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Review

The hormone-emotion-behavioural gene-neuromessenger labyrinth: Pertinent questions

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The discovery of behavioural genes has raised the prospect that behaviour may be governed, in part, by the actions of mutant gene products on the brain. These are mostly enzymes or proteins involved in processes related to neurotransmission. In addition, numerous studies have demonstrated the effects of specific hormones on behaviour. Furthermore, the ability of intense emotions to stimulate or suppress the synthesis of a variety of hormones is well-documented. An incredibly murky picture of multi-directional interrelationships between behavioural genes, emotions and biochemical messengers is emerging, making it increasingly difficult to distinguish between causes and effects. This article seeks to highlight a number of unresolved issues in this intriguing area of behavioural endocrinology and examine the ramifications of behavioural gene discoveries.

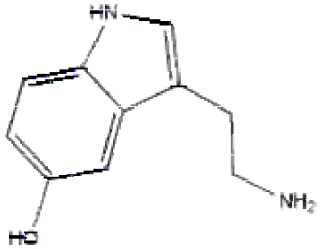
Keywords: Hormones, emotions, neuromessengers, HPA axis, behavioural genes.

INTRODUCTION

The complex interplay between behaviour and the endocrine system has long been recognized, but remains poorly understood. For many decades, hormone-induced mood and behaviour disorders have been associated with the menstrual cycle. Also, as far back as the 1800s, studies on animals demonstrated that castration caused marked alterations in behaviour patterns, characterized by a reduction in aggressive tendencies as well as a substantial decrease in libido. These provided the earliest lines of evidence suggesting that hormones, in this case testosterone, influence both human and animal behaviour. To a large extent, recent studies have confirmed many of the early findings. For instance, Brown et al. (2007) observed that testosterone levels were highest in the most dominant and aggressive captive male African and Asian elephant bulls. In recent times, the intricate relationships between hormones, behaviour and emotions has been further complicated by the discovery of scores of behavioural genes, raising questions about the extent to which such mutant genes influence human behaviour and how they might interact with hormones. Most behavioural genes encode neuromessengers (neurotransmitters and neuromodulators) or their transport proteins and receptors. Neuromessengers are biomolecules synthesized by the brain and central nervous system to mediate neural pathways (Figure 1). This article seeks to summarise current knowledge on the inextricable linkages between behaviour, hormones, neuromessengers and behavioural genes and examine the implications of behavioural gene discoveries.

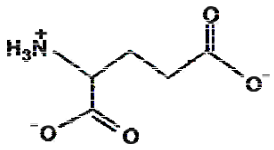
Emotions can suppress or stimulate hormone synthesis

There is ample evidence to support the assertion that in both humans and animals, intense emotions affect the synthesis and release of hormones. Reversible hyposomatotropism or psychosocial dwarfism is a striking example of the psychic regulation of hormonal levels. Genetic defects that interfere with the synthesis or secretion of growth hormone (GH), the main hormone responsible for postnatal skeletal growth, lead to abnormal short stature referred to as dwarfism. Psychosocial dwarfism is usually observed in children between the ages of 2 and 15 who have no such genetic defects but are profoundly unhappy (Powell et al., 1967; Money, 1977; Taitz and King, 1988). Their growth rates and circulating GH levels fall far below normal, leading to abnormal short stature, despite normal food intake. Interestingly, children suffering from psychosocial dwarfism experience a growth spurt as soon as they are



5-Hydroxytryptamine (serotonin)

[redacted]ine



Glutamic acid

-aminobutyric acid

Figure 1. Examples of neuromessengers.

moved to a happier environment (King and Taitz, 1985; Wales et al., 1992). Apparently, this resumption of normal growth and the normalization of circulating GH levels occur concurrently (Albanese et al., 1994). It would appear then that extreme emotional stress curtails the synthesis and/or release of GH by the somatotropes of the anterior pituitary. The mechanisms underlying this phenomenon are yet to be elucidated. Although many factors can influence the secretion of GH, two hypothalamic hormones namely growth hormone releasing hormone (GHRH) and somatostatin dominate. The former stimulates GH release while the latter inhibits it. Since the state of extreme unhappiness interferes with the normal regulatory processes governing the secretion of GH, it is possible that a neural factor mediating this state may over-ride the normal regulatory processes, by promoting somatostatin production, inhibiting GHRH syn-thesis or rendering anterior pituitary somatotropes insensitive to the actions of GHRH.

The far-reaching consequences of strong emotions on the endocrine system are also evident in pseudocyesis or false pregnancy. Pseudocyesis resembles pregnancy in most respects except that a foetus is absent. Invariably, it is associated with a strong desire to have a child as well as the conviction that one is pregnant (Kulcsar, 1951; Drife, 1985; Rosenberg et al., 1983; Paulman and Sadat, 1990; Hendricks-Matthews and Hoy, 1993). The physical signs include morning nausea, disruption of the menses, enlarged and tender breasts and abdominal distension. In a study by Yen et al. (1976), pseudocyesis was associated with markedly elevated basal levels of luteinizing hormone and prolactin. Psychic mechanisms were thought to have triggered the hypersecretion of these pregnancy-related hormones.

Persistent social subordination, a form of psychosocial stress, exerts profound effects on hormonal levels in dominant male African cichlid fish, *Astatotilapia burtoni,* which exhibit two phenotypes as part of a stratified social system. Dominant males are aggressive, territorial, physically larger and reproductively active. In sharp contrast, non-dominant males are smaller, non- aggressive and reproductively inactive (Fernald and Hirata, 1977). Parikh et al. (2006) observed that subjection of dominant *Astatotilapia burtoni* males to territory loss, which was tantamount to social suppression, resulted in a significant increase in cortisol levels coupled with a decrease in testosterone levels. These were indicative of stress and an inhibition of the reproductive system.

Thus, the relationship between hormones and emotions appears to be bi-directional (Liberzon et al., 2007) . On the one hand, hormones can influence emotions and behavioural systems, as is the case with testosterone, while on the other hand emotional stimuli can alter hormone production as outlined above. What are the mechanisms underlying the relationships between emotional stimuli and behaviour and the endocrine system?

Mechanisms mediating hormone-emotion-behaviour interactions

The hypothalamus plays a critical role in the neuroendocrine control of behaviours. For instance, in rats, electrical stimulation of a specific region of the hypothalamus, with distinct glutamatergic neurons co-expressing thyrothropin releasing hormone, evokes aggressive behaviour (Hrabovszky et al., 2005). Studies have shown that the hypothalamus also features promi-

nently in the mechanisms through which emotional or psychological stimuli affect the endocrine system. The psychological activation of the hypothalamic-pituitary-adrenal (HPA) axis, with the consequent release of cortisol, is by far the most extensively researched (Kirschbaum et al*.,* 1993; Richter et al., 1996). Although events downstream of the hypothalamus are better understood than the upstream mechanisms, it does appear that stress-related emotional stimuli are often processed by forebrain limbic circuitry leading to activation of the brain stem noradrenergic system and the release of norepinephrine in the paraventricular nucleus (for review, see Herman et al., 2003). Subsequently, corticotrophin-releasing hormone and arginine vasopressin are synthesized in the paraventricular neurons and released at axon terminals. They then act synergistically on the corticotrophs of the anterior pituitary to cause the release of adrenocorticotropic hormone, which stimulates the release of cortisol by the adrenal cortex. Excitatory neurotransmitters such as serotonin, dopamine and norepinephrine and other biochemical messengers including interleukin-1beta and cholecystokinin are known to play an important role in the psychosocial activation of the HPA axis, while endogenous opioids attenuate HPA axis stress responses (Russell et al., 2008).

The ability of hormones to promote the probability of specific behaviours may be mediated by their effects on the electrical activity of neurons, neurotransmitter release and neurotransmitter action. Unequivocal effects of steroid hormones on neural processes have been demonstrated. For example, progesterone administration to estrogen-primed female golden hamsters caused striking changes in neuronal activity levels and somatosensory responsiveness (Rose, 1986). Furthermore, progesterone-derived neuroactive steroids alter the functions of synaptic $GABA_A$ receptors and have been implicated in severe mood disorders that can occur during the menstrual cycle and after pregnancy (Stell et al., 2003) . Changes in brain testosterone and allopregnanolone biosynthesis elicit aggressive behavior in female mice through a neuronal mechanism that involves the GABAergic system (Pinna et al., 2005).

It is reasonable to postulate that the mechanisms underlying pseudocyesis and psychosocial dwarfism involve activation of gonadotropin releasing hormone-secreting hypothalamic neurons and inhibition of GHRH-secreting hypothalamic neurons by emotional stimuli processed by forebrain limbic circuitry. However, nagging questions pertaining to the emotional and psychological stimuli remain unanswered. Undoubtedly, individuals who undergo such experiences form only an infinitesimal percentage of unhappy children and desperate childless women. Do emotional stimuli and hormone-emotion relationships differ in the vast majority? Are psychosocial dwarfism and pseudocyesis induced solely by emotional stimuli or do pre-existing hormonal and/or brain neuromessenger imbalances exaggerate otherwise normal emotions to alter neural circuits which affect the hypothalamus?

Clearly, the interplay between social and behavioural state, extrinsic conditions and hormone responses are extremely intricate and much remains to be learned about the precise neural pathways through which psychosocial factors moderate the neuroendocrine system. In addition, the discovery that certain mutant genes are associated with antisocial human and animal behaviours has added a new dimension to this highly complex scenario.

Variant genes encode certain types of behaviour

A spectrum of behaviours such as violence, hyperphagia, smoking and alcohol-dependence are reported to be linked to an individual's genetic repertoire. Interestingly, most of these novel variant genes encode proteins that participate in the biosynthesis or degradation of neuromessengers, their receptors or transporters. A few examples are presented below.

Smoking behaviour

The seemingly irrepressible urge to smoke, at least in certain categories of smokers, may be inextricably linked one of several variant genes. One of these encodes serotonin and is reported to influence the initiation of smoking (Kremer et al., 2005). Also, individuals who lack a particular version of the cytochrome P450 (CYP) gene CYP2A6 are more likely to end up smoking than those who possess this gene (Tyndale and Sellers, 2002; Xu et al., 2003). Apparently, nicotine and a group of tobacco-specific nitrosamines are high-affinity substrates for this particular member of the cytochrome P450 mixed-function oxidase system. Associations between smoking behaviours and dopamine transporter gene (SLC6A3-9) as well as dopamine receptor genes have been documented (Comings et al., 1996; Vandenbergh et al., 2007). A variant of the gene that encodes monoamine oxidase, an enzyme which oxidises catecholamines and dopamine, has also been implicated in smoking behaviour (Costa-Mallen et al., 2005).

Morbid obesity

The perception that obese individuals simply choose to overindulge is now under siege. A common variant of the fat mass and obesity associated (FTO) gene has been reported to cause predisposition to childhood and adult obesity (Dina et al., 2007; Hunt et al., 2008). Boutin et al. (2003) have also reported a variant GAD2 gene for morbid obesity which encodes glutamic acid decarboxylase. This enzyme catalyzes the formation of gamma-

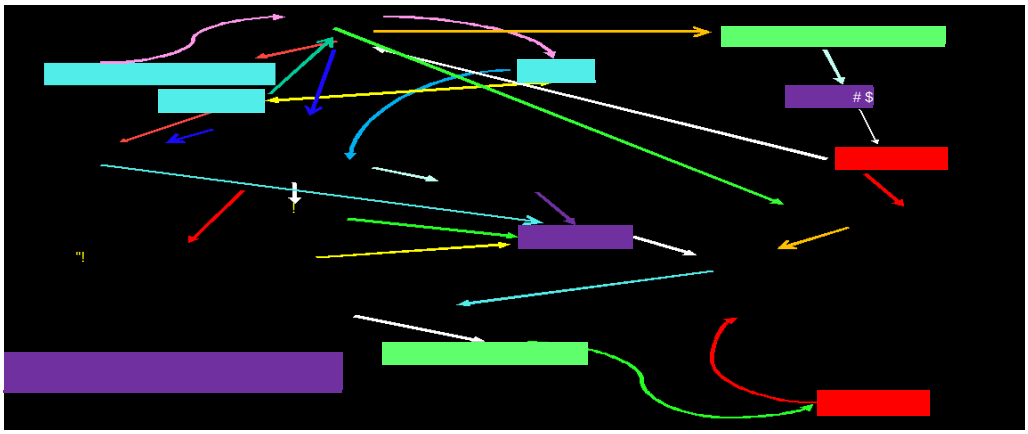


Figure 2. Complex multi-directional interrelationships between hormones, emotions and neuromessengers.

-aminobutyric acid (GABA), a neurotransmitter, which interacts with neuropeptide Y in the paraventricular nucleus to stimulate food intake. Neuropeptide Y is a 36 amino acid peptide which has been implicated in many neuropsychiatric disorders.

Alcohol-dependence

Contrary to the view that alcoholism is largely the result of irresponsible behaviour, anti-social alcoholism has now been linked to single nucleotide polymorphisms in a host of genes including the serotonin gene (Hill et al., 2002) and the GABA receptor, gamma 3 gene (GABRG3). In addition, associations between variant dopamine receptor (DRD1 and DRD2) genes and alcohol-dependence have recently been reported (Lucht et al., 2007; Batel et al., 2008). Dopamine is a neurotransmitter and a precursor for epinephrine and norepinephrine.

Violence and aggression

Genes and the environment have been implicated in violent behaviour (Viding and Frith, 2006; Moosajee, 2003). Twin and adoption studies have confirmed that individual differences in violent behaviour are heritable (Rhee and Waldman, 2002). Also, brain serotonin dysfunction is reported to induce aggression in mice lacking neuronal nitric oxide synthase (Chiavegatto et al., 2001). An assortment of genes has been implicated in aggression and genetic predisposition to violence. These include the genes encoding testosterone and Monoamine Oxidase A (MAOA) which oxidizes norepinephrine, serotonin as well as dopamine (Caspi et al., 2002; Pinna et al., 2005; Meyer-Lindenberg et al., 2006). Men who inherited a variant MAOA gene were reported to be more prone to violence if they had suffered abuse as children (Caspi et al., 2002). MAOA-deficient male mice had elevated brain levels of monoamines and exhibited increased aggressiveness (Cases et al., 1995).

Interestingly, MAOA-deficient female mice showed normal behaviour (Cases et al., 1995). What accounts for the difference? Again, 15% of children who inherited the MAOA variant gene and were severely maltreated did not become violent adults (Caspi et al., 2002), raising disturbing questions about the factors that lead to phenotypic expression. The hormonal regulation of gene expression is well-documented. Is behavioural gene expression also subject to hormonal regulation? Could emotional and psychological factors activate HP-target organ axes and ultimately alter the expression of behavioural genes by causing levels of particular hormones to plummet or rise? If intense emotions are capable of giving rise to the dramatic effects seen in pseudocyesis, could sheer determination over -ride the effects of a behavioural gene? Mention must also be made of the fact that the reported effect sizes of behavioural genes are often remarkably small (Berggren et al., 2006; Carter et al., 2004).

The Labyrinth

The emerging picture of the relationships between hormones, emotions, neuromessengers and behavioural genes is one of a gigantic labyrinth in which (1) novel behavioural genes influence human behaviour by encoding neuromessengers and allied biomolecules (2) hormones like testosterone induce specific desires and behaviour patterns and, (3) intense emotions and stress on the other hand curtail or induce the release of specific hormones and modulate the HP-target organ axes (Figure 2). It is tempting to speculate that strong emotions cause the brain to release neuromessengers that subsequently bind to receptors on the hypothalamus or pituitary and send signals that interfere with the transcription of genes encoding hormones.

The emotion-induced hypersecretion or hyposecretion may then translate into biochemical, physiological or physical alterations after the hormones in question interact with their cognate receptors to trigger signalling cascades. In the reverse scenario, evident in castration or late luteal phase dysphoria, changes in circulating hormone levels precede and provoke dramatic shifts in desires or moods presumably by impacting on the brain. Undoubtedly, the actions of neuromessengers and hormones are inextricably intertwined with emotions and it is now recognized that the axis is subject to pleiotropic regulation in which numerous neuromessengers such as dopamine, glutamate, GABA, neuropeptide Y and endorphins interact with the pituitary and alter its sensitivity to hypothalamic hormones.

Pertinent questions on moral responsibility

Finally, the issue of moral responsibility in relation to antisocial behavioural genes needs to be carefully examined. Across the globe, the basic premise of legal and penal systems is that persons of sound mind have the capacity to choose between right and wrong and are, therefore, morally responsible for their actions. Should individuals who are of sound mind, but are powerless to control the expression of their deviant behavioural genes bear moral responsibility for “gene-induced” antisocial behaviour? Also, if the ultimate purpose of punishment is reform and conscious manipulation of behavioural gene expression is impossible, is the subjection of such individuals to punishment not an exercise in futility?

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