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The hypothalamus: cross-roads of endocrine and behavioural regulation in grooming and aggression

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Abstract

Anatomical and functional studies show that the hypothalamus is at the junction of mechanisms involved in the exploratory appraisal phase of behaviour and mechanisms involved in the execution of specific consummatory acts. However, the hypothalamus is also a crucial link in endocrine regulation. In natural settings it has been shown that behavioural challenges produce large and fast increases in circulating hormones such as testosterone, prolactin, corticotropin and corticosterone. The behavioural function and neural mechanisms of such fast neuroendocrine changes are not well understood. We suggest that behaviourally specific hypothalamic mechanisms, at the cross-roads of behavioural and endocrine regulation, play a role in such neuroendocrine changes. Mild stimulation of the hypothalamic aggressive area, produces stress levels of circulating prolactin, corticotropin, and corticosterone. Surprisingly luteinizing hormone does not change. This increase in stress hormones is due to the stimulation itself, and not caused by the stress of fighting. Similar increases in corticosterone are observed during electrical stimulation of the hypothalamic self-grooming area. The corticosterone response during self-grooming-evoking stimulation is negatively correlated with the amount of self-grooming observed, suggesting that circulating corticosterone exerts a negative feedback control on grooming. Earlier literature, and preliminary data form our laboratory, show that circulating corticosterone exerts a fast positive feedback control over brain mechanisms involved in aggressive behaviour. Such findings suggest that the hormonal responses caused by the activity of behaviourally specific areas of the hypothalamus may be part of a regulation mechanism involved in facilitating or inhibiting the very behavioural responses that can be evoked from those areas. We suggest that studying such mechanisms may provide a new approach to behavioural dysfunctions associated with endocrine disorders and stress.

Keywords: Aggression; Grooming; Stress; Hypothalamus; Hormones; Corticosterone; Corticotropin; Prolactin; LH; Rat

1. Introduction

The hypothalamus is a phylogenetically old structure that is crucially involved in many behavioural responses that are essential to survival. The distinctive characteristics of hypothalamic responses, and the underlying anatomical organisation, suggests that the hypothalamus is a crucial node where circuits involved in exploratory appraisal in behaviour, link up with circuits involved in the execution of specific consummatory responses [1–10]. At the same time, many different endocrine and autonomic mechanisms are regulated in the hypothalamus. The presence of both behavioural and endocrine mechanisms in the hypothalamus suggests that there is a local functional link between endocrine and behavioural processes. In behaviour subserving homeostatic function, such as eating, drinking, maintaining salt balance, and thermoregulation, the advantages of functional relations between behavioural and endocrine mechanisms are evident. However, in hypothalamic behavioural responses such as aggression or self-grooming, no obvious homeostatic functions seems to be involved. Rather such responses constitute different kinds of reactions to external stressors [11–16].

1.1. Hypothalamic grooming and hypothalamic aggression

Hypothalamic grooming closely resembles grooming under natural conditions, such as grooming following stressors, grooming as a reaction to a disturbance of the body surface, or as a preliminary to resting behaviour, it consists of licking the paws, washing movements over the head, and fur licking, and it generally proceeds in cephalo-caudal direction [11–21]. However, the precise temporal pattern of hypothalamic grooming depends on the method of induction: electrical stimulation, local infusion of glutamate

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agonists, or neuropeptides [12–18,20,21]. Interestingly, scratching, a normal constituent of the care of the body surface [11], is absent in hypothalamic grooming. Hypothalamic aggression, closely resembles the most violent elements of aggressive behaviour observed under natural conditions, it consists of biting the dorsal surface of an opponent, and forceful kicking the body of the opponent either during a clinch fight, or while jumping in the direction of an opponent in an upright defensive position. The precise form of the attack depends on the behaviour and position of the opponent, and on the intensity of the stimulation. Increasing stimulation intensity generally activates the attack pattern in cephalo-caudal direction, from gentle bites to forcefull bites, accompanied by force-full hind paw kicks, delivered mid air during jumps or during clinch fights [19,22–26]. Interestingly sideways threat is absent [22,23] or suppressed [26] during hypothalamic stimulation, but not during induction of hypothalamic attack by local infusion of picrotoxin or bicuculline [27,28].

1.2. Hormones and hypothalamic responses

In natural settings aggressive behaviour is accompanied by fast increases in prolactin, corticotropin, α-melanocyte stimulating hormone, β-endorphin, testosterone and corticosterone [29–32]. Such hormonal responses allegedly help the organism to adapt to the stressors associated with the consequences of conflicts. Hypothalamic mechanisms have been implicated in such facilitation. Blood flow from the adrenals, and plasma catecholamine levels, increase following stimulation of hypothalamic areas involved in defense, flight and aggressive behaviour in the cat [33–40] and rat [41]. However, there is also an influence in the reverse direction, from circulating hormones to the central nervous system [42]. Corticosterone facilitates clawing responses in copulation of the rough skin newt [43–46]. Circulating hormones also influence central mechanisms involved in specific behavioural responses. Hypothalamic mechanisms have been implicated in the feedback of circulating hormones on central mechanisms. Estrogen, testosterone, FSH and LH facilitate or inhibit hypothalamic aggression in intact and gonadectomized, male and female cats [47] and rats [48]. Corticosterone injections immediately facilitate aggressive behaviour, in the rat, and antibodies against ACTH inhibit aggressive behaviour [49–51]. Moreover, infusions of cortisol into the anterior hypothalamus of the golden hamster facilitate aggressive behaviour [52,53]. Such fast effects of stress hormones on brain mechanisms involved in aggressive behaviour may well be involved in the facilitating carry-over effect of a previous aggressive encounter on to subsequent aggression [54–58]. We suggest that fast facilitating effects of stress hormones on brain mechanisms involved in aggressive behaviour could also contribute to the escalation of violence in humans under stressful conditions.

In this paper, we summarize what is known about the neural organization underlying hypothalamic responses, discuss the distinctive characteristics of the responses evoked, and demonstrate for the first time that a mild activation of the hypothalamic areas involved in specific behavioural responses is sufficient to evoke stress levels of prolactin, corticotropin, and corticosterone. Luteinizing hormone was studied because of the well known effects of testosterone on aggressive behaviour and hypothalamic aggression [3,47,48]. Corticotropine, and corticosterone were studied because of the fast aggression facilitating effects via hypothalamic mechanisms [52,53] on territorial aggression [49,50]. Moreover, deviant cortisol and prolactin responses to a serotonergic challenge have been observed in pathological hostility and impulse control in humans [59–63]. Similar findings have been reported for prolactin in monkeys [64].

2. Hypothalamic response organisation

2.1. Neural substrate hypothalamic responses

Almost 70 years after the first reports on the induction of attack behaviour from the hypothalamus in the cat [65,66] it is still not known precisely, which neurons do mediate hypothalamic behavioural responses. Aggressive responses can also be evoked by local infusion of GABA-antagonists [27,28] or mixtures of GABA-antagonists and glutamate [Haller et al., (in press)]. Grooming responses have been evoked by local infusion of a glutamate agonist [20,21] and oxytocin [13,15]. These findings imply, that cell bodies rather than passing fibres mediate the effects of stimulation. These findings also suggest that the activity of the mechanisms in which these responses can be evoked, depends on a balance of inhibitory and excitatory inputs on local cell bodies. Electrical stimulation apparently overrides the inhibitory influence.

Hypothalamic areas involved in specific responses have been extensively mapped using moveable electrodes [19,67–69]. Self-grooming is elicited from the dorsal aspects of the paraventricular nucleus and the adjacent areas of the hypothalamus. Aggression is induced from an area below the fornix, just lateral and frontal to the ventromedial nucleus in the hypothalamus. The hypothalamic aggressive area was delimited a decade ago as a specific area in two systematic distribution studies using a statistical analysis of a large number of electrode positions [19,69]. Only later it was recognized by anatomists as a specific area on cytoarchitectonic criteria [70,71]. The hypothalamic aggressive area (HAA) almost completely coincides with the intermediate hypothalamic area (IHA) [72]. Electronmicroscopic examination revealed the presence of about 17 000 neurons in the IHA, an area of with a volume of about 0.5 mm^3 [73].

Only a small, unilateral fraction of the IHA needs to be activated to produce an aggressive response. Plotting the