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Commentary

Interactions between the neural regulation of stress and aggression

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Summary

Socially aggressive interaction is stressful. What is more, social aggression is stressful for both dominant and subordinate animals. Much of the neurocircuitry for stress and aggression overlap. The pattern of neurochemical and hormonal events stimulated by social interaction make it clear that subtle differences in this pattern of response distinguish social rank. The neurotransmitter serotonin (5-HT) responds rapidly to stress, and also appears to play the most important role for inhibitory regulation of aggressive interactions. In addition, the adrenocortical/interrenal steroid hormones corticosterone and cortisol are responsive to stress and influence aggression. However, while 5-HT and glucocorticoids can both be inhibitory to aggression, the relationship between 5-HT and glucocorticoids is not straightforward, and much of the distinctions in function depend upon timing. Neither is inhibitory during the early stressful phase of aggression. This transmitter–hormone combination follows and influences a four-stage functional pattern of effect: (1) predisposed (positively or negatively) toward aggression, (2) motivated toward behavior, (3) responsive to stress (including aggression) and passively allowing aggression, and finally (4) chronically applied 5-HT and glucocorticoids inhibit aggression.

Key words: antagonism, attack, corticosterone, cortisol, dominant, dopamine (DA), fight, hostility, serotonin (5-HT), social stress, stages, subordinate, timeline.

Introduction

Aggressive behavior is manifest in numerous contexts, each of which imparts social or ecological meaning to the kind of antagonism that develops. Social and ecological significance are imparted even prior to aggressive interactions by contextual cues, including the status of the individuals involved. Social standing is influenced in part by previous interactions (Summers et al., 2005a) and the capacity to react to stressful conditions with adaptive neuroendocrine responses (Korzan et al., 2006b). The rate and probability of behavioral responses follows a linear pattern of behavioral, transmitter, and hormonal interaction that result in: (1) predisposition (positively or negatively) toward aggression (Ferrari et al., 2005), (2) motivation for behavior, which includes particular adaptations for coping with social stress (Koolhaas et al., 1999), (3) neuroendocrine responsiveness to the stress of aggression and, for some, (4) chronic social stress that inhibits aggression (Fig. 1).

While the stages of aggressive interaction necessarily follow parameters defined by stress responsiveness and motivation, there is also behavioral and psychological specificity for offensive or defensive aggression, and antagonisms arising from intruders, tormenters, territorial competition, maternal protection or rage. The neurocircuitry and the neurotransmitters and/or modulators involved are almost certainly fine-tuned for specific circumstances. In mammals, the underlying basic circuitry for aggressive behavior, however, appears to be focused on the anterior hypothalamus (Gregg and Siegel, 2001), sometimes including a region described as the attack area (Hrabovszky et al., 2005; Kruk et al., 1979), modified by a number of hypothalamic and extrahypothalamic afferents (Delville et al., 2000; Ferris et al., 1997). While the neurocircuitry for aggression appears to be evolutionarily conserved, the primacy of the anterior hypothalamus has yet to be confirmed in other vertebrates like fish and reptiles. Although there are numerous excitatory inputs to the system, which promote aggressive interaction, the primary regulatory control of aggression is inhibitory (Nelson and Chiavegatto, 2001). The accuracy of this proposition is easily verified by a simple observation: aggression is not unrelenting. Even among

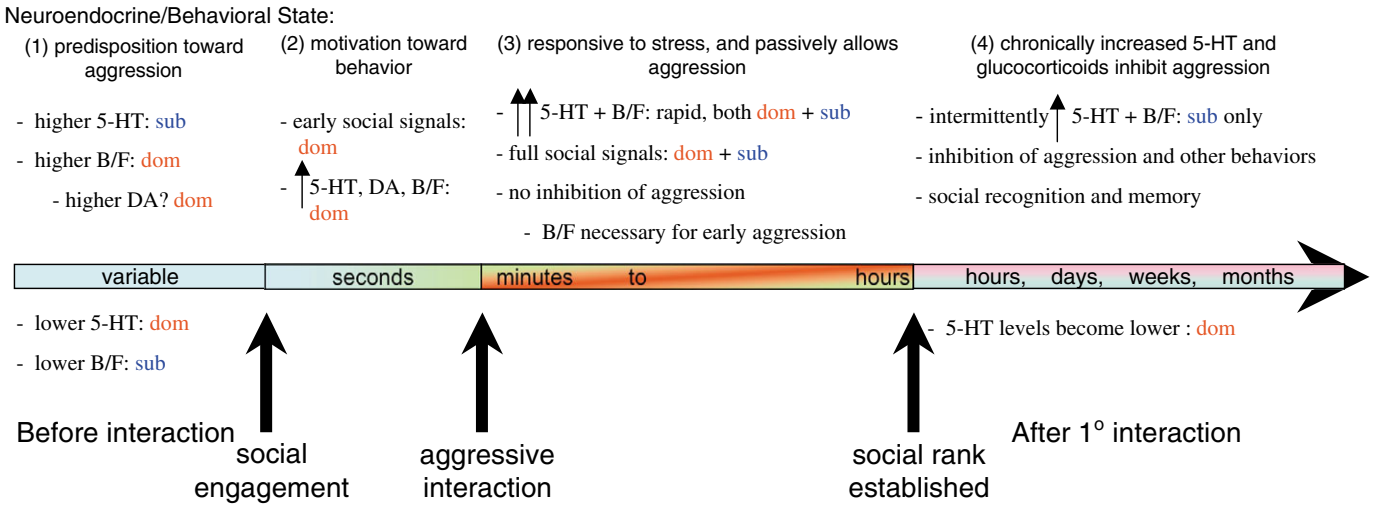

Fig. 1. The development of an aggressive social interaction over time progresses through distinct stages of neuroendocrine and behavioral state. In the first phase, prior to interaction baseline levels of plasma glucocorticoids (B=corticosterone in lizards, rats, mice, frogs, birds; F=cortisol in fish, humans, sheep, hamsters) and serotonergic and perhaps dopaminergic activity in brain regions associated with aggression and motivation influence the animal's predisposition (positively or negatively) toward aggression. The prefight neuroendocrine profile is distinctly different in individuals that will become dominant (dom), and those that will become subordinate (sub). At some point, when combatants meet and social engagement begins, early social signals and rapid changes in neuroendocrine profile of putatively dominant individuals generate motivation toward behavior. No aggression has occurred yet, but increased activity of glucocorticoids, serotonin (5-HT) and dopamine (DA) enhance the likelihood of heightened behavioral interaction, culminating in aggression. After aggression begins, both animals are fully responsive to stress, and expressing social signals. Aggression is very stressful, and for that reason, serotonergic and glucocorticoid activities rise dramatically and rapidly in animals that become dominant and those that become subordinate. Surprisingly neither elevated plasma glucocorticoid levels nor serotonergic activity inhibit aggression at this time. Glucocorticoids appear to be necessary for the full expression of early aggression, and elevated B or F plus increased serotonergic activity appear to passively allow aggression. Finally, after social rank is established, chronically elevated or applied 5-HT and glucocorticoids inhibit aggression. Chronic neuroendocrine state likely influences subsequent interactions.

territorial animals that must constantly protect resources, most of the time aggressive tendencies are held in check. Revealing aggressive potential is the consequence of numerous provocations in the normal life history of most animals and humans.

Therefore, in this review, we will consider neural systems that stimulate aggression, but we will focus on inhibitory regulation. That inhibitory regulation emanates primarily from one neurotransmitter system, serotonin (5-HT) (Nelson and Chiavegatto, 2001), but it is far from simple. Its complex nature is derived from neuroendocrine relationships between stress and aggression. The timeline on which these two interacting systems are co-expressed take place before, during and after socially aggressive interaction (Fig. 1). The timeline is suggested as a model of aggressive interaction in all vertebrates, but we especially draw from examples of evolutionarily conserved behavior and neuroendocrine adaptation in fish and lizards (Winberg and Nilsson, 1993; Summers et al., 2005c). We describe neurotransmitter and hormonal responses during four stages, where they: (1) influence predisposition (positively or negatively) toward aggression, (2) motivate behavior (3) are responsive to stress (including aggression) but passively allow aggression and finally (4) may chronically inhibit aggression.

Aggression neurocircuitry

Experimental inhibitory effects of 5-HT on aggressive behavior are most often the result of systemic application of serotonergic drugs, like selective 5-HT reuptake inhibitors (SSRI; usually a stage 4 type effect). However, a similar effect has been elicited in mammals by applying serotonergic drugs directly to the anterior hypothalamus (Vergnes et al., 1988; Ferris et al., 1999), inhibiting two types of excitatory neurons that stimulate agonistic behavior: AVP interneurons, and excitatory glutamatergic efferents (Hrabovszky et al., 2005) to the periaqueductal gray (PAG)/midbrain central gray (Roeling et al., 1994; Yao et al., 2001). The vasopressinergic neurons of the anterior hypothalamus show increased fos activity during aggression (Delville et al., 2000). This region of the brain can also be directly stimulated (as might happen in stage 3) electrically, hormonally (corticosterone), neurochemically (vasopressin=AVP; glutamate=Glu), and pharmacologically (V_{1A} receptor agonist; Kainate Glu receptor; γ-aminobutyric acid type A receptor=$GABA_A$ antagonist) to elicit aggression (Kruk et al., 2004; Kruk et al., 1979; Ferris and Delville, 1994; Ferris et al., 1997; Brody et al., 1969; Gregg and Siegel, 2001; Siegel et al., 1999). The capacity of the anterior hypothalamus to stimulate aggression is so reliable that some investigators refer to it as the 'attack area' (Halasz et al., 2002). The anterior

hypothalamus appears to provide the central point for integration of forebrain afferents that regulate aggression, and also provides a coordinated excitatory efferent output to the PAG (Roeling et al., 1994; Yao et al., 2001), on the way to motor efferents.

In addition to the internal vasopressinergic stimulation of glutamatergic aggression effectors, there are numerous other excitatory and inhibitory inputs to the anterior hypothalamus from limbic and other forebrain regions. Positive regulation of aggression has been noted for the medial amygdala, lateral septum and mediodorsal thalamic nucleus (Gregg and Siegel, 2001; David et al., 2004; Delville et al., 2000; Halasz et al., 2002). Inhibitory regulation of aggression (modifiable in stage 1) comes most directly from the raphé, which provides serotonergic innervation for most of the forebrain. Some serotonergic neurons of the hamster raphé show increased fos activity during aggression (Delville et al., 2000). In lizards and fish, aggressive interaction powerfully influences the raphé. In the lizard *Anolis carolinensis*, while serotonergic activity is rapidly increasing in limbic regions during aggressive interaction, it is concomitantly decreased in the raphé (Summers et al., 2003a). Similarly, in sex-changing fish, opposite levels of serotonergic activity are observed in the raphé and limbic terminal regions of saddleback wrasses during the aggressive phase in newly established males, which reverses when the courtship phase ensues (Larson et al., 2003).

Cross linkage of aggression and stress circuitry

There are several lines of evidence that aggression and stress are linked, and that part of the reason that they are reciprocally interrelated is that both mobilize activity in specific brain regions, presumably linked by different but cooperative circuitries. This cross linkage is in play during all four stages of aggressive interaction, modifying predisposition, motivation, and active aggression. This interface across circuitries is apparently developed during fetal through pubertal maturation, as stress-related transmitters such as 5-HT are less effective inhibiting aggression during puberty than in adults (Taravosh-Lahn et al., 2006). When stressful conditions are present during development, effects can be measured in the neural circuitries that regulate both aggression and stress, and in some brain regions those circuitries coincide. Repeated or chronic stress applied during puberty accelerates the progression of development of aggressive behaviors in male hamsters (Wommack et al., 2003; Delville et al., 2003), accompanied by neuroendocrine changes in brain regions like medial amygdala and bed nucleus of the stria terminalis (BNST) that are active in both stress and aggression (Wommack et al., 2004). Stressful conditions such as frustration (absence of reward) stimulates a significant increase in synaptic activity in the neural circuitry controlling aggression (David et al., 2004). Producing stress by removing reward can provoke intense aggression (Gallup, 1965; Azrin et al., 1966; Cherek and Pickens, 1970).

Serotonergic inhibition of aggression

The role of 5-HT and serotonergic circuits in regulating aggressive interaction has been well documented, with a plethora of studies demonstrating that acute or chronic application of 5-HT or serotonergic drugs inhibit aggression in a wide range of vertebrates, including: rainbow trout, coral reef fish, electric fish, the lizard *Anolis carolinensis*, pigeons, sparrows, hamsters, mice, rats, dogs and humans (see Summers et al., 2005b). In addition, a microdialysis study in rats has demonstrated decreased 5-HT release in prefrontal cortex, but not nucleus accumbens, during aggression (van Erp and Miczek, 2000). However, a variety of studies have also demonstrated increased serotonergic activity in the brain during aggressive interaction (stage 3) (see Winberg and Nilsson, 1993; Summers et al., 2005b), often measured in regions of the brain that are known to be involved in regulating aggression, and also increasing at a time when inhibition of aggression would be maladaptive. Additionally, a number of recent studies, looking at specific local changes, or specific receptor activity, cast doubt on inhibitory regulatory effect of 5-HT on aggression (de Boer and Koolhaas, 2005; de Almeida et al., 2005). Even antidepressant treatments, including selective 5-HT reuptake inhibitors, have been demonstrated to increase aggression in rats when administered chronically (Mitchell, 2005; Mitchell and Redfern, 1997; Mitchell and Redfern, 1992). Recent work on the 5-HT_3 receptor in hamsters demonstrates that action at this receptor can have both stimulatory and inhibitory effects on aggression (Ricci et al., 2005; Ricci et al., 2004).

In *A. carolinensis*, inhibitory effects (similar to stages 1 or 4) of serotonergic action have been demonstrated with SSRIs including fluoxetine and sertraline (Deckel, 1996; Larson and Summers, 2001), and 5-HT_1, 5-HT_2 and 5-HT_3 receptor agonists (Deckel and Fuqua, 1998). However, like other vertebrates, serotonergic activity rises rapidly during aggressive interaction in this lizard, and stays elevated for the duration of aggressive interaction (Summers et al., 2003a). The change occurs within 90 s, and has been demonstrated to occur within 30 s in the lizard *Sceloporus jarrovi*, just when the lizards are initiating combat (stage 3) and being most aggressive (Matter et al., 1998; Summers et al., 2005c). It is also the period when the social sign stimulus (eyespots) is having an effect on social rank formation (Summers, 2002; Summers et al., 2005a). Specific aspects of the stereotypical aggressive displays of this species (Baxter, 2003) increase serotonergic turnover, and activity at 5-HT_{1B} (Baxter, 2001) and 5-HT_{2C} receptors (Baxter et al., 2001b). Although 5-HT does not appear to actively constrain aggression during combat, as serotonergic activity is highest at the peak of aggressive interaction, 5-HT does appear to have an inhibitory effect prior to aggressive behavior commencing (stage 1), based on elevated serotonergic activity measured prior to social interaction in males likely to become subordinate (Summers et al., 2005b; Korzan et al., 2006b). The effect of 5-HT on aggression is found specifically, and only, in regions of aggression neurocircuitry (Baxter, 2001; Baxter et al., 2001b;

Summers et al., 2005b). Within that circuitry 5-HT is negatively correlated with aggression in lateral septum, nucleus accumbens, striatum, medial amygdala, anterior hypothalamus, raphé and locus ceruleus. Less aggressive male *A. carolinensis* have significantly more serotonergic activity in those regions, suggesting that 5-HT actively inhibits the aggressive posture of those males.

As in lizards, dyadic fights for social dominance in rainbow trout *Oncorhynchus mykiss* initially results in elevated plasma cortisol and brain serotonergic activity in both winners and losers (stage 3), even though winners show no sign of behavioral inhibition (Øverli et al., 1999). Thus, it seems as if only long-term elevation of brain serotonergic activity results in a suppression of aggressive behavior (stages 1 or 4). This suggestion is also supported by the results from a series of studies on the effects of elevated dietary intake of the amino acid L-tryptophan (Trp) on aggressive behavior in rainbow trout. The essential amino acid Trp is the precursor of 5-HT, and in rainbow trout (Aldegunde et al., 2000; Aldegunde et al., 1998; Johnston et al., 1990) as well as in mammals (Moir and Eccleston, 1968; Friedman et al., 1972), the rate of 5-HT synthesis appears to be limited by Trp availability. In juvenile rainbow trout elevated dietary intake of Trp results in suppression of aggressive behavior (as in stage 1), but only after feeding the fish Trp-supplemented feed for 7 days (Winberg et al., 2001). Feeding the fish Trp-supplemented feed for 3 days had no effect on aggressive behavior even though the effects of elevated dietary Trp on brain 5-HT synthesis are rapid (Winberg et al., 2001; Lepage et al., 2003). Moreover, following seven days of supplementary Trp the effects on aggressive behavior were pronounced whereas the effects on brain serotonergic activity were very modest (Lepage et al., 2003; Winberg et al., 2001; Lepage et al., 2005a), suggesting that mechanisms other than a direct effect of Trp on the rate of 5-HT synthesis and release are involved. The inhibitory effects of 5-HT on aggressive behavior have been suggested to be counteracted by an early activation of brain norepinephrine (NE) and dopamine (DA) systems (stages 2 or 3) during agonistic interaction (Höglund et al., 2001; Winberg and Nilsson, 1992; Winberg et al., 1991). However, Trp supplemented feed had no effect on brain DA or NE, and the time course of the effects of Trp on aggressive behavior does not seem to be related to Trp induced effects on these catecholaminergic systems (Lepage et al., 2003). In addition to its relatively modest effects on brain 5-HT, supplementary dietary Trp resulted in elevated plasma levels of melatonin (Lepage et al., 2005b). In fact, this effect was much more pronounced than the effect on 5-HT, and trout receiving Trp supplemented feed displayed drastically elevated daytime plasma melatonin. Although melatonin appears to contribute to aggressive behavior in hamsters (Demas et al., 2004; Jasnow et al., 2002), Trp-stimulated plasma melatonin did not appear to mediate the effects of Trp on aggressive behavior in trout (Lepage et al., 2005a). While social aggression between trout does raise plasma melatonin, the results suggest that altered production contributes to the physiological and behavioral profiles of subordinate rather than aggressive fish (Larson et al., 2004). Even in hamsters, aggression stimulated by increased melatonin appears to be mediated by glucocorticoids (Demas et al., 2004). What is more, treatment with the SSRI, citalopram, for 7 days closely mimicked the effects of Trp (Lepage et al., 2005a). These results suggest that the effects of elevated dietary intake of Trp on aggressive behavior are mediated by the serotonergic system even though the effects on brain 5-HT turnover, as indicated by brain levels of 5-hydroxyindoleacetic acid (5-HIAA) and 5-HIAA/5-HT ratios (Lepage et al., 2003; Lepage et al., 2002; Winberg et al., 2001), are relatively modest. In fact, in the study by Winberg et al. (Winberg et al., 2001) the lowest dose of Trp applied had no significant effects on brain 5-HIAA levels or 5-HIAA/5-HT ratios even though the effects on aggressive behavior were pronounced. Thus, if the brain serotonergic system is mediating the effects of elevated dietary Trp on aggressive behavior mechanisms other than increased 5-HT biosynthesis and release are likely to be involved. It is noticeable that the anti-depressive effects of SSRI show a time course strikingly similar to the anti-aggressive effects of Trp; although the effects of SSRI on aggressive behavior can be as rapid as a single treatment (Perreault et al., 2003; Taravosh-Lahn et al., 2006). Also, similar to elevated dietary Trp, a 1-week treatment with citalopram reduces aggressive behavior in rainbow trout (Lepage et al., 2005a), as does sertraline treatment in *Anolis* lizards (Larson and Summers, 2001). Long-term elevation of 5-HT release (stage 4), whether induced by chronic stress, elevated dietary Trp, or SSRI treatment, could well cause a downregulation of somatodendritic 5-HT autoreceptors, in turn resulting in a delayed upregulation of 5-HT neurotransmission in terminal fields (Mongeau et al., 1997). The anti-depressive effects of SSRIs have been suggested to depend on actions influencing densities and transduction mechanisms of post- and/or pre-synaptic 5-HT receptors, resulting in such a delayed increase of 5-HT postsynaptic effects in specific brain regions. It is tempting to suggest that the effects of dietary Trp and SSRI on aggressive behavior in rainbow trout are mediated by a similar mechanism. In fact, preliminary results suggest a downregulation of 5-HT_{1A} receptor mRNA expression in the raphé area of rainbow trout fed Trp-supplemented feed for 1 week (P.-O. Thörnqvist, O. Lepage and S. Winberg, unpublished results).

Even though the long-term stress-induced elevation in brain serotonergic activity (during stages 1 or 4) is likely to be an important factor mediating behavioral inhibition in subordinate animals, other neurotransmitter systems are most likely to also be involved. Interestingly, Trp-supplemented feed, as well as SSRI, lowers the number of attacks performed against a small conspecific intruder but neither has any effect on the attack latencies (Lepage et al., 2005a). Social subordination, on the other hand, results in a lower number of attacks performed against the intruder as well as longer attack latencies (Lepage et al., 2005a). Thus, rainbow trout in which brain serotonergic activity has been stimulated by means of elevated dietary Trp or SSRI treatment attack the intruder as fast as control fish, but

in fish treated with Trp or SSRI, aggression does not escalate to the same level as in control fish.

Dopamine and motivation

Although high levels of 5-HT in specific regions of aggression neurocircuitry apparently can inhibit agonistic interaction before it begins (stage 1) (Summers et al., 2005b), under specific ethological or environmental conditions this tonic inhibition must be overridden. Elevated motivation for aggression (stage 2) appears to be the province of dopaminergic action, and aggressive social interaction stimulates dopaminergic as well as serotonergic activity in limbic brain regions. The limbic functions of dopamine (DA) seem to include integrative regulation of a variety of related activities including aggression (Höglund et al., 2005; Kramarcy et al., 1984), social status (Winberg and Nilsson, 1992), motor activity (Waters et al., 2005), learning and perhaps most important, motivation and reward (Korzan et al., 2006a). All of these parameters influence social interaction, and are integrated as a part of neural regulation of social stress. During social interactions between male *A. carolinensis*, increased hypothalamic DA and increased DA in substantia nigra and ventral tegmental areas (SN/VTA) were associated with increased aggressive behavior and status (Korzan et al., 2006a). Elevated dopaminergic activity is usually associated with greater aggressiveness and elevated social status, but very high levels may even limit aggressive interaction (Höglund et al., 2005).

In Arctic charr *Salvelinus alpinus*, dominant fish show elevated brain dopaminergic activity (Winberg et al., 1991) and L-3,4-dihydroxyphenylalanine (L-DOPA) treatment, which elevates DA activity, increases the chance of fish to become dominant in dyadic fight for social dominance with a size matched conspecific (Winberg and Nilsson, 1992). Moreover, in this species L-DOPA treatment counteracts the stress-induced elevation of brain 5-HT activity and plasma cortisol concentrations (Höglund et al., 2001).

Like most vertebrates, locomotor activity stimulates increased DA in striatum of lizards (Waters et al., 2005). However, during aggressive displays and attacks, changes observed in dopaminergic activity in nuclei associated with motor activity like striatum seem to be coupled with expression of specific stereotyped movements associated with social communication more than general motor activity (Korzan et al., 2006a; Baxter, 2003; Baxter et al., 2001a; Baxter, 2001; Clark et al., 2000). The striatum and nucleus accumbens are closely linked, as are level of motivation and stereotyped social behavior.

Increases in DA and dihydroxyphenylacetic acid (DOPAC) in the nucleus accumbens occur when males successfully achieve dominant status and may be representative of motivation and reward. Effects of social interaction on dopaminergic activity in hippocampal and amygdalar nuclei appear consistent with current literature on neurochemical changes associated with memory formation. Together it suggests that the combination of social signal perception, social rank and behavioral expression, but not any single factor (Summers et al., 2005a), may be the impetus for the changes in dopaminergic activity associated with formation of dominant and subordinate status.

Glucocorticoid influence on aggression

The adrenocortical or interrenal steroid hormones corticosterone and cortisol influence aggression and serotonergic activity (Summers et al., 2005c). The influence of glucocorticoids on serotonergic function is much easier to summarize. Glucocorticoids increase serotonergic function, both acutely and chronically (Summers et al., 2003b; Summers et al., 2000), the latter primarily through increased activity of the synthetic enzyme tryptophan hydroxylase (TpH) (see Summers et al., 2005b). However, the effects of glucocorticoids on aggressive behavior, like that of 5-HT, is much more complex, and depends on context and timing (Summers et al., 2005c). The simplest description is that chronically elevated glucocorticoids generally inhibit aggression, but acutely applied corticosteroids do not. In fact, glucocorticoids applied acutely to mammals (rodents at least), especially applied directly to the anterior hypothalamus, stimulate aggressive behavior (Hayden-Hixson and Ferris, 1991; Kruk et al., 2004). In addition, chronic glucocorticoid deficiency promotes abnormal, even pathological, aggressive attack in rats (Haller and Kruk, 2006; Haller et al., 2004; Haller et al., 2001). In other vertebrates, short-term elevation of glucocorticoids appears to passively allow aggressive behavior (see Summers et al., 2005c), but that is not the entire story.

Among lizards, the stress of aggressive interaction stimulates a rapid increase in corticosterone for both winners and losers (Summers et al., 2005c), as well as males and females (Woodley et al., 2000); with the type and duration of interaction determining the manner of glucocorticoid secretion (Knapp and Moore, 1995). A video image of an aggressive *Anolis carolinensis* is enough stimulus to elicit corticosterone secretion in a conspecific (Yang and Wilczynski, 2003). In the lizard *A. carolinensis*, while acute corticosterone administration does not affect aggressive interaction between two males, acute administration of the glucocorticoid receptor blocker mifepristone (RU486) does (Summers et al., 2005c). Blocking glucocorticoid receptors reduces aggressive attacks and displays during the early critical portion (first 7 min) of aggressive behavior, but not later. This suggests that glucocorticoids are necessary for aggressive behavior, if only permissively. In addition, putatively dominant, precipitously active [or proactive as per (Koolhaas et al., 1999)] male *A. carolinensis* have significantly higher baseline glucocorticoid concentrations prior to any social interaction (Summers et al., 2005b).

In rainbow trout, short-term treatment with cortisol increases activity of fish challenged by a conspecific intruder whereas long-term treatment with cortisol has the opposite effect, inhibiting the increase in activity induced by the presence of

the intruder (Øverli et al., 2002). However, cortisol had no effects on locomotor activity in rainbow trout not challenged by an intruder. The effects of cortisol on aggressive behavior show a similar pattern, long-term treatment inhibiting aggression in rainbow trout whereas short-term treatment appears to have the opposite effect (Øverli et al., 2002). Thus, cortisol has dose- and context-dependent effects on behavioral responsiveness in rainbow trout, suggesting that cortisol could be a factor contributing to the divergent behavioral effects of short- and long-term social stress, long-term social stress resulting in an obvious behavioral inhibition whereas short-term social stress may have the opposite effect (Øverli et al., 2002).

Serotonergic modulation of stress responsiveness

Aggressive interaction is stressful for both the winner and the loser (Summers et al., 2005a; Summers et al., 2005c; Øverli et al., 1999). Therefore, it is not surprising that neural and hormonal indices of stress responsiveness are elevated for all participants of combative social interaction during aggression. Inasmuch as acute serotonergic and glucocorticoid responses during aggression are not inhibiting active and combative social interaction (Summers et al., 2005b; Summers et al., 2005c), the function of elevated central serotonergic activity and plasma corticosteroid concentrations appears to be associated with stress (Winberg and Nilsson, 1993).

Neural and hormonal stress responses that occur during aggressive interaction are very rapid (Summers, 2001; Summers et al., 2005c). Serotonergic activity in the brain is elevated within 30 s in dominant territorial males (Matter et al., 1998). What is more, by 90 s, concomitant with elevated serotonergic activity in brain regions like nucleus accumbens, plasma glucocorticoid levels are also increased, at least in dominant males (Summers et al., 2005c). In addition, both the serotonergic and glucocorticoid responses are similar in timing and magnitude in response to physical stressors like exercise and restraint as in response to social stress (Emerson et al., 2000; Summers et al., 2005c).

The serotonergic system is generally believed to stimulate hypothalamic-pituitary-adrenal/interrenal (HPA/HPI) axis activity, and brain 5-HIAA/5-HT ratios have been found to correlate with plasma levels of cortisol and adrenocorticotropic hormone (ACTH) in rainbow trout and Arctic charr (Øverli et al., 1999; Höglund et al., 2000; Winberg and Lepage, 1998). However, inhibitory effects of 5-HT on the glucocorticoid response have also been reported. For instance, in salmonid fish, the selective 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*N*-propylamino) tetralin (8-OH-DPAT) may have either stimulatory or inhibitory effects on HPI axis activity depending on dose and context. In undisturbed fish 8-OH-DPAT stimulates HPI axis activity (Höglund et al., 2002; Winberg et al., 1997). By contrast, if administered at low doses to stressed Arctic charr, 8-OH-DPAT has the opposite effect, suppressing the stress-induced elevation of plasma ACTH and cortisol (Höglund et al., 2002). Similarly, stimulation of brain 5-HT activity by elevated dietary levels of Trp results in slightly elevated basal plasma levels of cortisol, but at the same time the stress-induced elevation of plasma ACTH and cortisol concentrations is drastically reduced (Lepage et al., 2003; Lepage et al., 2002). The effect of dietary Trp on HPI axis reactivity follows the same time-course as the effects on aggressive behavior (discussed above) (Lepage et al., 2003). Moreover, the effects of Trp on HPI axis reactivity cannot be explained by effects on brain catecholaminergic systems or plasma melatonin (Lepage et al., 2005a; Lepage et al., 2003). Thus, Trp effects on HPI axis reactivity is most likely mediated by the brain 5-HT system, but not necessarily by direct effects on 5-HT synthesis and release, since such effects would be more rapid than the effects observed on HPI axis reactivity. Instead, effects on pre- and postsynaptic 5-HT receptor densities are more likely as a mechanism mediating these effects of dietary Trp on the glucocorticoid response.

A timeline for social stress

Socially interacting individuals perceive, generate, and integrate various relevant sensory stimuli during an interaction. For male *A. carolinensis* that includes visual stimuli such as eyespots and stereotyped behavior. However, even before social interactions occur (Fig. 1), the neuroendocrine status of an individual (stage 1), perhaps influenced by previous interactions (stage 4), can influence the rate and probability of the behavioral responses (Summers et al., 2005b). Tonic neuroendocrine status sets the stage for behavioral tone (stage 1), which is primarily inhibitory regulation of aggressive behavior. High serotonergic activity in reactive submissive subordinate males, and those that will become so appears to inhibit aggression. On the other hand, in putatively proactive (Koolhaas et al., 1999) and aggressive dominant males, tonically low 5-HT release lowers the threshold, making aggression much more rapid and likely. Neuroendocrine tone prior to aggressive interaction may be subsequently influenced by motivational factors (stage 2), including perception of a combatant and his sign stimuli, which corresponds to changes in dopaminergic activity in specific brain nuclei. Brief presentation of a simulated opponent is effective in evoking rapid changes in neuroendocrine activity. While sympathetically mediated plasma catecholamine levels were no different from increases elicited by environmental disturbance, social challenge caused distinct changes in accumbal and amygdalar DA and 5-HT levels (Watt et al., 2006). Changes in the amygdala are associated with general social threat presence. In concert with amygdalar activity, the level of perceived social threat, individual variation in threat level assessment, and motivation to convey aggressiveness, all affect monoamine levels in the nucleus accumbens. This suggests that perception of a non-displaying opponent is sufficient both for recognition of social context and for inducing rapid activity changes in key

forebrain limbic nuclei to initiate appropriate behavioral responses. The latency to aggressive behavior, attack and darkening of the eyespot sign stimuli are most rapid in those that become dominant. However, regardless of level of aggressive behavioral expression and individual social status, once agonistic interactions begin, stress related elevation in serotonergic activity in aggression neurocircuitry and glucocorticoids in plasma occurs rapidly. For a short period, aggressive behavior is elevated in both dominant and subordinate animals, despite high serotonergic and glucocorticoid activity (stage 3). However, the stress response of dominant males to this aggressive interaction is relatively short lived, and serotonergic activity along with glucocorticoid concentrations return to normal. For subordinate males, chronically elevated glucocorticoid (Greenberg et al., 1984) and serotonergic activity (stage 4) limits aggressive behavior while they are in contact with the dominant male, and again if they are reintroduced to the same dominant male. Presumably, these chronically elevated stress chemicals may be reflected in the elevated serotonergic activity measured before aggressive interaction (stage 1). However, subordinate males actually are more aggressive in a second aggressive bout when the dominant male that he is fighting is unknown to him (Forster et al., 2005). Whether elevated glucocorticoids plays a role in enhanced aggression towards an unknown opponent remains to be tested. Previous interactions are known to influence aggressive responses, even if it simply involves watching aggression between other individuals (Oliveira et al., 2001; Oliveira et al., 1998). In addition, bullied individuals react more aggressively toward a different smaller opponent (Øverli et al., 2004).

Conclusion

The central neurotransmitter serotonin and the adrenocortical/interrenal steroid hormones corticosterone and cortisol are important for both stress and aggression. While much of the neurocircuitry for stress and aggression overlap, the timing of responsiveness for 5-HT and glucocorticoids does not. That is, 5-HT and glucocorticoids can both be inhibitory to aggression, but are not inhibitory during the early stressful phase of aggression. This transmitter–hormone combination follows a linear pattern of effect: (1) influencing predisposition (positively or negatively) toward aggression, (2) influencing motivation toward behavior (3) responsive to stress (including aggression) and passively allowing aggression, and finally (4) chronically applied 5-HT and glucocorticoids inhibit aggression. The pattern of neurochemical and hormonal events stimulated by social interaction make it clear that socially aggressive interaction is stressful. Although social aggression has been demonstrated to be stressful for both dominant and subordinate animals, subtle differences in the pattern of response distinguish social rank. Understanding the mechanisms that promote those subtle distinctions are necessary to understand the relationship between stress and aggression more clearly.

List of abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	serotonin
8-OH-DPAT	8-hydroxy-2-(di-*N*-propylamino) tetralin
ACTH	adrenocorticotropic hormone
AVP	vasopressin
BNST	bed nucleus of the stria terminalis
DA	dopamine
DOPAC	dihydroxyphenylacetic acid
$GABA_A$	γ-aminobutyric acid type A
Glu	glutamate
HPA/HPI	hypothalamic-pituitary-adrenal/interrenal axis
L-DOPA	L-3,4-dihydroxyphenylalanine
NE	norepinephrine
PAG	periaqueductal gray
SN/VTA	substantia nigra and ventral tegmental areas
SSRI	selective 5-HT reuptake inhibitors
TpH	tryptophan hydroxylase
Trp	L-tryptophan

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