The male fight-flight response: A result of SRY regulation of catecholamines?

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Presenting the idea

Males and females differ in their biobehavioural response to stress, where males exhibit a heightened sympathetic response to stress compared with females. Specifically, Taylor et al. [1] propose that the classic ''fight-or-flight'' response to stress is adaptive for males, whilst females engage in a so-called ''tend-and-befriend'' response to stress. We propose that the Y-chromosome gene, SRY (sex-determining region on the Y chromosome), provides a genetic basis for the heightened sympathetic reactivity to stress and thus predominance of ''fight-flight'' response in males. Our idea is based on studies that demonstrate (i) the presence of SRY in brain regions and peripheral tissues abundant in catecholamines, (ii) the regulation of catecholamine synthesis and breakdown by SRY, and (iii) the role of SRY in voluntary movement and blood pressure in males.

Introduction

Throughout history, males and females have been under divergent pressures of selection, which perhaps reflect the biochemical, physiological and behavioural differences observed between the sexes. Sex dimorphisms are observed in a variety of biological processes such as cognition, food preference, novelty seeking, aggression and response to stress. Responsivity to stress is of particular interest, as it encompasses an array of sex differences for which underlying mechanisms are now emerging. Primary response to stress is characterised by sympathetic nervous system activation of the adrenal glands, resulting in the secretion of catecholamines into the bloodstream, widely known as the ''fight-or-flight'' response. However, most clinical and basic studies that support this theory were performed only in males and did not consider sex differences in the data analysis. Taylor et al. [1] proposed that the ''fight-flight'' response geared toward aggression or fleeing may be adaptive for males, but may not address the differential challenges faced by females, particularly those arising from maternal care of offspring. Rather, female responses to stress may build on maternal-caregiving processes that downregulate sympathetic and hypothalamic-pituitary-adrenal axis response to stress. Such responses would be oxytocin-mediated, and modulated by oestrogen and endogenous opioids [1].

Evidence from clinical and basic research studies support this hypothesis, as males exhibit heightened sympathetic reactivity to stress that is associated with elevated cardiovascular responses and plasma catecholamines. Males have higher resting sympathetic nerve activity to muscles [2–4] and show greater increases in adrenaline [5], blood pressure [6], and total peripheral resistance responses to various stressors [6–8]. Similarly, sex differences are observed in catecholaminergic neurons in the brain with respect to their anatomy, biochemistry and function. For instance, embryonic midbrain cells yield more catecholamine cells when cultures are composed of XY cells than

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Abbreviations:
MAO-A, monoamine oxidase-A; **SNc**, substantia nigra pars compacta; **SRY**, sex determining region on the Y chromosome; **TH**, tyrosine hydroxylase.

XX cells [9], whilst there are significantly more dopamine neurons in the male rat substantia nigra pars compacta (SNc) than in the female [10]. Along these lines, positive emission tomography scans revealed that men have markedly greater dopamine release from the striatum than women following administration of amphetamine [11]. Together, sex differences in sympathetic reactivity to stress and catecholaminergic neurotransmission may provide a mechanism by which divergent responses to stress evolved.

The mechanisms driving sex differences in stress response are less clear. Traditionally, the organisational and activational influences of sex hormones were considered to be the only biological factors that determine sexual differentiation of the brain and other tissues. However, emerging evidence suggests that genetic factors play a role, especially sex-specific genes on the sex chromosomes [9, 10, 12, 13]. The Y-linked gene, SRY (sex-determining region on the Y chromosome), is an obvious candidate to examine, given its role in male sex-determination, and its expression in catecholamine-abundant tissues, and its role as a regulator of motor and sympathetic nervous system function in males.

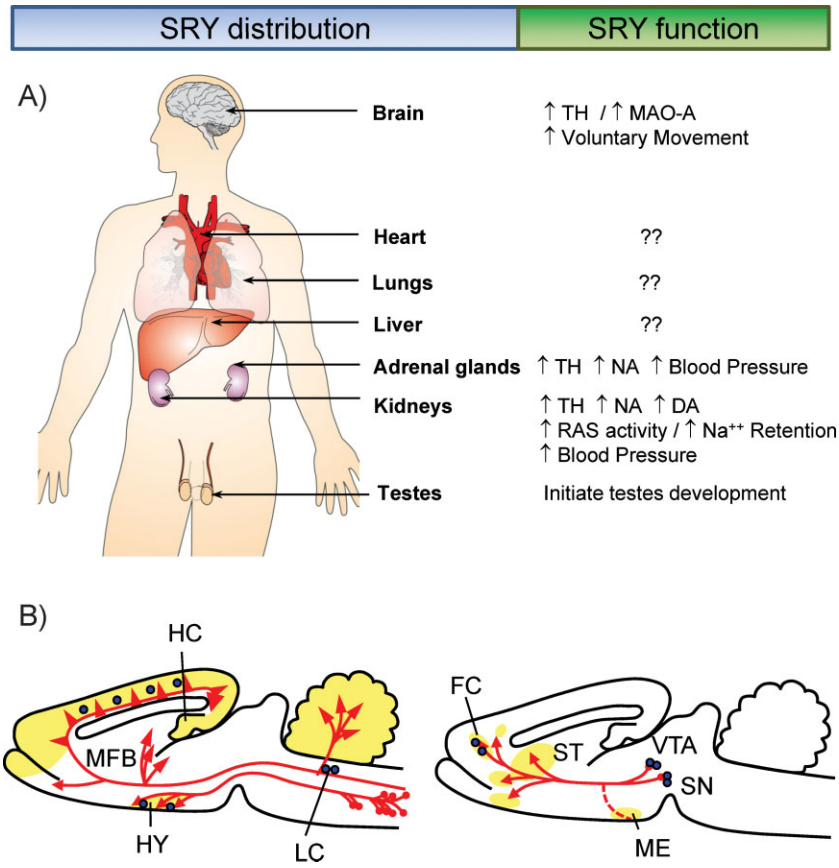

Figure 1. A: Distribution and function of SRY in the brain and peripheral tissues in males. **B**: Distribution of SRY mRNA in noradrenergic (left) and dopaminergic (right) pathway in the rodent brain. Line drawings of sagittal sections of the rat brain, depicting SRY mRNA (blue circle), and catecholaminergic cell bodies (red dot) and axon projections (red line and arrow). The sites depicted are taken from observations in rat and mouse [12, 20, 22]. DA, dopamine; FC, frontal cortex; HC, hippocampus; HY, hypothalamus; LC, locus coeruleus; MAO-A, monoamine oxidase A; ME, median eminence; MFB, medial forebrain bundle; NA, noradrenaline; RAS, renin-angiotensin system; ST, striatum; SN, substantia nigra; TH, tyrosine hydroxylase VTA, ventral tegmental area.

SRY is expressed and biologically active in the brain and peripheral tissues

SRY is a key male sex-determining gene that directs embryonic gonads to develop as testes [14]. The testes then secrete gonadal hormones, which exert organisational (early) and activational (post-natal) effects to masculinise the rest of the body. If the *SRY* gene is absent or mutated, the testes do not form, and the female phenotype develops [15]. The *SRY* gene encodes a transcription factor containing an HMG box that recognises specific DNA sequences in gene regulatory regions (promoters/enhancers) to stimulate transcription [16]. Interestingly, SRY is expressed in numerous tissues outside the testis including the adrenal glands, kidneys, lungs, heart and brain (Fig. 1A)[10, 17], suggesting roles other than sex determination. *SRY* mRNA is expressed in brain regions such as the SNc, ventral tegmental area, locus coeruleus and hypothalamus in rodents [10, 18] and in the hypothalamus, frontal and temporal cortex in humans [19] (Fig. 1B). The expression of SRY in catecholamine-abundant tissues led investigators to assess whether SRY regulated genes are involved in the synthesis and breakdown of catecholamines. Initial studies in a rat catecholaminergic cell line demonstrated that SRY regulates the transcription of tyrosine hydroxylase (TH; a synthetic enzyme for catecholamines) via AP-1 binding sites on the *TH* promoter [18]. Similarly, SRY regulates common variants of the proximal promoter of *TH* in humans [20]. The gene encoding monoamine oxidase-A (MAO-A), an enzyme that inactivates catecholamines via removal of an amine group, was identified as another neural target of *SRY* [21]. Promoter analysis identified that *SRY* binds directly to the *MAO-A* promoter in vitro and in vivo and increases MAO-A catalytic activity [21]. Hence, the expression of *SRY* in adult male tissues allows for a mechanism of sexual dimorphism independent of circulating gonadal hormones, in which *SRY* may activate catecholamine biosynthesis in a direct, cell-autonomous manner.

SRY regulates voluntary movement and sympathetic nerve activity in males

Direct actions of SRY in the brain were first demonstrated in a seminal study by Dewing et al. [10], which assessed the anatomical and behavioural consequences of downregulating SRY expression in the rat SNc. Immunohistochemical studies showed that SRY protein co-localises exclusively in TH positive neurons in both the male mouse and rat SNc, a brain region crucial for control of voluntary movement. Knockdown of *SRY* in the rat SNc, via chronic injection of antisense *SRY* oligonucleotides, resulted in a significant reduction in TH-positive neurons, compared to the control side in the male rat SNc [10]. The reduction in TH-positive neurons was associated with quantifiable motor defects in the contralateral forelimb, suggesting that SRY acts as a transcriptional activator of nigrostriatal dopamine pathway and motor function in adult males [10]. SRY also has a functional role in peripheral tissues in males, specifically the sympathetic nervous system. Transfection of *SRY* into the adrenal medulla of male rats raised adrenal TH content and plasma noradrenaline levels, resulting in an increase in blood pressure [22]. Similarly, *SRY* delivered to the kidney increased renal TH content and plasma noradrenaline and dopamine levels in normotensive male rats [23]. Recent studies have demonstrated that that *SRY* increases the activity of multiple renin-angiotensin system genes and activates the renin-angiotensin system in vivo [24], which may contribute to sex differences in blood pressure. Together, these studies demonstrate that SRY exerts direct male-specific actions in the adult brain and peripheral tissues to regulate catecholamine-dependent functions, such as voluntary movement and blood pressure.

SRY: A genetic basis for the predominance of fight-flight response in males?

It is clear that the *SRY* exerts male-specific effects in tissues outside the testis, such as regulating motor function and sympathetic nerve activity. In view of this, we propose that direct actions of SRY on catecholamine-dependent functions provide a genetic basis for the observation that the "fight-flight" response is predominantly manifested in males, as opposed to females. The presence of SRY in the male brain and peripheral tissues may provide a "priming" mechanism to augment catecholamine synthesis and breakdown required in a "male" response to stress that is predominantly sympathetically driven. Specifically, SRY may exert direct actions in peripheral tissues to increase catecholamine release and blood flow to muscles and peripheral organs, in the frontal cortex (inhibit MAO-A) to stimulate aggression, in the SNc (increase TH and dopamine) to increase movement, and in the locus coeruleus to increase noradrenaline secretion and sympathetic tone. The presence of SRY in brain regions such as the ventral tegmental area [10], medial mammillary bodies [10] and hippocampus (Helena Sim and Vincent Harley, unpublished observations) are also consistent with male-biased traits such as competitiveness, impulsivity and spatial awareness. A recent study demonstrated that SRY down-regulates oestrogen receptor β expression in vitro [25], suggesting that SRY could be acting as a compensatory factor for the lack of oestrogen in males. From the evolutionary standpoint, males are "hunter-gatherers", competing with each other for food, resources and females. Hence, SRY may have evolved in the brain and periphery to influence male-biased behaviours, as well as initiate testis development and thus gonadal hormone production.

Implications for SRY in male-biased neurological disorders

The emerging role for SRY in catecholamine pathways also raises the possibility that altered functioning of SRY may underlie certain male-biased disorders such as Parkinson's disease (PD), autism, attention-deficit/hyperactive disorder and schizophrenia, which all share the common feature of altered catecholamine function and greater prevalence in males [26–28]. PD, which results from the progressive loss of dopamine neurons in the SNc, shows greater prevalence and a faster rate of disease progression in men [27]. Whilst SRY may normally constitutively regulate male dopamine neurons in the SNc [10], altered expression or function of SRY could increase the vulnerability of these dopamine neurons to injury and thus PD in males. Abnormal expression or regulation of SRY during development may contribute to affective disorders such as autism, which is strongly biased towards males (4 to 11 times higher in males) and is thought to represent an extreme of the male brain (i.e. impaired empathising and enhanced systemising) [28]. A regulatory mutation in human *SRY* gene or a SRY binding site mutation in its target gene, which specifically altered its expression/function in the brain, kidneys or adrenal glands could contribute to male-biased cardiovascular disorders such as hypertension. In support of this speculation, the Y chromosome and *SRY* account for a significant portion of the blood pressure increase in males in the spontaneously hypertensive rat model of hypertension [29], whilst mutations in a SRY binding site in human *TH* have a significant correlation with blood pressure [20, 30]. These possibilities, however, have yet to attract major research attention, with limited knowledge available on mechanisms, which regulate *SRY* transcription, and the way that SRY regulates its target genes. Nonetheless, a better understanding of the aetiology and identification of novel SRY polymorphisms in these conditions will be essential for the development of novel therapeutic strategies, such as gender-specific medicines.

Conclusion

Emerging evidence indicates that the key male-sex determining gene, *SRY*, exerts "maleness" outside the testes, acting directly on the brain and peripheral tissues to regulate movement and blood pressure in males. In view of this, we propose that SRY provides a genetic basis to explain why the "fight-flight" response is manifested mainly in males rather than females. These findings foreshadow extensive future studies

needed to determine the temporal and spatial expression pattern of SRY in the brain and other tissues and to identify other key target genes of SRY and the underlying mechanisms involved. Considering the role of SRY in mediating dopaminergic function in the SNc, it would be of great interest to assess the neurochemical and behavioural consequence of SRY knockdown in other catecholamine abundant regions where SRY is expressed (e.g. VTA and LC). SRY is unlikely to be the only sex-specific gene to be responsible for sex differences, as X- and Y-linked genes such as Usp9x, *Xist*, and *Uty* may also participate in sex differences in brain development and function [12, 13]. However, these recent studies highlight that the importance of sex-specific genes must be considered along with the effects of gonadal hormones when investigating sexually dimorphic phenotypes. Hence, better understanding the degree and nature of interactions between the sex-specific genes, gonadal hormones and epigenetic pathways, will undoubtedly shed light on what predisposes men or women to certain behavioural phenotypes and neuropsychiatric disorders.

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