to regulate protein synthesis through a genomic action, they can also modulate neural activity via non-genomic mechanisms such as modifying the permeability of nerve cell membranes. This suggests the existence of membrane receptors for the steroid in addition to nuclear receptors. These non-genomic effects result in changes in electrical potential possibly through cyclic adenosine monophosphate activation and the release of neurotransmitters into the synapse (56). One of the primary actions of the steroid hormones thus may be to regulate the opening of ion channels in the cell membrane.

It is widely accepted that steroid hormones modulate behaviour through indirect actions on neurotransmission in the central nervous system. It is assumed that their activity is related to the density of steroid receptors in these areas (57). When the distribution of steroid hormone receptors in the brain is compared with the distribution of neurotransmitter pathways, a close relationship is observed (Figure 2); for example, the distribution pattern of estrogen receptors correlates well with that of noradrenaline, dopamine and serotonin (5-HT) nerve pathways in the rat (58). When a steroid hormone alters the electrical activity of a target neuron along one of these pathways the amount of neurotransmitter released from that neuron is altered. For example, it was found that normal fighting in mice decreased when there was an accelerated release of certain amines (59).

However it should be stressed that the neural circuits underlying aggression are themselves plastic, i.e. neurotransmitter modulation may not be the only way testosterone can affect aggression in adulthood. For instance, levels of aggression tend to fluctuate during the year in many animals according to their mating season: when the breeding season approaches and the gonads recrude, aggression increases with a corresponding elevation in testosterone levels (60).

Effects of testosterone on neurotransmitter pathways

Many studies have been undertaken that implicate 5-HT in modulating aggression. In general, increased activity of serotonergic synapses inhibits aggression: studies in male rhesus monkeys showed that those with low levels of 5-hydroxyindoleacetic acid (5-HIAA) were more aggressive (30,61,62). Furthermore, fluoxetine, a serotonin reuptake inhibitor, tends to decrease aggression in both animals and humans. Strong evidence suggests that these effects are mainly mediated via 5-HT_{1A} and 5-HT_{1B} receptors (63). This is supported by various animal studies: 5-HT_{1A} agonists decrease aggression and defensive behaviour in wild rats (64); gene knockout mice lacking the 5-HT_{1B} receptor (equivalent to 5-$HT_{1D\beta}$ in humans) showed greatly enhanced intruder confrontation aggression (65).

Testosterone may also be involved in the arginine vasopressin (AVP) system, since an AVP receptor antagonist injected into the anterior hypothalamus of male golden hamsters was found to block their offensive aggression (66). This is supported by evidence that male golden hamsters have androgen-sensitive AVP receptors in the ventrolateral hypothalamus and castration leads to a loss of AVP binding (67). Furthermore, there appear to be 5-HT synapses on AVP neurons in the anterior hypothalamus and the AVP immunopositive boutons and hippocampo-septal axon terminals frequently terminate on the same somatospiny neurons on the lateral septum. Therefore, perhaps testosterone promotes aggression by lowering 5-HT levels thus removing a potential inhibitory influence on AVP.

Testosterone has also been found to influence the density of $GABA_A$ receptors. Testosterone-treated rats have a decreased density of $GABA_A$ receptors in several brain regions (68) and several studies have implicated low levels of GABA with aggression (69,70). Coincidently, a role for GABAergic inhibition has been implicated in odour coding and in particular $GABA_A$ antagonists caused lowering of the response threshold to odours (70,71). Therefore high-attacking animals would have a better perception of the olfactory cues leading to rapid recognition of the opponent.

There is also evidence to support a direct role of noradrenaline in aggression (72). Adrenoceptor blocking drugs such as phentolamine (alpha receptor blocker) or obsidan (beta blocker) caused a decrease in aggression and testosterone levels in dominant mice (73). It has been suggested that noradrenaline heteroceptors terminate on presynaptic 5-HT neurons raising the possibility of interaction between the two transmitter systems (72).

Finally, testosterone has been found to suppress dopamine turnover in the anterior hypothalamus of male rats (74) which was thought to be involved in androgen-dependent aggression, although studies tend to support a positive relationship between central dopamine function and aggression (72). There have also been suggestions that acetylcholine and glutamate are involved in testosterone-mediated aggression.

OTHER FACTORS INVOLVED IN TESTOSTERONE-MEDIATED AGGRESSION

Research into human forms of behaviour such as aggression is complicated by the complex manner in which humans tend to behave. For example, studies have found that aggressive encounters are influenced by

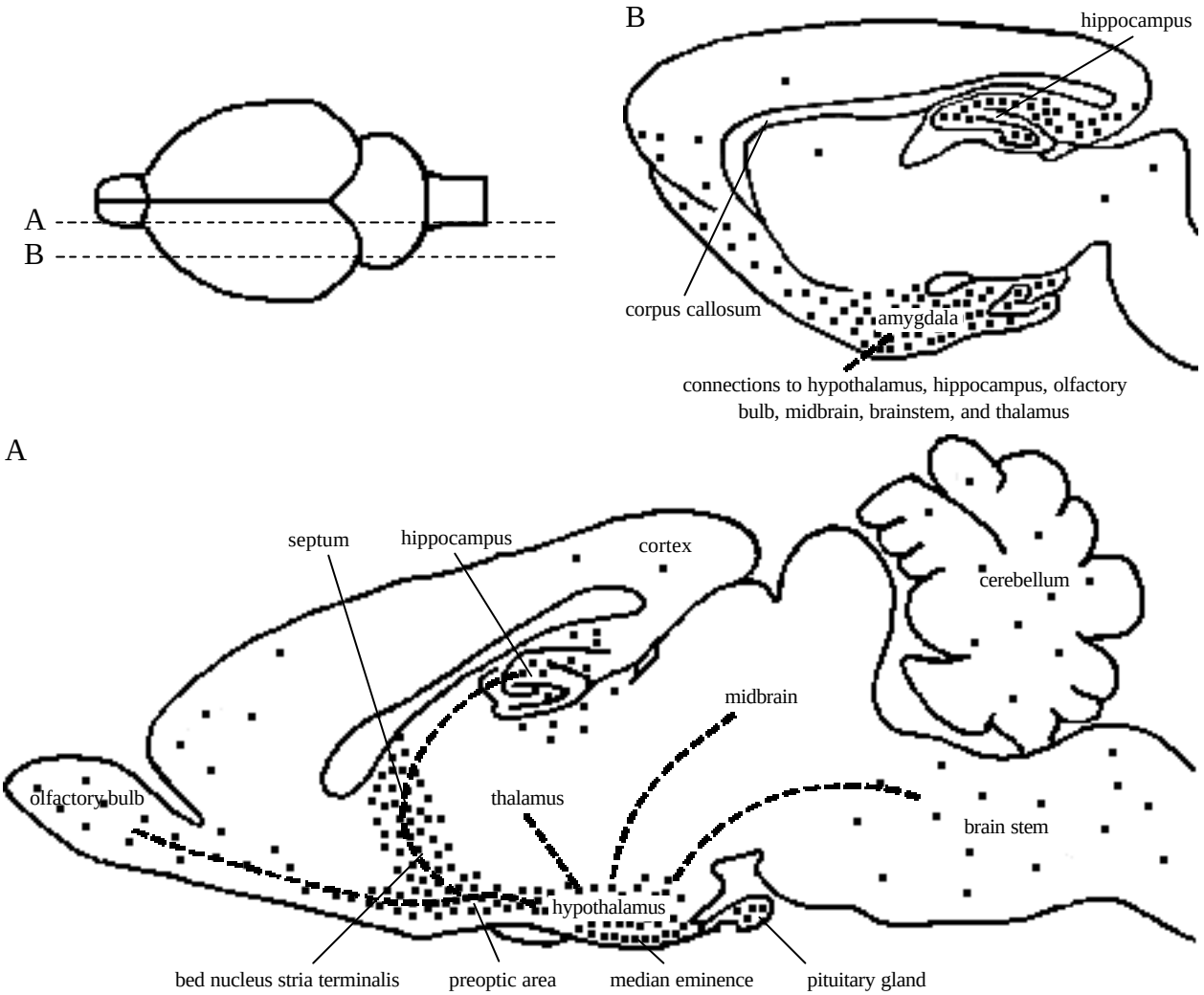

Figure 2. Neural circuits underlying aggression as shown in the rat brain. Original work by Hess in 1928 (26) found that 'sham rage' occurred after electrical stimulation of the hypothalamus. More recently, a continuous stretch of points through the hypothalamus have been mapped out in rats which when stimulated resulted in aggressive behaviour (27). Furthermore it appeared that for each form of aggression, there appeared to be different representations within the hypothalamus. For example, stimulation and lesion studies point to a strong lateral hypothalamic involvement in predatory and intermale aggression whereas the anterior hypothalamus is involved in fear-induced and irritable aggression. As such the neural systems underlying these different forms of aggression seem to converge from various parts of the brain within the hypothalamus (28). Various lesion, electrophysiological and morphological studies suggest that the neural control of aggressive behaviour, in particular the associated movements, are programmed by neural circuits in the brain stem whose activity appears to be controlled by various structures in the limbic system such as the hypothalamus and amygdala (29,30). In turn, important pathways lead from the hypothalamus through the medial forebrain bundle to the limbic cortex through the amygdala and septum. There are also connections from the olfactory bulb (31). Interestingly, high densities of androgen and estrogen receptors were found in these areas (32). Schematic diagrams show parasagittal views of the rat brain at a medial (A) and lateral (B) position. The neural circuits thought to be involved in aggressive behaviour are indicated as dotted lines. Dots represent areas found to contain androgen and estrogen receptors. Notice the overlap between the indicated neural circuits and the regions of highest androgen and estrogen receptor density.

learning, i.e. the outcome of the first encounter influenced subsequent fights (75). There is also evidence that aggression is in itself rewarding. For example, when animals with lateral hypothalamic electrodes were allowed to control the stimulation, they pressed the levers with high frequencies suggesting the presence of 'positive' feelings (76). Interestingly, self-stimulation rates were decreased when the animals were castrated and increased again after hormone substitution.

Other research has indicated that testosterone may be correlated with aggressive motives and competitiveness rather than violence *per se*. Serotonin function on the other hand may function to limit aggression to an

appropriate time, setting and intensity. Overall the results indicate that while subjects with high levels of testosterone exhibit more aggression, the aggressive encounters are stopped before they escalate into dangerous forms of aggression (77). Other factors implicated in aggression include involvement of the Y chromosome (78,79), alcohol (80) and the role of olfaction (81-84).

PROBLEMS WITH PREVIOUS STUDIES

Most studies of testosterone and aggression have measured plasma total testosterone levels which can be problematic since in plasma the free fraction accessible to the central nervous system is only about 2% (85). It was therefore proposed that accurate reflection of central androgen activity might be better obtained by cerebrospinal fluid (CSF) free testosterone (77). Furthermore, investigators found that in rhesus monkeys testosterone was related to overall aggressiveness whereas low levels of CSF 5-HIAA were related to impulsivity. This has implications on a variety of studies where impulsivity was regarded as a predisposition or even a type of aggression.

In addition, there are species differences in the structures involved in the different types of aggression. The cingulate gyrus is involved in fear-induced aggression in the monkey but irritable aggression in the cat and dog. The effects of stress are also problematic since they have been found to reduce testosterone in man and other animals. Therefore stress induced by defeat would naturally depress testosterone levels (86). Related to this, it was found that sexual stimulation (87) and exercise (88) increase testosterone levels and many of the behaviours elicited in the studies probably have an element of sexual motivation which has been shown to be estrogen dependent (89).

Although there is strong evidence that testosterone is involved in aggression, it must be stressed that perhaps other hormones are involved. After castration, many hormone systems are disrupted which could confound the experiment. For example, aggression was more closely related to luteinizing hormone than testosterone in the male starling (90). Review and clarification of behavioural measures is therefore recommended.

CONCLUSION

There is strong evidence in animals that testosterone is directly associated with aggression, although this correlation is not as strong in humans. Testosterone appears to mediate its effects during a critical time period shortly after birth during which it sensitizes certain neuronal circuits in the brain. As a result, in adulthood, when these circuits are stimulated again by steroids, aggressive behaviour is elicited perhaps through modulation of specific neurotransmitter pathways. However, it must be remembered that hormones themselves do not directly cause behaviours, but induce chemical changes in certain neurons, affecting the likelihood of certain behavioural outcomes as a result of modulation of particular neural pathways (91). Furthermore, gonadal hormones are only one of a myriad of influences on aggressive behaviour. Since testosterone is present in males that are not aggressive as well as in those that are, it is obvious that another factor(s) is involved, such as cognition and environmental circumstances which have been found to affect the expression of aggression (60,92).

Scientists are limited in that they cannot perform experimental procedures in humans as they have done in animals and since the behaviour patterns in humans are so different from animals, rendering it difficult to extrapolate from animals to humans. As it was put recently “there is a danger of triviality and truism, or even misleading simplification, in many of our extrapolations and animal models” (76). As such we should remember that correlation does not necessarily indicate causation and in many studies such assumptions have been made. Before experiments can be done to investigate these correlations, we need to be sure that the types of aggression we are looking into are testosterone-dependent and eliminate other factors that could confound the results.

REFERENCES

1. Nemeroff CB. Clinical significance of psychoneuroendocrinology in psychiatry: focus on the thyroid and adrenal. Journal of Clinical Psychiatry 1989; 50 Suppl: 13-20.
2. Rubin RT. Pharmacoendocrinology of major depression. European Archives of Psychiatry and Neurological Sciences 1989; 238: 259-267.
3. Povey D, Cotton J. Recorded Crime Statistics: England and Wales. October 1998 to September 1999. London: Home Office Research Development and Statistics (RDS) Directorate; 2000.
4. Olweus D, Mattson A, Schalling D, Low H. Circulating testosterone levels and aggression in adolescent males: a causal analysis. Psychosomatic Medicine 1988; 50: 261-272.
5. Ehlers CL, Rickler KC, Hovey JE. A possible relationship between plasma testosterone and aggressive behavior and social dominance in man. Psychosomatic Medicine 1980; 36: 469-475.
6. Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ. Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. Journal of Clinical Endocrinology and Metabolism 1994; 78: 711-716.
7. Susman E, Granger D, Murowchick E, et al. Gonadal and adrenal hormones: developmental transitions and aggressive behaviour. in: understanding aggressive behaviour in children. In: Ferris C, Grisso T, eds. Understanding Aggressive Behaviour in Children. Annals of the New York Academy of Sciences 1996; 794: 18-30.
8. Halpern CT, Udry JR, Campbell B, Suchindran C. Relationships between aggression and pubertal increases in testosterone: a panel analysis of adolescent males. Social Biology 1993; 40: 8-24.
9. Kreuz L, Rose R. Assessment of aggressive behavior and

plasma testosterone in a young criminal population. Psychosomatic Medicine 1972; 34: 321-332.
10. Clare A. On Men: Masculinity in Crisis. London: Chatto & Windus; 2000.
11. Buss AH. The Psychology of Aggression. New York: Wiley; 1961.
12. Moyer KE. Kinds of aggression and their physiological basis. Communications in Behavioural Biology 1968; 2: 65-87.
13. Bermond B, Mos J, Meelis W, et al. Aggression induced by stimulation of the hypothalamus: effects of androgens. Pharmacology, Biochemistry and Behavior 1982; 16: 145-155.
14. Albert DJ, Jonik RH, Walsh ML. Hormone-dependent aggression in male and female rats: experiential, hormonal, and neural foundations. Neuroscience and Biobehavioural Reviews 1992; 16: 177-192.
15. Simon N, Whalen R, Tate M. Induction of male-typical aggression by androgens but not estrogens in adult female mice. Hormones and Behavior 1985; 19: 204-212.
16. Edwards DA. Early androgen stimulation and aggressive behavior in male and female mice. Physiology and Behavior 1969; 4: 333-338.
17. Brain PF. Hormones and Aggression. Annual Research Reviews. Vol. 1. Montreal: Eden Press; 1977.
18. Seward JP. Aggressive behaviour in the rat: general characteristics, age and sex differences. Journal of Comparative Psychology 1945; 38: 423-430.
19. Beach FA. Bisexual mating behaviour in the male rat - effects of castration and hormone administration. Physiological Zoology 1945; 18: 390-402.
20. Levy IV, King IA. The effects of testosterone propionate on fighting behaviour in young male C57BL/10 mice. Anatomical Record 1953; 117: 562.-563.
21. Persky H, Smith KD, Basu GK. Relation of psychologic measures of aggression and hostility to testosterone production in man. Psychosomatic Medicine. 1971; 33: 265-277.
22. McKinney TD, Desjardins C. Postnatal development of the testis, fighting behaviour and fertility in house mice. Biology of Reproduction 1973; 9: 370-378.
23. Van de Poll NE, Taminiau MS, Endert E, Louwerse AL. Gonadal steroid influence upon sexual and aggressive behaviour of female rats. International Journal of Neuroscience 1988; 41: 271-286.
24. Albert DJ, Jonik RH, Walsh ML. Influence of combined oestradiol and testosterone implants on the aggresiveness and nonaggressive female rats. Physiology and Behavior 1993; 53: 709-713.
25. McEwen BS. Interactions between hormones and nerve tissue. Scientific American 1976; 235: 48-58.
26. Hess WR. Stammganglian-reizversuche, 10 tagung der deutschen physiologischen gesell schaft. Frankfurt am Main. Ber. Ges. Physiol 1928; 42: 554-555.
27. Kruk MR, Van der Laan CE, Mos J, et al. Comparison of aggressive behaviour induced by electrical stimulation in the hypothalamus of male and female rats. Progress in Brain Research 1984; 61: 303-314.
28. Kaada B Brain mechanisms related to aggressive behaviour. UCLA Forum in Medical Sciences 1967; 7: 95-133.
29. Albert DJ, Petrovic DM, Walsh ML, Jonik RH. Medial accumbens lesions attenuate testosterone-dependent aggression in male rats. Physiology and Behavior 1989; 46: 625-631.
30. Carlson N. Emotion. In: Carlson N, ed. Physiology of Behavior, 6th edition. Boston: Allyn and Bacon; 1998.
31. Johnson R. Aggression in Man and Animals. Philadelphia: W.B. Saunders Company; 1972.
32. Sar M, Stump WE. Distribution of androgen-concentrating neurons in the rat brain. In: Stumpf WE, Grant LD, eds. Anatomical Neuroendocrinology. Basel: Karger; 1975: 254-261.
33. Schlinger BA, Callard GV. Aromatization mediates aggressive behavior in quail. General and Comparative Endocrinology 1990; 79: 39-53.
34. Schlinger BA, Callard GV. Aromatase activity in quail brain: correlation with aggressiveness. Endocrinology 1989; 124: 437-443.
35. Naftoli F, Garcia-Segura LM, Keefe D, et al. Estrogen effects on the synaptology and neural memebranes of the rat hypothalamic arcuate nucleus. Biology of Reproduction 1990; 42: 21-28.
35. Schlinger BA, Callard GV. Estrogen receptors in quail brain: a functional relationship to aromatase and aggresiveness. Biology of Reproduction 1989; 40: 268-275.
36. Guillot PV, Roubertoux PL, Crusio WE. Hippocampal mossy fibre distributions and intermale aggression in seven inbred mouse strains. Brain Research 1994; 660: 167-169.
37. Sluyter F, Jamot L, van Oortmerssen GA, Crusio WE. Hippocampal mossy fiber distributions in mice selected for aggression. Brain Research 1994; 646: 145-148.
38. Dixson AF. Sexual and aggressive behaviour of adult male marmosets (*Callithrix jacchus*) castrated neonatally, prepubertally, or in adulthood. Physiology and Behavior 1993; 54: 301-307.
39. Motelica-Heino I, Edwards DA, Roffi J. Intermale aggression in mice: does hour of castration after birth influence adult behaviour? Physiology and Behavior 1993; 53: 1017-1019.
40. Hutchison JB. Post-castration decline in behavioural responsiveness in intrahypothalamic androgen in doves. Brain Research 1974; 81: 169-181.
41. Guhl AM, Craig JV, Mueller CD. Selective breeding for aggresiveness in chickens. Poultry Science 1960; 39: 970-980.
42. Resko JA, Feder HH, Goy RW. Androgen concentrations in plasma and testis of developing rats. Journal of Endocrinology 1968; 40: 485-491.
43. Bronson FH, Desjardins C. Aggressive behavior and seminal vesicle function in mice: differential sensitivity to androgen given neonatally. Endocrinology 1969; 85: 971-974.
44. Simon N, McKenna S, Lu S, Cologer-Clifford A. Development and expression of hormonal regulating aggression. In: Ferris C, Grisso T, eds. Understanding Aggressive Behaviour in Children. Annals of the New York Academy of Sciences 1996; 794: 8-17.
45. Money J. Influence of hormones on sexual behavoir. Annual Review of Medicine 1965; 16: 67-82.
46. Klein WP, Simon NG. Timing of neonatal testosterone exposure in the differentiation of estrogenic regulatory systems for aggression. Physiology and Behavior 1991; 50: 91-93.
47. Peters PJ, Bronson FH, Whitsett JM. Neonatal castration and intermale aggression in mice. Physiology and Behaviour 1972; 8: 265-268.
48. Da Vanzo JP, Chamberlain JK, Garris DR, Swanson MS. Regional [3H] testosterone uptake in the brain of isolated non-aggressive mice. Brain Research 1986; 369: 224-230.
49. De Ruiter AJ, Feitsma LE, Keijser JN, et al. Differential perinatal testosterone secretory capacity of wild house mice testes is related to aggresiveness in adulthood. Hormones and Behavior 1993; 27: 231-239.
50. Gandelman R, Rosenthal C, Howard SM. Exposure of female mouse fetuses of various ages to testosterone and the alter activation of intraspecific fighting. Physiology and Behavior 1980; 25: 333-335.
51. Mann MA, Svare B. Prenatal testosterone exposure elevates maternal aggression in mice. Physiology and Behavior 1983; 30: 503-507.
52. Gartner J, Whitaker-Azmitia P. Developmental factors influencing aggression: animal models and clinical correlates.

In: Ferris C, Grisso T, eds. Understanding Aggressive Behaviour in Children. Annals of the New York Academy of Sciences 1996; 794: 113-120.
53. Compaan JC, Hutchison JB, Wozniak A, et al. Brain aromatase activity and plasma testosterone levels are elevated in aggressive male mice during early ontogeny. Developmental Brain Research 1990; 82: 185-192.
54. Baum MJ, Erskine MS, Kornberg E, Weaver CE. Prenatal and neonatal testosterone exposure interact to affect differentiation of sexual behaviour and partner preference in female ferrets. Behavioural Neuroscience 1990; 104: 183-198.
55. Weisz J, Ward IL. Plasma testosterone and progesterone titers of pregnant rats, their male and female fetuses and neonatal offspring. Endocrinology 1980; 106: 306-316.
56. Szego CM. Mechanisms of hormone action: parallels in receptor-mediated signal propagation for steroid and peptide effectors. Life Sciences 1984; 35: 2383-2396.
57. Hayden-Hixson DM, Ferris CF. Steroid-specific regulation of agonistic responding in the anterior hypothalamus of male hamsters. Physiology and Behavior 1991; 50: 793-799.
58. Grant LD, Stumpf WE. Hormone uptake sites in relation to CNS biogenic amine systems. In: Stumpf WE, Grant LD, eds. Anatomical Neuroendocrinology. Basel: Karger; 1975: 254-261
59. Welch BL, Welch AS. Aggression and the biogenic amine neuro-humors. In: Garattini S, Sigg EB, eds. Aggressive Behaviour. New York: Wiley; 1969.
60. Thiessen DD. The Evolution and Chemistry of aggression. Springfield: Charles C. Thomas; 1976.
61. Mehlman PT, Higley JD, Faucher I, et al. Correlation of CSF 5-HIAA concentration with sociality and the timing of emigration in free-ranging primates. American Journal of Psychiatry 1995; 152: 907-913.
62. Sundblad C, Eriksson E. Reduced extracellular levels of serotonin in the amygdala of androgenized female rats. European Neuropsychopharmacology 1997; 7: 253-259.
63. Goldman D, Lappalainen J, Ozaki N. Direct analysis of candidate genes in impulsive disorders. In: Bock G, Goode J, eds. Genetics of Criminal and Antisocial Behaviour. Ciba Foundation Symposium 194. Chichester: John Wiley & Sons; 1996.
64. Blanchard D, Shepherd JK, Rodgers RJ, Blanchard RJ. Evidence for differential effects of 8-OH-DPAT on male and female rats in the anxiety/defence test battery. Psychopharmacology Series (Berlin) 1988; 106: 531-539.
65. Sadou F, Amara DA, Dierich A. Enhanced aggressive behaviour in mice lacking 5-HT_{1B} receptor. Science 1994; 265: 1875-1878.
66. Delville Y, Mansour KM, Ferris CF. Serotonin blocks vasopressin-facilitated offensive aggression: interactions within the ventrolateral hypothalamus of golden hamsters. Physiology and Behavior 1996; 59: 813-816.
67. Delville Y, Mansour KM, Ferris CF. Testosterone facilitates aggression by modulating vasopressin receptors in the hypothalamus. Physiology and Behavior 1996; 60: 25-29.
68. Earley CJ, Leonard BE. The effect of testosterone and cyproterone acetate on the concentration of gamma-aminobutyric acid in brain areas of aggressive and non-aggressive mice. Pharmacology, Biochemistry and Behavior. Psychosomatics 1976; 17: 138-142.
69. Cunha GR, Cooke PS, Bigsby R, Brody JR. Ontogeny of sex steroid receptors in mammals. In: Parker M, ed. Nuclear Hormone Receptors: Molecular Mechanisms, Cellular Functions, Clinical Abnormalities. London: Academic Press; 1991: 235-268.
70. Guillot PV, Chapouthier G. Olfaction, GABAergic neurotransmission in the olfactory bulb, and intermale aggression in mice: modulation by steroids. Behavior Genetics 1996; 26: 497-504.
71. Duchamp-Viret P, Duchamp A. GABAergic control of odor-induced activity in the frog olfactory bulb: possible GABAergic modulation of granule cell inhibition action. Neuroscience 1993; 56: 905-914.
72. Coccaro E. Neurotransmitter correlates of impulsive aggression in humans. In: Ferris C, Grisso T, eds. Understanding Aggressive Behaviour in Children. Annals of the New York Academy of Sciences 1996; 794: 82-89.
73. Serova LI, Zhokova AV, Kozlova ON, Naumenko EV. The participation of adrenoreceptors in regulating dominant behavior and gonadal endocrine function in male mice of different genotypes [abstract]. Zhurnal Vysshei Nervnoi Deiatelnosti Imeni I.P. Pavlova 1994; 44: 85-90.
74. Simpkins J, Kalra S, Kalra P. Variable effects of testosterone on dopamine activity in several microdissected regions in the preoptic area and medial basal hypothalamus. Endocrinology 1983; 112: 665-669.
75. Chase ID. Dynamics of hierarchy formation: the sequential development of dominance relationships. Behavior 1982; 80: 218-238.
76. Van de Poll NE, van Goozen SH. Hypothalamic involvement in sexuality and hostility: comparative psychological aspects. Progress in Brain Research 1992; 93: 773-779.
77. Higley JD, Mehlman PT, Poland RE, et al. CSF testosterone and 5-HIAA correlate with different types of aggressive behaviors. Biological Psychiatry 1996; 40: 1067-1082.
78. Carlier M, Roubertoux PL, Kottler, Degrelle H. Y chromosome and aggression in strains of laboratory mice. Behavior Genetics 1990; 20: 137-156.
79. Rudd BT, Galal OM, Casey MD. Testosterone secretion rates in normal males and males with an XYY complement. Journal of Medical Genetics 1968; 5: 286-288.
80. Winslow JT, Ellingboe J, Miczek KA. Effects of alcohol on aggressive behavior in squirrel monkeys: influence of testosterone and social context. Psychopharmacology 1988; 95: 92-98.
81. Wood RI, Newman SW. Hormonal influence on neurons of the mating behavior pathway in male hamsters. In: Micevych P, Hammer RP, eds. Neurobiological Effects of Sex Steroid Hormones. Cambridge: Cambridge University Press; 1995: 3-39
82. Monti-Bloch L, Jennings-White C, Berliner D. The human vomeronasal system: a review. In: Murphy C, ed. Olfaction and Taste XII: An International Symposium. Annals of the New York Academy of Sciences 1998; 855: 373-388.
83. Prabhakaran V, Sobel N, Desmond JE, et al. Comparison of brain activation following stimulation with odors and vomeropherins. Chemical Senses 1997; 22: 771.
84. Monti-Bloch L, Diaz-Sanchez V, Jennings-White C, Berliner DL. Modulation of serum testosterone and autonomic function through stimulation of the male human vomeronasal organ (VNO) with pregna-4,20,diene-3,6-dione. Journal of Steroid Biochemistry and Molecular Biology 1998; 65: 237-242.
85. Pardridge WM Serum bioavailability of sex steroids. Clinics in Endocrinology and Metabolism 1986; 15: 259-278.
86. Christiansen K, Krussman R, Couwenbergs C. Sex hormones and stress in the human male. Hormones and Behavior 1985; 19: 426-440.
87. Krussman R., Christiansen K, Couwenbergs C. Relations between sex hormone levels and sexual behavior in men. Archives of Sexual Behavior 1986; 15: 429-445.
88. Sutton JR, Coleman MJ, Casey J, Lazarus L. Androgen responses during physical exercise. BMJ 1973; 1: 520-522.
89. Adkins EK, Boop JJ, Koutnik DL, et al. Further evidence that androgen aromatization is essential for the activation of copulation in male quail. Physiology and Behavior 1980; 24: 441-446.

90. Davis DE. The hormonal control of aggressive behavior. Proceedings of XIII International Ornithology Congress 1963; 994-1003.
91. McEwen B. Endocrine effects on the brain and their relationship to behavior. In: Siegel G, ed. Basic Neurochemistry, 5th edition. London: Raven Press; 1994.
92. Beeman EM. The effect of male hormone on aggressive behaviour on mice. Physiological Zoology 1947; 20: 373-405.

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