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European Journal of Pharmacology 526 (2005) 21–35
www.elsevier.com/locate/ejphar

Review

Glucocorticoid interaction with aggression in non-mammalian vertebrates: Reciprocal action

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Accepted 23 September 2005
Available online 18 November 2005

Abstract

Socially aggressive interaction is stressful, and as such, glucocorticoids are typically secreted during aggressive interaction in a variety of vertebrates, which may both potentiate and inhibit aggression. The behavioral relationship between corticosterone and/or cortisol in non-mammalian (as well as mammalian) vertebrates is dependent on timing, magnitude, context, and coordination of physiological and behavioral responses. Chronically elevated plasma glucocorticoids reliably inhibit aggressive behavior, consistent with an evolutionarily adaptive behavioral strategy among subordinate and submissive individuals. Acute elevation of plasma glucocorticoids may either promote an actively aggressive response via action in specialized local regions of the brain such as the anterior hypothalamus, or is permissive to escalated aggression and/or activity. Although the permissive effect of glucocorticoids on aggression does not suggest an active role for the hormone, the corticosteroids may be necessary for full expression of aggressive behavior, as in the lizard *Anolis carolinensis*. These effects suggest that short-term stress may generally be best counteracted by an actively aggressive response, at least for socially dominant proactive individuals. An acute and active response may be evolutionarily maladaptive under chronic, uncontrollable and unpredictable circumstances. It appears that subordinate reactive individuals often produce compulsorily chronic responses that inhibit aggression and promote submissive behavior.

Keywords: Agonistic; Corticosterone; Cortisol; Serotonin; Social; Stress

Contents

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doi:10.1016/j.ejphar.2005.09.059

1. Aggression is stressful

Social conflict in vertebrates often includes posturing or stereotypical displays to invoke agonistic intent, and may be followed by specifically aggressive actions. Ancient evolutionary conservation of the mechanisms involved, results in similar behavioral neuroendocrine integration in vertebrates from fish to mammals, in which both displays and actual aggression are salient stressors for the target of aggression, but also for the aggressor (Miczek et al., 2002; Øverli et al., 1999). The indications that social interactions are stressful are an upregulated expression of stress related genes (Buitenhuis et al., 2003; Feldker et al., 2003; Kollack-Walker et al., 1999; Lesch and Merschdorf, 2000; Martinez et al., 2002; Miczek et al., 2001, 2004)—including genes associated with the heritability of stress coping styles (Benus et al., 1991; Korte et al., 2005; Pottinger and Carrick, 2001), increased activity of stress related neurotransmitters, such as serotonin (5-hydroxytryptamine, 5-HT) in regions of the brain that comprise the stress and aggressions neurocircuitries (see Section 1.1 below) (Blanchard et al., 1993; Korzan and Summers, 2004; Øverli et al., 2004b; Summers et al., 2003a), and increased secretion and plasma concentrations of the glucocorticoid stress hormones: corticosterone and cortisol (see Section 2 below). In addition, the reverse is also true: stress promotes aggression (Øverli et al., 2004b). Stress is a major factor promoting aggression and violence in humans (Barnett et al., 1991; Tardiff, 1992).

1.1. Overlapping neural circuitry

Aggression and stress are related, in part, because the central circuitries serving aggressive response and behavior, and those serving behavioral and neuroendocrine responses to stressful conditions, overlap, at least in mammals. In other vertebrates, the circuitries serving aggression and stress responsiveness are not so well known, but appear to involve many of the same regions of the brain (Greenberg et al., 1979, 1984b, 1988; Greenberg, 1983, 2003; Øverli et al., 2004b; Summers et al., 2003a, in press). The regions connected by the neural circuitry that produces aggression in mammals, and that modify aggression, also appear to be relevant for birds, reptiles and fish as well, and probably include the medial amygdala, hippocampus, septum, bed nucleus of the stria terminalis, mediodorsal thalamic nucleus, ventral tegmentum, periaqueductal gray, and anterior hypothalamus (David et al., 2004; Delville et al., 2000; Gregg and Siegel, 2001; Halasz et al., 2002; Kruk, 1991). The central and medial amygdala, nucleus accumbens, and adjacent regions in the hypothalamus are involved in both stress and aggression. Stimulating the neural circuitry of one system, in these regions, will impact activity in the circuitry of the other. For example, frustration in the absence of reward produces, is a stressful condition that influences motivation, and additionally stimulates a significant increase in synaptic activity in the neural circuitry controlling aggression (David et al., 2004). Intense aggression can be provoked by the stress and frustration produced by removing reward (Azrin et al., 1966; Cherek and Pickens, 1970; Gallup, 1965). These effects may be influenced by the development of both aggression and stress circuitries, as repeated or chronic stress applied during puberty alters the progression of development of aggressive behaviors in male (Delville et al., 2003; Wommack et al., 2003) but not female hamsters (Taravosh-Lahn and Delville, 2004), accelerating the onset of adult aggression.

In mammals, the circuitries of neural and endocrine stress responses, and those mediating aggressive behavior appear to converge in the hypothalamus, from where the ultimate output is directed. The hypothalamus contains critical and adjacent elements for both aggression, the anterior hypothalamus (attack area), and neuroendocrine stress responsiveness, the paraventricular nucleus. These adjacent regions of the hypothalamus are directly interconnected (Roeling et al., 1994). The output of the paraventricular nucleus is the portal vasculature of the median eminence, through which corticotropin releasing hormone stimulates secretion of pituitary corticotropin (adrenocorticotropic hormone or ACTH). The cells generating output from the anterior hypothalamus that produce aggressive behavior are excitatory glutamatergic efferents to the periaqueductal or midbrain central gray (Roeling et al., 1994). Direct stimulation of either area produces the identical glucocorticoid response, although the corticotropin (ACTH) response to stimulation of the attack area was much smaller (Kruk et al., 1998). Taken together with the faciliatory response of corticosterone on aggression (see Section 3 below) the data suggest a mutually stimulatory interaction between hypothalamic regions, and perhaps other brain mechanisms, involved in aggression and the stress response (Kruk et al., 2004).

1.2. Social rank

A number of studies have indicated that aggressive interaction is stressful for both dominant and subordinate members of a social hierarchy (Fig. 1) (Øverli et al., 1999; Summers, 2002; Summers et al., 2003a). The structure and consequences of socially derived stress are not equivalent, as dominant animals must aggressively establish and defend territories and maintain priority access to scarce resources (Creel et al., 1996; Kotrschal et al., 1998; Packer et al., 1995), while persistent subordination is chronically stressful (Greenberg et al., 1984a; Summers et al., 1998a; Summers, 2002). The level or

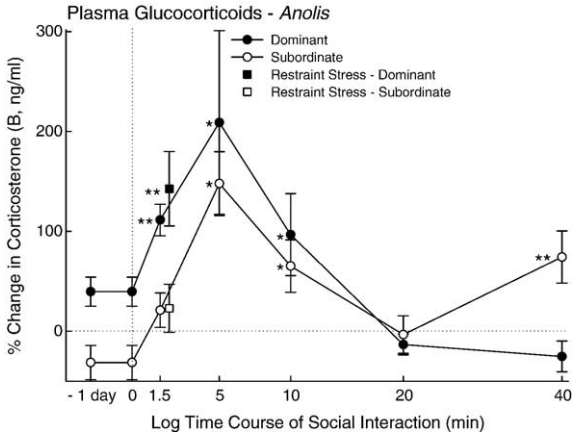

Fig. 1. Mean plasma corticosterone (±S.E.M.) as a percent of control levels (control=0% on the *y* axis) over time (on a log scale), for dominant (black circles) and subordinate (open circles) male *Anolis carolinensis* during aggressive interaction. This graph is comprised of data amalgamated from several experiments (although control means were always similar, each set of experimental animals were only compared to their own control). Animals compared at 1.5 and 5 min were reacting to a video image of an aggressive conspecific, and at all other time points against a real opponent. Also compare corticosterone levels stimulated by a non-social stressor, after 1.5 min of restraint in lizards previously determined to be dominant (black square) or subordinate (open square). Data points at and before the zero time point have not been subject to aggressive interaction, but were determined to be proactive/aggressive and dominant (black circles) or reactive/less aggressive and subordinate (open circles) by testing reaction time to feeding and courtship. Means designated with * are significantly different from controls, and means designated ** are significantly different from other samples at the same point.

timing of corticosteroid secretion due to subordination may depend on the characteristics of the social system (Abbott et al., 2003; Goymann and Wingfield, 2004). In addition, the glucocorticoids produced by social stress may influence rank. Fish with experimentally elevated plasma glucocorticoids are more likely to become subordinate when paired with an untreated control (DiBattista et al., 2004). What is more, fish with a limited response to stressors; tend to become dominant in dyadic encounters with highly stress responsive conspecifics (Øverli et al., 2004a; Pottinger and Carrick, 2001).

2. Glucocorticoid response to aggression

Aggression produces an acute, rapid elevation in plasma glucocorticoid concentrations, early in the course of an agonistic encounter (Fig. 1) (Schuurman, 1980; Summers et al., 2003a). In fact, prior to observable engagement in aggressive behavior, rats begin secreting elevated levels of plasma glucocorticoids (Haller et al., 1995). Dominant males have a rapid but short lived elevation of plasma glucocorticoids, whereas subordinate individuals also exhibit acute glucocorticoid secretion which may be often converted into chronically elevated glucocorticoid concentrations (Blanchard et al., 1993; Øverli et al., 1999; Winberg and Lepage, 1998; Yodyingyuad et al., 1985).

Aggressive social interaction stimulates a potent increase in plasma cortisol concentrations in a variety of fish including *Astatotilapia* (*Haplochromis*) burtoni, Arctic charr (*Salvelinus alpinus*), and rainbow trout (*Oncorhynchus mykiss*) (Elofsson et al., 2000; Fox et al., 1997; Winberg and Lepage, 1998). While both more aggressive dominant fish, and less aggressive subordinate fish respond to aggressive interaction with elevated plasma cortisol concentrations, the timing and magnitude of the response is different (Fig. 2A) (Øverli et al., 1999). The cortisol response in aggressive dominant fish is very brief, significantly elevated by 5 minutes, but returned to baseline by 3 h of interaction in a stable hierarchy where the dominant individual is not challenged. Less aggressive subordinate fish also respond quickly, but show continued escalation of cortisol levels over time (Øverli et al., 2004a) that remain elevated for more than 24 h (Øverli et al., 1999; Winberg and Lepage, 1998). Such chronic elevation of plasma cortisol in less aggressive subordinate trout may influence their level of responsiveness, by reducing corticotropin sensitivity of interrenal cells and cortisol output (Sloman et al., 2002).

Similarly in mammals, repeatedly subjugated hamsters had lower cortisol levels following defeat than controls (Wommack et al., 2004). However, it may be more important to consider the intensity of the aggressive interaction, as in male convict cichlids (*Archocentrus nigrofuciatus*), both winners and losers exhibit significantly elevated cortisol levels, it is in escalated interactions that cortisol is amplified most (Earley et al., in press). Subsequent behavioral events also affect cortisol secretion. Dominant rainbow trout subjected to defeat by a larger fish show significantly elevated plasma cortisol levels (Fig. 2B), but when they are allowed to reassert dominant behavior by bullying by a subordinate fish, aggression increases dramatically (compared to the first encounter with the subordinate; Fig. 2C), but while cortisol levels and hippocampal serotonergic activity remain significantly elevated, they fall from their highest levels (Øverli et al., 2004b).

The lizard *Anolis carolinensis* provides an constructive example of how aggressive interaction between males stimulates enhanced glucocorticoid secretion (Summers, 2002). Green anoles (*A. carolinensis*) will respond to actual aggression, or a video image of conspecific aggression, with elevated plasma corticosterone (Figs. 1, 4B). Anoles subjected to 10 min of aggressive display in a video image over 5 days, exhibit elevated corticosterone consistently over 1, 3 and 5 days, even though aggressive displays returned to the image were reduced by day 5 (Yang and Wilczynski, 2003). This type of chronic response is preceded by a very rapid reaction to aggressive social stress. The most reactive males (these males are likely to be dominant, see below) express elevated corticosterone only 90 s after the beginning of an aggressive (video) encounter (Watt et al., 2004). Although dominant social status cannot be established by aggressively displaying to a video image, males whose dominant status was established by a previous aggressive interaction with a conspecific also show elevated plasma corticosterone 90 s after a nonsocial stressor (Fig. 1, square symbols), whereas subordinate males do not (Watt et al., 2005). After 5 min of aggression towards a video image, not only proactive dominant males have elevated plasma glucocorticoids (Watt et al., 2004). Although there is an initial distinction in glucocorticoid responsiveness based on social rank, socially aggressive interaction is stressful for all combatants, and elevated

glucocorticoids are evident after 10 min in both dominant and subordinate males (Summers et al., 2003a). Regardless of the duration of the aggressive social encounter, dominant males have corticosterone concentrations that return to baseline levels by 20 min of social interaction and are never elevated again. Social status influences both acute and chronic glucocorticoid responsiveness, because although plasma corticosterone concentrations of subordinate males also return to baseline at 20 min, they are elevated again after 40 min of social interaction (Summers et al., 2003a) and also after 3 weeks of cohabitation (Greenberg et al., 1984a). Even though persistent subordination suggests chronically elevated glucocorticoids, *A. carolinensis* males that will become subordinate in an aggressive encounter staged later, have significantly lower glucocorticoid concentrations prior to the fight (Summers et al., 2005b; Fig. 1).

In other reptiles such as the northern fence lizard (*Sceloporus undulatus*) and male copperhead snakes (*Agkistrodon contortrix*) aggressive social or territorial interaction also stimulated elevated plasma corticosterone concentrations (Klukowski and Nelson, 1998), which may be rank (Schuett and Grober, 2000) or season specific (Smith and John-Alder, 1999). Juvenile male green iguanas (*Iguana iguana*) produce elevated secretion of plasma corticosterone to upon exposure to adult males (Alberts et al., 1994). In still other reptiles, such as the mountain spiny lizard (*Sceloporus jarrovi*), tree lizards (*Urosaurus ornatus*), or green turtle (*Chelonia mydas*) aggressive interaction did not appear to influence corticosterone or testosterone (lizards only) secretion (Jessop et al., 1999; Moore, 1987; Thompson and Moore, 1992). However, in further studies of aggression in freely living *S. jarrovi* plasma corticosterone is elevated in both males and females (Woodley et al., 2000), and serotonergic systems in are rapidly activated in territorial males (Matter et al., 1998). In addition, in *U. ornatus* it is the type and duration of interaction that determines the manner of corticosterone secretion (Knapp and Moore, 1995). In longer interactions, dominant males had lower plasma corticosterone levels than did subordinate males over the first day, but this difference subsequently disappeared. Winners of short-term encounters on the other hand, had elevated plasma corticosterone levels which peaked the day after the encounter (Knapp and Moore, 1995). Similarly, among displaying

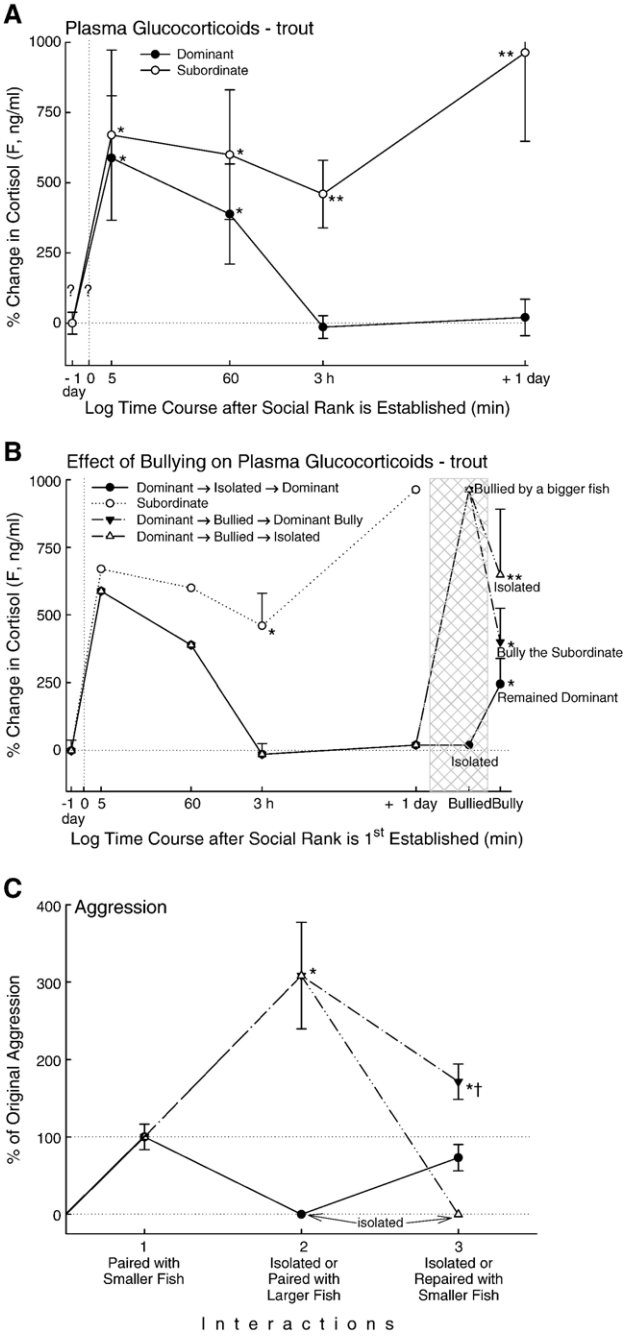

Fig. 2. A) A slightly different view of mean plasma corticosterone (±S.E.M.) as a percent of control levels (control=0% on the *y* axis) over time (on a log scale), for dominant (black circles) and subordinate (open circles) male rainbow trout *Oncorhyncus mykiss* after social rank has been achieved, so aggressive behavior is emanating only from the dominant male. Means designated with * are significantly different from controls, and means designated ** are significantly different from other samples at the same time point. B) Bullying has a dramatic effect on plasma glucocorticoid levels. Fish in the bullying study were dominant fish, larger than their opponent in the original dyad. The portion of graph B to the left of the hatched bars is simply a copy of graph A to depict the changes in cortisol during the first interaction. After the first interaction, fish were either isolated or matched with a much larger fish (they were bullied). The cortisol levels represented in the hatched section of the graph depicting the effects of bullying are *fictitious*; simply a guess estimate of the effects of being bullied by a larger fish stolen from the last point on graph A. Actual mean plasma cortisol (±S.E.M.) as a percent of control levels (control=0% on the *y* axis) were measured following a third interaction, where the original fish, dominant after the first interaction, were either returned to the dyad with a smaller fish after isolation (black circle), returned to the dyad with a smaller fish after being bullied (black inverted triangle), or isolated after being bullied. Fish bullied by larger conspecifics exhibit elevated cortisol, but those that had access to a smaller fish after, had lower cortisol levels and higher levels of aggression C. C) Aggressive acts during three consecutive interactions, as a percentage of the number of aggressive acts per individual during the first 10 min interaction with a smaller conspecific (100%). During the second interaction, each fish was either paired with a larger fish or isolated. Interaction with a larger fish increased aggressive activity (* indicates an increase in aggression compared to the original interaction). During the third interaction each fish was either isolated (after second interaction with a larger fish) or re-paired with a smaller conspecific. While re-pairing with a small conspecific after isolation resulted in levels of aggression approximately equal to the original interaction, re-pairing after a second interaction with a large fish yielded higher levels of aggression (†indicates an increased aggression compared with other groups during the third interaction).

male jacky dragons (*Amphibolurus muricatus*) those exhibiting limited territorial response showed no change in corticosterone or testosterone, but high-level territorial responders exhibited acute corticosterone increases when faced with an intruder (Watt et al., 2003). The results of these studies, especially the distinctions resulting from the work by Watt et al. or Knapp and Moore, suggest that social rank plus intensity and duration of the interaction will define the profile of corticosterone secretion, and is suggestive of a pattern in which short term elevation of glucocorticoids stimulates aggression, as has been demonstrated in rodents.

Among birds, there appears to be different styles for coping with social stress, and aggressive interaction provokes varying responses in plasma glucocorticoids. In the pied flycatcher (*Ficedula hypoleuca*) territorial intrusion was enough to raise plasma corticosterone concentrations, regardless of whether the resident attacked the intruder (Silverin, 1993). When flycatchers responded aggressively, there was a significant negative correlation between number of attacks and plasma corticosterone (Silverin et al., 2004). Confrontation with an aggressive resident male great tit (*Parus major*) stimulates a relatively rapid increase in fecal corticosterone levels (Carere et al., 2003). However, like mammals and fish, less aggressive great tits showed a trend for a higher corticosteroid response compared to more aggressive birds, which showed almost no response. On the day after the challenge by an aggressive resident the less aggressive birds exhibited significantly reduced corticosteroid secretion, probably due to an increased negative feedback (Carere et al., 2003). Similarly, more aggressive chickens have lower plasma corticosterone and brain serotonin than less aggressive birds (van Hierden et al., 2002). Among male Japanese quail however, winners of aggressive interactions had a greater elevation of corticosterone early in the fight (7 min) than losers (Ramenofsky, 1985). On the other hand, when redwing blackbirds were caught at the height of an aggressive encounter they exhibited no change in plasma corticosterone levels (Harding and Follett, 1979). The differences in response may depend on social rank or role, as resident European starlings (*Sturnus vulgaris*) showed no change in corticosterone levels to intruders, but the intruders all developed elevated corticosterone within 30 min (Nephew and Romero, 2003).

3. Aggression mediated by glucocorticoid action

Acute glucocorticoid treatment stimulates increased aggressive behavior in rats (Kruk et al., 2004; Mikics et al., 2004), mice (Brain and Haug, 1992) and hamsters (Hayden-Hixson and Ferris, 1991). Increased adrenal axis reactivity is also correlated with human aggression (Guerra et al., 1995; Vaux and Ruggiero, 1983). As most of the mechanisms and circuitry for aggression and stress appear to be evolutionarily conserved, we suspected that a similar, evolutionarily adaptive relationship between glucocorticoids and social aggression would be evident in other vertebrates. An evolutionarily adaptive relationship would necessarily include a mechanism that would not prevent the escalation of aggressive activity during the most socially stressful period, and it must also include variable response based on social rank.

3.1. Predisposition for aggression—glucocorticoid influence

The differential response of glucocorticoids based on social rank in response to aggression may be based on fundamentally distinct behavioral and physiological phenotypes, built from specific genetic predisposition, stressful maternal or environmental conditions in utero or in ovo, and early life history. Behavioral and physiological traits are linked in such a way that opposing stress coping styles (Koolhaas et al., 1999) result in a coherent set of consistent responses, which are characteristic for social rank or position. Proactive stress coping styles are characterized by a high level of aggression, active attempts to counteract the stressful stimuli, low hypothalamus-pituitary-adrenal (HPA) axis responsiveness, but high sympathetic reactivity. Reactive or passive coping involves immobility, low levels of aggression, elevated HPA axis responsiveness, and low sympathetic reactivity. Individual stress coping styles are present in rainbow trout such that the heritable magnitude of the cortisol response to stress also predicts behavioral and social rank (Øverli et al., 2001, 2002b, 2004a; Pottinger and Carrick, 1999; Pottinger and Carrick, 2001). Specifically, trout that evince a weak cortisol response to stress (as compared with highly responsive fish) show a strong tendency to become socially dominant (Pottinger and Carrick, 2001), a more rapid recovery of food intake after transfer to a novel environment, a reduced locomotor response in a territorial intrusion test (Øverli et al., 2001), and increased ability to form or recall memories of a stressful event (Moreira et al., 2004).

In the lizard *Anolis carolinensis*, and in rainbow trout, it is possible to predetermine the level of aggressiveness and the future social rank of males (Øverli et al., 2004a; Summers et al., 2005b). It has been known for some time with *A. carolinensis*, that the latency to darkening of the postorbital skin (eyespots) at the beginning of an aggressive encounter would accurately predict social rank at the end of the encounter (Korzan et al., 2004; Larson and Summers, 2001; Summers et al., 2005a; Summers and Greenberg, 1994). Not surprisingly, the magnitude and latency of aggression are also correlated strongly with eyespot latency (Höglund et al., 2005; Summers et al., 2005a), such that rapid eyespot formation, and elevated aggression occur in individuals that will become dominant. However, the possibility of a dichotomy in stress coping styles suggested that aggressiveness, and social rank, could be predicted before any fighting occurs, and such is the case in both anoles and trout. *Anolis* lizards and trout that recover from the stress of capture and transfer to a new environment more quickly, confirmed by a shorter latency to resumption of eating, are more proactive, and are more aggressive more quickly (Korzan et al., 2004; Øverli et al., 2004a). Aggressive dominant lizards are also prone to court females more rapidly. When these putatively aggressive lizards are examined before fighting they exhibit elevated plasma corticosterone concentrations (Fig. 1), and reduced serotonergic activity in regions of the brain associated with aggression

(Summers et al., 2005b). Similarly, between two congeneric *Peromyscus* mice, the more aggressive species has higher basal corticosterone levels (Bester-Meredith and Marler, 2001). Among rainbow trout there is a very strong negative correlation between stress-induced cortisol levels and aggressiveness, regardless of whether the animals are prone to have high or low responsiveness to physical stress (Øverli et al., 2004a). There are several questions prompted by the data collected from predetermining rank in trout or lizards. Do prior stress tests, and the level of cortisol they provoke exclude a short-term positive relationship between glucocorticoids and aggression in fish? The most highly aggressive fish were in the highly responsive group, and had higher cortisol levels than trout that were less responsive to physical stress, but became dominant (Øverli et al., 2004a). Are elevated basal corticosterone concentrations in proactive lizards associated with promoting aggressive behavior in these animals?

3.2. Glucocorticoids stimulate or limit aggression

The effect of acute corticosteroid treatment in rats is evident, and very rapidly produced (less than 7 min), with intraperitoneal, intracerebroventricular or intrahypothalamic injections (Hayden-Hixson and Ferris, 1991), suggesting that glucocorticoid stimulated aggression is centrally mediated, but amenable to changes in peripheral glucocorticoids that are stimulated by stress. For example, an acute surge of corticosterone produced by stimulating the anterior hypothalamus facilitates the aggressive response also produced by the hypothalamic stimulation (Kruk et al., 2004). The importance of the role of peripheral glucocorticoids is also corroborated by experiments in which adrenalectomy (Kruk et al., 2004), or peripherally inhibited corticotropin (ACTH) or corticosterone impede aggressive behavior, the latter reversed by corticosterone treatment (Haller et al., 1996; Mikics et al., 2004). This is especially significant because aggression itself is stressful enough to increase plasma glucocorticoid concentrations. In addition to being rapidly produced, glucocorticoid stimulated aggression is rather long lasting (over 25 min). The more rapid effects were demonstrated to be mediated by non-genomic mechanisms, while the later phases of aggressive encounters were mediated by classical genomic mechanisms requiring protein synthesis (Mikics et al., 2004), however it is important to remember that rapid effects are potentially mediated by very fast genomic effects as well (Joëls and de Kloet, 1994). The rapid effects of glucocorticoids on aggression play a role in a fast positive feedback system that links stress with aggression (Kruk et al., 2004) (see Section 5).

In the female fish *Aequidens pulcher* immersion in cortisol increased both submissive and aggressive behaviors (Munro and Pitcher, 1985). The glucocorticoid synthesis inhibitor metyrapone greatly reduced aggression, suggesting that the role of cortisol was to facilitate aggressive components of behavior, however, the effects of metyrapone were not reversed by cortisol treatment. The duration of cortisol treatment appears to be important for its effect on aggression. In rainbow trout given exogenous cortisol in their feed, longer term treatment (48 h) produced a significant reduction in both locomotion and aggression (Øverli et al., 2002a). On the other hand, acute treatment (1 h) not only increased locomotory behavior, but did not inhibit aggression. Acute cortisol treatment produced small, not statistically significant, increases in aggressive acts and reduction in latency to attack, which suggest at least a short-term permissive relationship between glucocorticoids, behavioral activation and aggression. If glucocorticoids allow aggressive behavior to continue during early combative progression, it may be the necessary evolutionary precursor to short-term glucocorticoid exposure enhancing aggressive behavior. Alternatively, it may be that some trout are predisposed to react to short-term elevated glucocorticoids with aggressive behavior, while others are not.

In the lizards *Anolis sagrei* and *Uta stansburiana* long term (7 or 12 days) corticosterone implants significantly inhibit all forms of aggressive display and attack and blocked gonadal activity as well (DeNardo and Licht, 1993; Tokarz, 1987). Blocking corticosterone synthesis (using metyrapone) in the green anole (*A. carolinensis*) had no effect on aggressive behavior toward a video image of aggressive males (Yang and Wilczynski, 2003). Similarly, an acute intraperitoneal injection of corticosterone (2 mg/kg) 30 min prior to aggressive interaction in *A. carolinensis* had no effect on the level of aggression displayed (Fig. 3A). These data suggest that during the early stages of aggressive interaction glucocorticoids are permissive to aggressive behavior, but that more prolonged elevation of glucocorticoids inhibit aggressive social interaction. However, when the glucocorticoid receptor blocker mifepristone (RU486, 20.16 mg/kg) was delivered acutely (30 min prior), there was significant (two way main effect: $F_{8449}=2.67$, $P<0.007$; drug effect: $F_{2449}=3.13$, $P<0.045$) inhibition of aggressive activity between male green anoles, suggesting that glucocorticoids are necessary, if only in a permissive role. This seems a likely reason that putatively dominant, proactive male *A. carolinensis* have significantly higher baseline glucocorticoid concentrations prior to any social interaction (Fig. 1). The necessity for glucocorticoids to ensure a full and vigorously aggressive social interaction appears to be most important during the initiation and early phases of aggressive interaction, as it is only during the first 7 min of social interaction that blocking glucocorticoid receptors limited aggression (Fig. 3B). This is significant because, it is during the initial phases of aggression when the celerity of the social sign stimulus (darkening of postorbital skin: eyespots) in this species limits aggression and promotes social dominance (Korzan et al., 2000; Korzan et al., 2002; Summers and Greenberg, 1994), and the period when proactive males show a shorter latency to aggression (Korzan et al., 2004), and the latency to aggression and eyespot darkening are linked (Höglund et al., 2005).

Chronic elevation by exogenous glucocorticoids appears to have one of four effects in birds. In chickens (*Gallus gallus domesticus*) chronic elevation of plasma corticosterone prenatally, by applying it in ovo resulted in decreased aggression (feather pecking) after hatching (Lay and Wilson, 2002), but corticosterone applied continuously to the food of adults stimulated an increase in feather pecking (El lethey et al.,

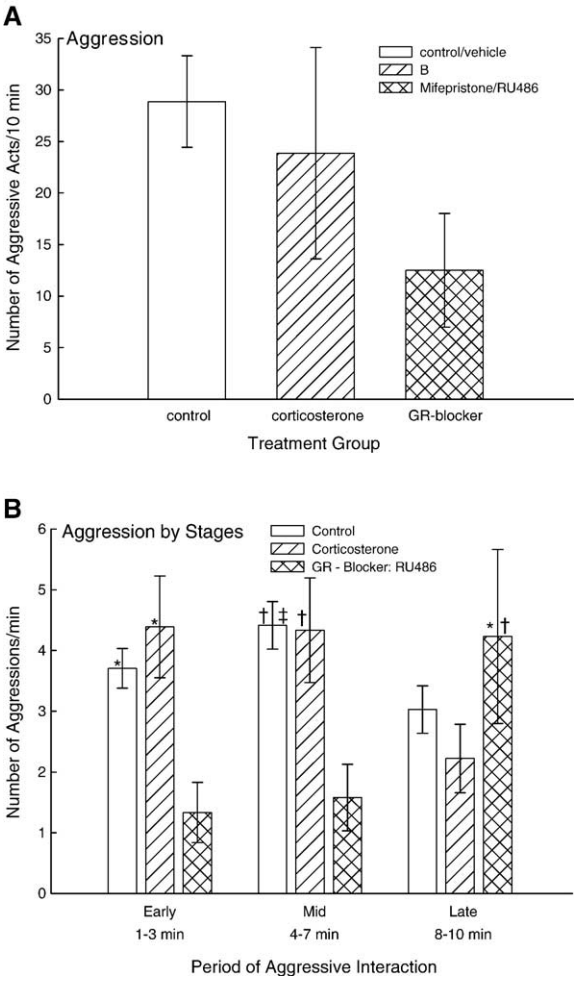

Fig. 3. A) Corticosterone (2 mg/kg) given via intraperitoneal injection to one male of a pair, 30 min prior to combat between these two males permits unabated aggressive behavior (measured as total aggressive acts; mean±S.E.M.). B) The glucocorticoid receptor blocker mifepristone (RU486, 20 mg/kg) given to one combatant of a pair 30 min prior limited aggression (aggressive acts per min) in that combatant for the first 7 min of social interaction, that is during the early (1 to 3 min; * indicates groups with significantly more aggression than lizards treated with glucocorticoid receptor blocker at this time period) and middle (4 to 7 min; †indicates groups with significantly more aggression than lizards treated with glucocorticoid receptor blocker from 4 to 7 min) stages, but had no effect on the last stage (8 to 10 min; ‡indicates significantly>controls at 8–10 min). Males treated with the glucocorticoid receptor blocker displayed significantly less aggression during the first 7 min than controls or corticosterone treated lizards at that time, and also significantly less aggression than the same males treated with glucocorticoid receptor blocker during the last 3 min.

2001). In addition male chickens treated prenatally with exogenous corticosterone were also subject to more aggression (Lay and Wilson, 2002). Chronically elevated corticosterone applied to adult white crowned sparrows (*Zonotrichia leucophrys gumbelii*) resulted in decreased territorial aggression (Meddle et al., 2002). On the other hand the frequency of conflicts was not correlated with average corticosterone level in red knots (*Calidris canutus*) (Reneerkens et al., 2002). Similar to fish, experimentally elevated corticosterone caused no significant decrease in male territorial aggressive behavior in male tree sparrows (Astheimer et al., 2000) Smith's longspur, (*Calcarius pictus*) (Meddle et al., 2003), or male ducklings (*Anas platyrhynchos*) (Deviche, 1979), which like fish and lizards may represent an evolutionarily adaptive mechanism permissive to aggression during the most stressful early stages of aggression (Summers et al., 2005a). The differences in corticosteroid effects on aggression may result from different social, environmental or physiological conditions, such as rank, reproductive activity or incubation periods (Meddle et al., 2002; Nephew and Romero, 2003).

4. Glucocorticoids influence neurotransmitters that regulate aggression

A wide variety of neurotransmitters and modulators influence aggression, including 5-HT, anabolic steroids, dopamine, GABA, glutamate, nitric oxide, vasopressin and of course, glucocorticoids. Of these neurochemical mediators of aggression, the one most studies suggest is responsible for limiting aggression is 5-HT. In fact, despite the fact that many other molecules appear to be involved, it has recently been suggested that 5-HT remains the primary molecular determinant of inter-male aggression, and that the influence of all other modifiers of aggression is accomplished indirectly through 5-HT signaling (Nelson and Chiavegatto, 2001). This view may be complicated by the recent evidence that 5-HT can both stimulate and inhibit aggression via 5-HT_3 receptors (Ricci et al., 2004, 2005b).

4.1. Glucocorticoid influence on 5-HT

Although the exact mechanism remains elusive, the inhibitory effects of 5-HT on aggression have been widely demonstrated (Nelson and Chiavegatto, 2001; Summers et al., 2005b). As 5-HT plays an essential role in regulating aggression, what affect do glucocorticoids have modulating this effect?

First, timing of social stress responses during aggressive interaction results in a concomitant rise in serotonergic activity and HPA production of glucocorticoids (Fig. 4A, B) (Summers, 2002). In addition, a similar but opposite correlation of glucocorticoids, serotonergic activity and aggression occurs in males prior to fighting (Summers et al., 2005b). It is important to consider that the correlations between concentrations of glucocorticoids and 5-HT are caused by direct or indirect interactions between the systems that produce them. The rate-limiting steps in 5-HT synthesis include tryptophan uptake and tryptophan hydroxylase activity, which are stimulated by stress and elevated plasma glucocorticoid concentrations (Azmitia and McEwen, 1969, 1974; Hillier et al., 1975). Glucocorticoids appear to act directly on neuron terminals to modify tryptophan uptake, and permissively induce tryptophan hydroxylase to regulate 5-HT synthesis (Neckers and Sze, 1975; Sze et al., 1976). The result is that both corticotropin (ACTH) and glucocorticoids, stimulate central 5-HT formation from tryptophan (Millard et al., 1972; Millard and Gal, 1971). The behavioral outcome of the relationship between glucocorticoids and 5-HT synthesis can be quite serious, especially if they become faulty as in humans, where a specific subtype of depression driven by anxiety and aggression is precipitated by stressors and cortisol, but produces

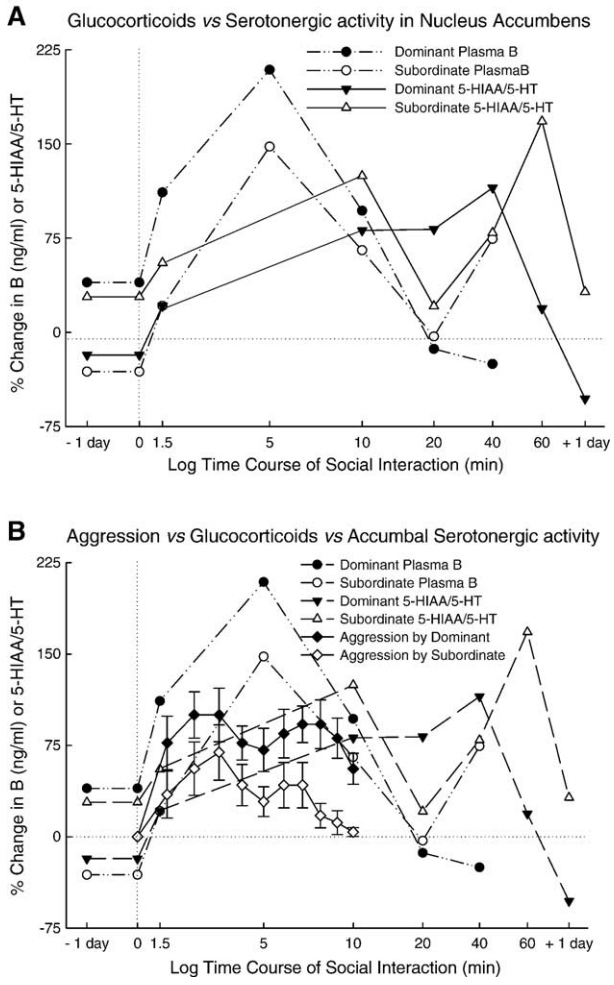

Fig. 4. A) Comparison of mean plasma corticosterone (circles dashed line) and serotonergic activity (estimated by 5-HIAA/5-HT) in nucleus accumbens as a percent of control levels (control=0% on the *y* axis) over time (on a log scale), for dominant (black symbols) and subordinate (open symbols) male *Anolis carolinensis* during aggressive interaction. Notice that there are temporally specific points at which corticosterone and serotonergic activity are positively correlated (after agonistic interaction begins), and where they are negatively correlated (before aggression begins). B) Add a comparison to the temporal resolution of aggressive interaction (% aggressive acts±S.E.M), which between size-matched male *A. carolinensis* is mostly concluded by 10 min.

reduced, rather than enhanced, 5-HT synthesis and 5-HT_{1A} sensitivity (Van Praag, 1996).

In addition to influencing synthesis, glucocorticoids appear to also rapidly stimulate 5-HT release. Glucocorticoids directly delivered via dialysis to specific regions of the brain (including amygdala, medial prefrontal cortex, and hippocampus) stimulate increased 5-HT overflow (Inoue and Koyama, 1996; Summers et al., 1998b, 2003b) within minutes.

Glucocorticoids delivered peripherally by ingestion or injection also stimulate increased central 5-HT levels (Luine et al., 1993; Summers et al., 2000). In addition, adrenalectomy changes 5-HT concentration in the brain (Azmitia et al., 1970; De Maio, 1959), decreases 5-HT turnover, and is reversed by corticosterone substitution (de Kloet et al., 1982; Korte-Bouws et al., 1996). Rapid effects of glucocorticoids may also occur via 5-HT_{1A} mediated hyperpolarization (Joëls, 2001; Karten et al., 2001). Some rapid effects of glucocorticoids on serotonergic transmission and ionic currents appear to require DNA binding of glucocorticoid receptors (Karst et al., 2000), although glucocorticoids also have non-genomic mechanisms available via membrane receptors (Orchinik et al., 1991, 1992).

Serotonin receptor subtypes 5-HT_{1A}, 5-HT_{1B}–HT_2, 5-HT_6, and 5-HT_7 receptors and 5-HT transporter (5-HT_T) are also affected by adrenalectomy, glucocorticoids, and stress (Le Corre et al., 1997; Mendelson and McEwen, 1991, 1992a,b; Yau et al., 1997), perhaps via glucocorticoid mediation of mRNA expression, as has been demonstrated for 5-HT_{1A}, 5-HT_7, and 5-HT_T (Chalmers et al., 1993; Kuroda et al., 1994; Le Corre et al., 1997). Glucocorticoids appear also to influence 5-HT binding to 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptors (Kuroda et al., 1994; Mendelson and McEwen, 1992a,b). Glucocorticoids effect the most basic events associated with serotonergic production, release, receptor expression and binding, and ion current, and as such glucocorticoids exert a broad influence on serotonergic activities in the brain (McEwen et al., 1986), which is widely innervated by serotonergic terminals (Greenberg et al., 1990; Jacobs and Azmitia, 1992).

In should not be forgotten that, reciprocally, 5-HT is a part of the neurochemical milieu that regulates the hypothalmo-pituitary-adrenal axis via limited direct innervation of the hypothalamic paraventricular nucleus (Herman and Cullinan, 1997), with synaptic contact between 5-HT terminals and neurons containing corticotropin releasing hormone (Liposits et al., 1987). Direct stimulation of corticotropin releasing hormone release by 5-HT has been demonstrated in vitro (Calogero et al., 1989; Tsagarakis et al., 1989). In addition, 5-HT also regulates sympathetic nervous system function, and may also play a role in limbic regulatory actions (Chaouloff, 1993; Dinan, 1996). Serotonin has been demonstrated to stimulate adrenal axis activity in a variety of organisms from fish (Lepage et al., 2003; Winberg et al., 1997; Winberg and Lepage, 1998) to humans (Lewis and Sherman, 1984; O'Keane and Dinan, 1991).

Serotonin in the hypothalamus has been directly linked with aggressive behavior, especially associated with its influence on the neuropeptide vasopressin (Ferris et al., 1997).

4.2. Glucocorticoid influence on vasopressin or vasotocin

The neuroactive peptide vasopressin has been localized to cells in the anterior hypothalamus that enhance activity of the glutamatergic output, and enhance aggressive behavior. Administration of vasopressin has a positive effect on aggression and dominance behavior in voles (Winslow et al., 1993), hamsters (Bamshad and Albers, 1996; Ferris et al., 1997), and in humans cerebrospinal fluid vasopressin correlates positively with aggression (Coccaro et al., 1998). In rats facing antagonism from more aggressive rats, although corticosterone levels increase, plasma vasopressin concentrations do not (Suzuki et al., 1998). Perhaps that is because rats subjected to aggression and social subordination stress exhibit an increase in stored hypothalamic vasopressin while corticosterone levels are high (De Goeij et al., 1992). In normal stress axis negative feedback,

glucocorticoids regulate vasopressin as well as corticotropin-releasing factor (Urban et al., 1991), but in hyperanxious rats it is vasopressin via the vasopressin V_{1A} receptor which produces hyper-glucocorticoid responses through diminished negative feedback (Keck et al., 2002). This is an important environmental/physiological alteration of glucocorticoid sensitivity as corticosteroids modify V_{1A} receptor gene and protein expression in the brain via several glucocorticoid response elements (GRE) in the promoter and enhancer region of the gene (Watters et al., 1996a,b). Although glucocorticoids also appear to diminish vasopressin in extrahypothalmic regions of the brain, at least in the medial amygdala or bed nucleus of the stria terminalis, the effect is indirect via inhibition of androgens that regulate the vasopressin gene (Urban et al., 1991; Watters et al., 1998). The most important question still remaining about glucocorticoid regulation of vasopressin is whether glucocorticoids play a special role regulating vasopressin in the anterior hypothalamus, where both vasopressin and glucocorticoids are effective in stimulating aggression.

As the evolutionary precursor to vasopressin, vasotocin could play a similar role augmenting aggression. However, in starlings (*Sturnus vulgaris*) where crowded conditions stimulated aggressive interaction, peripherally injected vasotocin reduced aggressive behavior while stimulating plasma corticosterone (Nephew et al., 2005). In other wild birds, where central injection of the stress neuropeptide corticotropin releasing factor reduced territorial aggression, vasotocin had no effect (Romero et al., 1998).

4.3. Glucocorticoid influence on GABA

The γ-aminobutyric acid (GABA) type A receptor ($GABA_A$) is implicated in aggressive behavior bimodally, both enhancing and reducing aggressive acts and behavior (Miczek et al., 2002). This effect is related to GABA synthesis, via the enzyme GAD_{65}, and function in specific aggression areas, such as anterior hypothalamus and medial amygdala (Grimes et al., 2003; Ricci et al., 2005a). Defensive aggression and predatory attack appear to be interrelated via a GABAergic pathway between the subsets of neural circuitry that serve these two kinds of aggression (Gregg and Siegel, 2001). There has been a long-established link between alcohol, which binds to the $GABA_A$ receptor, and heightened aggressive behavior (Miczek et al., 1993, 1994a,b). Aggression induced by alcohol can be potentiated by benzodiazepines, which also bind to the $GABA_A$ receptor. Steroids produced in the brain de novo, like allopregnanolone, that are positive allosteric modulators of $GABA_A$ receptor function, have been demonstrated to heighten aggressive behavior (Fish et al., 2002a).

Although there is no suggestion that physiological concentrations of glucocorticoids effect ligand binding or GABA-stimulated Cl^- uptake via $GABA_A$ receptors, glucocorticoids have been demonstrated to alter GABA function by modifying $GABA_A$ receptor subunit expression and heterogeneity (Orchinik et al., 1994a,b, 1995, 2001). In addition, a glucocorticoid that binds only weakly to classic mineralocorticoid and glucocorticoid receptors, tetrahydrodeoxycorticosterone (THDOC) is a potent positive allosteric modulators of $GABA_A$ Cl^- influx. This neurosteroid has been demonstrated to inhibit conflict and aggressive behavior (Auta et al., 1993; Barbaccia, 2004; Kavaliers, 1988).

4.4. Glucocorticoid influence on glutamate systems

Glutamate acting at the levels of the hypothalamus and the periaqueductal gray, and as transmitter between them facilitates aggressive behavior in a variety of vertebrates (Brody et al., 1969; Gregg and Siegel, 2001; Hoffmann et al., 1993; Marcucci and Giacalone, 1969; Roeling et al., 1994; Siegel et al., 1999). Two kinds of glutamate receptors that are functionally linked, AMPA and NMDA receptors appear to mediate these effects (Brodkin et al., 2002; Carobrez et al., 2001; Ossowska et al., 1997; Vekovischeva et al., 2004). This role of glutamate on aggression may require both concomitant changes in GABA and socially aggressive experience. A microdialysis study of naive and experienced rats (recent and previous) suggests that only combined perfusion of the glutamate agonist kainate and the $GABA_A$ receptor antagonist bicuculline together into the hypothalamic attack area caused a significant increase in aggressive behavior, and only in animals with a recent aggressive experience (Haller et al., 1998). It is experience, and reinforcing its influence, where plasma glucocorticoids may impact on glutamate function and aggression, and do so in more than one way. First, aggression appears to activate the same neurocircuitry associated with reward that is stimulated during drug addiction, and certain drugs of addiction also promote aggression (DeLeon et al., 2002; Fish et al., 2002b; Melloni et al., 1997; Miczek and Tidey, 1989). Second, stress and glucocorticoids promote addiction and especially its social reinforcing mechanisms (Piazza and Le Moal, 1997). Stress and glucocorticoids also regulate glutamate NMDA receptors (Bartanusz et al., 1995; Meyer et al., 2004; Weiland et al., 1997). Glutamate from the hippocampus and central amygdala produce context dependent increases of dopamine in the nucleus accumbens. Receptors for NMDA and glucocorticoids appear to be necessary for development of behavioral sensitization, promote addiction, and enhance relapse (Deroche-Gamonet et al., 2003). Similarly increased accumbal dopamine may be stimulated by glucocorticoids enhancing the effect of glutamate acting on NMDA and AMPA receptors that induce burst firing of ventral tegmental neurons (Cho and Little, 1999). Therefore, glucocorticoid influence of glutamatergic activity may be most important for setting contextual events and conditions that reinforce aggressive behavior, much as they do for addiction, and affecting the likelihood of repetitive aggressive events.

In the lizard *A. carolinensis*, aggression stimulates upregulation of subunits of the glutamate NMDA receptor in CA_3 region of the hippocampus, where NR_{2A} and NR_{2B} subunits are increased in both dominant and subordinate males (Meyer et al., 2004). Increased NR_{2A} and NR_{2B} subunits in the CA_3 region, but not dentate gyrus, may also be established by exogenous corticosterone. This is important because, in mammals coincident upregulation of $NR_{2A}+NR_{2B}$ stimulates NR_1 upregulation, and more importantly, an increase in the total number of NMDA

receptors (Saito et al., 2003). In our experiments, expression of NR_{2B} subunits is enhanced to a greater degree than NR_{2A} subunits (Summers et al., 2005a). Genetically over-expressed hippocampal NR_{2B} subunits enhance learning (Tang et al., 1999) and knock-out mice lacking 5-HT_{1A} receptors have reduced hippocampally dependent learning (Sarnyai et al., 2000). These results suggest that stress-related glutamatergic, serotonergic and glucocorticoid changes in the hippocampus may modify critical learning events important for recognizing opponents during aggression, and learning social status roles. Male *A. carolinensis* are capable of distinguishing familiar opponents after one aggressive interaction of 10 min (Forster et al., 2005). There was no distinction in NR_2 subunit upregulation across social status, which suggests that learning the elements and characteristics of social rank is important for both dominant and subordinate males.

5. Reciprocal integration and timing

The key to distinguishing the effect of glucocorticoids on aggression, and the resulting outcome in social status, may be the celerity, magnitude and duration of the glucocorticoid response. This is because, while social interactions have an immediacy that promotes stress responses from both dominant and subordinate individuals, chronic social subordination involves long-term neuroendocrine stress activity that imposes deleterious physiological consequences and influence future aggressive encounters and rank (DeVries et al., 2003; Gilmour et al., 2005; Sloman and Armstrong, 2002; Summers, 2002; Summers et al., 2005a,b). In mammals, the combined elements of the hypothalamic attack area stimulating adrenal axis secretion of glucocorticoids, just as actual aggression does, and peripheral glucocorticoids rapidly mediating aggression stimulated centrally via the hypothalamus, suggests a fast positive feedback mechanism to the adrenocortical stress response promoting central neurocircuitry that enhance aggressive interaction (Kruk et al., 2004). The short-term nature of positive glucocorticoid feedback promoting aggression may be facilitated by the pulsatile nature of glucocorticoid secretion (Lightman et al., 2000, 2002). These highly adaptive responses to social aggression that promote actively aggressive responses in rodents have not, as yet, been demonstrated in all vertebrates. However, the pattern of evidence suggests at least a permissive effect of short-term glucocorticoid secretion (Fig. 3A, B). However, even though glucocorticoids may be permissive in some animals, rather than stimulatory to aggression, it does not mean that they are not necessary, and the effect of glucocorticoid receptor activity to permit aggression, may be most important in the initial phases of combative interaction (Fig. 3B). The necessity for and permissive role of glucocorticoids during the initial phases of aggression is followed by strongly inhibitory influence of chronically elevated glucocorticoid secretion that often accompanies social subordination or environmental conditions that produce uncontrollable and unpredictable circumstances.

A critical juncture therefore, is the time between the acute and chronic phases in stress responsiveness, and glucocorticoid secretion, where permissive or stimulatory actions must be integrated with the suppressive effect of glucocorticoids (Sapolsky et al., 2000). There appears to be a distinction in the sensitivity of the glucocorticoid response at this time period, and in the initial phase of aggressive interaction, between potentially dominant and subordinate individuals. There are also significant differences between dominant and subordinate, or proactive and reactive individuals in baseline concentrations of plasma glucocorticoids, the timing and magnitude of response to aggression and other stressors, and the propensity for mounting a secondary long-term glucocorticoid response to social or other stressors. These differences are reflected in several neurotransmitter systems, many of which are influenced by the presence of elevated plasma glucocorticoid concentrations (Fig. 4A). Specifically, at least in *A. carolinensis*, serotonergic activity in brain regions that in mammals are a common part of stress, aggression and addiction neurocircuitry, such as nucleus accumbens are positively correlated with glucocorticoid levels and also positively correlated with aggression (Fig. 4B). At the point in time when aggression is most intense, at the beginning of combative interaction, two neurochemicals often associated with inhibiting aggression, are on the rise. Clearly they are not inhibiting aggression at this time, but prior to aggressive interaction, serotonergic activity is negatively correlated, and plasma glucocorticoid concentrations are positively correlated with aggressive potential. To fully understand the progression and consequences of aggressive interaction, it is the specific local neuroendocrine events that must be investigated at the two critical time points: 1) initiation of aggression, and 2) the confluence of acute and chronic stress responses.

6. Conclusions

The relationship between glucocorticoids in non-mammalian as well as mammalian vertebrates appears to be very complex, with behavioral results dependent on timing, magnitude, context, and coordination of physiological and behavioral responses. Corticosterone and/or cortisol appear to have the capacity for both potentiating as well as inhibiting aggression. Consistently across vertebrate taxa chronically elevated glucocorticoids inhibit aggressive behavior. This is consistent with an evolutionarily adaptive behavioral strategy among subordinate and submissive individuals, and is characteristic of that group. Acute stress on the other hand, may generally be best counteracted by an actively aggressive response, while such a response would be evolutionarily maladaptive under chronic, uncontrollable and unpredictable circumstances. The collected evidence indicates that short-term glucocorticoid action in the brain, perhaps in specialized local regions such as the anterior hypothalamus, either promotes an actively aggressive response, or is necessary but permissive to escalated aggression and/or activity. The acute proactively aggressive response appears to be more available to dominant individuals. Subordinate or reactive individuals often reveal neuroendocrine machinery that produces compulsory chronic responses that inhibit aggression and promote submissive behavior.

Acknowledgements

Our work is supported by NIH grants P20 RR1 5567, R03 MHO68303 and ROl DA019921 (GLF), R03 MH068364 (MJW), 1 F31 MH64983 (WJK).

References

Abbott, D.H., Keverne, E.B., Bercovitch, F.B., Shively, C.A., Mendoza, S.P., Saltzman, W., Snowdon, C.T., Ziegler, T.E., Banjevic, M., Garland Jr., T., Sapolsky, R.M., 2003. Are subordinates always stressed? A comparative analysis of rank differences in cortisol levels among primates. Horm. Behav. 43, 67–82.

Alberts, A.C., Jackintell, L.A., Phillips, J.A., 1994. Effects of chemical and visual exposure to adults on growth, hormones, and behavior of juvenile green iguanas. Physiol. Behav. 55, 987–992.

Astheimer, L.B., Buttemer, W.A., Wingfield, J.C., 2000. Corticosterone treatment has no effect on reproductive hormones or aggressive behavior in free-living male tree sparrows, *Spizella arborea*. Horm. Behav. 37, 31–39.

Auta, J., Romeo, E., Kozikowski, A., Ma, D., Costa, E., Guidotti, A., 1993. Participation of mitochondrial diazepam binding inhibitor receptors in the anticonflict, antineophobic and anticonvulsant action of 2-aryl-3-indoleacetamide and imidazopyridine derivatives. J. Pharmacol. Exp. Ther. 265, 649–656.

Azmitia, E.C., McEwen, B.S., 1969. Corticosterone regulation of tryptophan hydroxylase in midbrain of the rat. Science 166, 1274–1276.

Azmitia, E.C., McEwen, B.S., 1974. Adrenalcortical influence on rat brain tryptophan hydroxylase activity. Brain Res. 78, 291–302.

Azmitia, E.C., Algeri, S., Costa, E., 1970. In vivo conversion of ^{3}H-L-tryptophan into ^{3}H-serotonin in brain areas of adrenalectomized rats. Science 169, 201–203.

Azrin, N.H., Hutchison, R.R., Hake, D.F., 1966. Extinction-induced aggression. J. Exp. Anal. Behav. 9, 191–204.

Bamshad, M., Albers, H.E., 1996. Neural circuitry controlling vasopressin-stimulated scent marking in Syrian hamsters (*Mesocricetus auratus*). J. Comp. Neurol. 369, 252–263.

Barbaccia, M.L., 2004. Neurosteroidogenesis: relevance to neurosteroid actions in brain and modulation by psychotropic drugs. Crit. Rev. Neurobiol. 16, 67–74.

Barnett, O.W., Fagan, R.W., Booker, J.M., 1991. Hostility and stress as mediators of aggression in violent men. J. Fam. Violence 6, 217–241.

Bartanusz, V., Aubry, J.M., Pagliusi, S., Jezova, D., Baffi, J., Kiss, J.Z., 1995. Stress-induced changes in messenger RNA levels of *N*-methyl-D-aspartate and AMPA receptor subunits in selected regions of the rat hippocampus and hypothalamus. Neuroscience 66, 247–252.

Benus, R.F., Bohus, B., Koolhaas, J.M., van Oortmerssen, G.A., 1991. Heritable variation for aggression as a reflection of individual coping strategies. Experientia 47, 1008–1019.

Bester-Meredith, J.K., Marler, C.A., 2001. Vasopressin and aggression in cross-fostered California mice (*Peromyscus californicus*) and white-footed mice (*Peromyscus leucopus*). Horm. Behav. 40, 51–64.

Blanchard, D.C., Sakai, R.R., McEwen, B., Weiss, S.M., Blanchard, R.J., 1993. Subordination stress: behavioral, brain, and neuroendocrine correlates. Behav. Brain Res. 58, 113–121.

Brain, P.F., Haug, M., 1992. Hormonal and neurochemical correlates of various forms of animal "aggression". Psychoneuroendocrinology 17, 537–551.

Brodkin, E.S., Goforth, S.A., Keene, A.H., Fossella, J.A., Silver, L.M., 2002. Identification of quantitative trait Loci that affect aggressive behavior in mice. J. Neurosci. 22, 1165–1170.

Brody, J.F., DeFeudis, P.A., DeFeudis, F.V., 1969. Effects of micro-injections of L-glutamate into the hypothalamus on attack and flight behaviour in cats. Nature 224, 1330.

Buitenhuis, A.J., Rodenburg, T.B., van Hierden, Y.M., Siwek, M., Cornelissen, S.J., Nieuwland, M.G., Crooijmans, R.P., Groenen, M.A., Koene, P., Korte, S.M., Bovenhuis, H., van der Poel, J.J., 2003. Mapping quantitative trait loci affecting feather pecking behavior and stress response in laying hens. Poult. Sci. 82, 1215–1222.

Calogero, A.E., Bernardini, R., Margioris, A.N., Bagdy, G., Gallucci, W.T., Munson, P.J., Tamarkin, L., Tomai, T.P., Brady, L., Gold, P.W., 1989. Effects of serotonergic agonists and antagonists on corticotropin-releasing hormone secretion by explanted rat hypothalami. Peptides 10, 189–200.

Carere, C., Groothuis, T.G., Mostl, E., Daan, S., Koolhaas, J.M., 2003. Fecal corticosteroids in a territorial bird selected for different personalities: daily rhythm and the response to social stress. Horm. Behav. 43, 540–548.

Carobrez, A.P., Teixeira, K.V., Graeff, F.G., 2001. Modulation of defensive behavior by periaqueductal gray NMDA/glycine-B receptor. Neurosci. Biobehav. Rev. 25, 697–709.

Chalmers, D.T., Kwak, S.P., Mansour, A., Akil, H., Watson, S.J., 1993. Corticosteroids regulate brain hippocampal 5-HTlA receptor mRNA expression. J. Neurosci. 13, 914–923.

Chaouloff, F., 1993. Physiopharmacological interactions between stress hormones and central serotonergic systems. Brain Res. Rev. 18, 1–32.

Cherek, D.R., Pickens, R., 1970. Schedule-induced aggression as a function of fixed-ratio value. J. Exp. Anal. Behav. 14, 309–311.

Cho, K., Little, H.J., 1999. Effects of corticosterone on excitatory amino acid responses in dopamine-sensitive neurons in the ventral tegmental area. Neuroscience 88, 837–845.

Coccaro, E.F., Kavoussi, R.J., Hauger, R.L., Cooper, T.B., Ferris, C.F., 1998. Cerebrospinal fluid vasopressin levels: correlates with aggression and serotonin function in personality-disordered subjects. Arch. Gen. Psychiatry 55, 708–714.

Creel, S., Creel, N.M., Monfort, S.L., 1996. Social stress and dominance. Nature 379, 212.

David, J.T., Cervantes, M.C., Trosky, K.A., Salinas, J.A., Delville, Y., 2004. A neural network underlying individual differences in emotion and aggression in male golden hamsters. Neuroscience 126, 567–578.

De Goeij, D.C., Dijkstra, H., Tilders, F.J., 1992. Chronic psychosocial stress enhances vasopressin, but not corticotropin-releasing factor, in the external zone of the median eminence of male rats: relationship to subordinate status. Endocrinology 131, 847–853.

de Kloet, E.R., Kovacs, G.L., Szabo, G., Telegdy, G., Bohus, B., Versteeg, D.H., 1982. Decreased serotonin turnover in the dorsal hippocampus of rat brain shortly after adrenalectomy: selective normalization after corticosterone substitution. Brain Res. 239, 659–663.

DeLeon, K.R., Grimes, J.M., Connor, D.F., Melloni Jr., R.H., 2002. Adolescent cocaine exposure and offensive aggression: involvement of serotonin neural signaling and innervation in male Syrian hamsters. Behav. Brain Res. 133, 211–220.

Delville, Y., De Vries, G.J., Ferris, C.F., 2000. Neural connections of the anterior hypothalamus and agonistic behavior in golden hamsters. Brain Behav. Evol. 55, 53–76.

Delville, Y., David, J.T., Taravosh-Lahn, K., Wommack, J.C., 2003. Stress and the development of agonistic behavior in golden hamsters. Horm. Behav. 44, 263–270.

De Maio, D., 1959. Influence of adrenalectomy and hypophysectomy on cerebral serotonin. Science 129, 1678–1679.

DeNardo, D.F., Licht, P., 1993. Effects of corticosterone on social behavior of male lizards. Horm. Behav. 27, 184–199.

Deroche-Gamonet, V., Sillaber, I., Aouizerate, B., Izawa, R., Jaber, M., Ghozland, S., Kellendonk, C., Le Moal, M., Spanagel, R., Schutz, G., Tronche, F., Piazza, P.V., 2003. The glucocorticoid receptor as a potential target to reduce cocaine abuse. J. Neurosci. 23, 4785–4790.

Deviche, P., 1979. Effects of testosterone propionate and pituitary-adrenal hormones on the social behaviour of male ducklings (*Anas platyrhynchos* L.) in two test situations. Z. Tierpsychol. 49, 77–86.

DeVries, A.C., Glasper, E.R., Detillion, C., 2003. Social modulation of stress responses. Physiol. Behav. 79, 399–407.

DiBattista, J.D., Anisman, H., Whitehead, M., Gilmour, K.M., 2004. The effect of cortisol on social status and brain monoaminergic activity in freshwater rainbow trout (*Oncorhynchus mykiss*). Comp. Biochem. Physiol., A 137, S17.

Dinan, T.G., 1996. Serotonin and the regulation of hypothalamic-pituitary-adrenal axis function. Life Sci. 58, 1683–1694.

Earley, R.L., Edwards, J.T., Aseem, O., Felton, K., Blumer, L.S., Karom, M., Grober, M.S., (in press). Social modulation of cortisol: contest intensity trumps outcome. Physiol. Behav.

El lethey, H., Jungi, T.W., Huber-Either, B., 2001. Effects of feeding corticosterone and housing conditions on feather pecking in laying hens (*Gallus gallus domesticus*). Physiol. Behav. 73, 243–251.

Elofsson, U.O., Mayer, I., Damsgard, B., Winberg, S., 2000. Intermale competition in sexually mature arctic charr: effects on brain monoamines, endocrine stress responses, sex hormone levels, and behavior. Gen. Comp. Endocrinol. 118, 450–460.

Feldker, D.E., Datson, N.A., Veenema, A.H., Meulmeester, E., de Kloet, E.R., Vreugdenhil, E., 2003. Serial analysis of gene expression predicts structural differences in hippocampus of long attack latency and short attack latency mice. Eur. J. Neurosci. 17, 379–387.

Ferris, C.F., Melloni Jr., R.H., Koppel, G., Perry, K.W., Fuller, R.W., Delville, Y., 1997. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. J. Neurosci. 17, 4331–4340.

Fish, E.W., De Bold, J.F., Miczek, K.A., 2002a. Aggressive behavior as a reinforcer in mice: activation by allopregnanolone. Psychopharmacology (Berl) 163, 459–466.

Fish, E.W., DeBold, J.F., Miczek, K.A., 2002b. Repeated alcohol: behavioral sensitization and alcohol-heightened aggression in mice. Psychopharmacology (Berl) 160, 39–48.

Forster, G.L., Watt, M.J., Korzan, W.J., Renner, K.J., Summers, C.H., 2005. Opponent recognition in male green anoles, *Anolis carolinensis*. Anim. Behav. 69, 733–740.

Fox, H.E., White, S.A., Kao, M.H., Fernald, R.D., 1997. Stress and dominance in a social fish. J. Neurosci. 17, 6463–6469.

Gallup, G.G., 1965. Aggression in rats as a function of frustrative nonreward in a straight alley. Psychon. Sci. 3, 99–100.

Gilmour, K.M., DiBattista, J.D., Thomas, J.B., 2005. Physiological causes and consequences of social status in salmonid fish. Integr. Comp. Biol. 45, 263–273.

Goymann, W., Wingfield, J.C., 2004. Allostatic load, social status and stress hormones: the costs of social status matter. Anim. Behav. 67, 591–602.

Greenberg, N., 1983. Central and autonomic aspects of aggression and dominance in reptiles. In: Ewert, J.P., Capranica, R.R., Ingle, D.J. (Eds.), Advances in Vertebrate Neuroethology. Plenum, New York, pp. 1135–1143.

Greenberg, N., 2003. Sociality, stress, and the corpus striatum of the green anolis lizard. Physiol. Behav. 79, 429–440.

Greenberg, N., MacLean, P.D., Ferguson, J.L., 1979. Role of the paleostriatum in species-typical display behavior of the lizard (*Anolis carolinensis*). Brain Res. 172, 229–241.

Greenberg, N., Chen, T., Crews, D., 1984a. Social status, gonadal state, and the adrenal stress response in the lizard, *Anolis carolinensis*. Horm. Behav. 18, 1–11.

Greenberg, N., Scott, M., Crews, D., 1984b. Role of the amygdala in the reproductive and aggressive behavior of the lizard, *Anolis carolinensis*. Physiol. Behav. 32, 147–151.

Greenberg, N., Font, E., Switzer, R.C., 1988. The reptilian striatum revisited: studies on Anolis lizards. In: Schwerdtfeger, W.K., Smeets, W.J.A.J. (Eds.), The Forebrain of Reptiles. Karger, Basel, pp. 162–177.

Greenberg, N., Summers, C.H., Desan, P.H., 1990. Central monoamines and behavior in the lizard, *Anolis carolinensis*. Abstr. - Soc. Neurosci. 16, 920.

Gregg, T.R., Siegel, A., 2001. Brain structures and neurotransmitters regulating aggression in cats: implications for human aggression. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 25, 91–140.

Grimes, J.M., Ricci, L.A., Melloni, R.H., 2003. Glutamic acid decarboxylase (GA_{65}) immunoreactivity in brains of aggressive, adolescent anabolic steroid-treated hamsters. Horm. Behav. 44, 271–280.

Guerra, N.G., Huesmann, L.R., Tolan, P.H., Van Acker, R., Eron, L.D., 1995. Stressful events and individual beliefs as correlates of economic disadvantage and aggression among urban children. J. Consult. Clin. Psychol. 63, 518–528.

Halasz, J., Liposits, Z., Meelis, W., Kruk, M.R., Haller, J., 2002. Hypothalamic attack area-mediated activation of the forebrain in aggression. Neuroreport 13, 1267–1270.

Haller, J., Barna, I., Baranyi, M., 1995. Hormonal and metabolic responses during psychosocial stimulation in aggressive and nonaggressive rats. Psychoneuroendocrinology 20, 65–74.

Haller, J., Kiem, D.T., Makara, G.B., 1996. The physiology of social conflict in rats: what is particularly stressful? Behav. Neurosci. 110, 353–359.

Haller, J., Abraham, I., Zelena, D., Juhasz, G., Makara, G.B., Kruk, M.R., 1998. Aggressive experience affects the sensitivity of neurons towards pharmacological treatment in the hypothalamic attack area. Behav. Pharmacol. 9, 469–475.

Harding, C.F., Follett, B.K., 1979. Hormone changes triggered by aggression in a natural population of blackbirds. Science 203, 918–920.

Hayden-Hixson, D.M., Ferris, C.F., 1991. Steroid-specific regulation of agonistic responding in the anterior hypothalamus of male hamsters. Physiol. Behav. 50, 793–799.

Herman, J.P., Cullinan, W.E., 1997. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci. 20, 78–84.

Hillier, J., Hillier, J.G., Redfern, P.H., 1975. Liver tryptophan pyrrolase activity and metabolism of brain 5-HT in rat. Nature 253, 566–567.

Hoffmann, A., Brazil Romero, S.M., de Oliveira, L.M., 1993. Agonistic behavior and its cardiovascular components elicited by microinjection of L-glutamic acid into the basal midbrain of the toad *Bufo paracnemis*. Brain Behav. Evol. 4, 316–325.

Höglund, E., Korzan, W.J., Watt, M.J., Forster, G.L., Summers, T.R., Johannessen, H.F., Renner, K.J., Summers, C.H., 2005. Effects of L-DOPA on aggressive behavior and central monoaminergic activity in the lizard *Anolis carolinensis*, using a new method for drug delivery. Behav. Brain Res. 156, 53–64.

Inoue, T., Koyama, T., 1996. Effects of acute and chronic administration of high-dose corticosterone and dexamethasone on regional brain dopamine and serotonin metabolism in rats. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 20, 147–156.

Jacobs, B.L., Azmitia, E.C., 1992. Structure and function of the brain serotonin system. Physiol. Rev. 72, 165–229.

Jessop, T.S., FitzSimmons, N.N., Limpus, C.J., Whittier, J.M., 1999. Interactions between behavior and plasma steroids within the scramble mating system of the promiscuous green turtle, *Chelonia mydas*. Horm. Behav. 36, 86–97.

Joëls, M., 2001. Corticosteroid actions in the hippocampus. J. Neuroendocrinol. 13, 657–669.

Joëls, M., de Kloet, E.R., 1994. Mineralocorticoid and glucocorticoid receptors in the brain. Implications for ion permeability and transmitter systems. Prog. Neurobiol. 43, 1–36.

Karst, H., Karten, Y.J., Reichardt, H.M., de Kloet, E.R., Schutz, G., Joels, M., 2000. Corticosteroid actions in hippocampus require DNA binding of glucocorticoid receptor homodimers. Nat. Neurosci. 3, 977–978.

Karten, Y.J., Stienstra, C.M., Joëls, M., 2001. Corticosteroid effects on serotonin responses in granule cells of the rat dentate gyrus. J. Neuroendocrinol. 13, 233–238.

Kavaliers, M., 1988. Inhibitory influences of the adrenal steroid, 3α, 5α-tetrahydrodeoxycorticosterone on aggression and defeat-induced analgesia in mice. Psychopharmacology (Berl) 95, 488–492.

Keck, M.E., Wigger, A., Welt, T., Muller, M.B., Gesing, A., Reul, J.M., Holsboer, F., Landgraf, R., Neumann, I.D., 2002. Vasopressin mediates the response of the combined dexamethasone/CRH test in hyper-anxious rats: implications for pathogenesis of affective disorders. Neuropsychopharmacology 26, 94–105.

Klukowski, M., Nelson, C.E., 1998. The challenge hypothesis and seasonal changes in aggression and steroids in male northern fence lizards (*Sceloporus undulatus hyacinthinus*). Horm. Behav. 33, 197–204.

Knapp, R., Moore, M.C., 1995. Hormonal responses to aggression vary in different types of agonistic encounters in male tree lizards, *Urosaurus ornatus*. Horm. Behav. 29, 85–105.

Kollack-Walker, S., Don, C., Watson, S.J., Akil, H., 1999. Differential expression of c-*fos* mRNA within neurocircuits of male hamsters exposed to acute or chronic defeat. J. Neuroendocrinol. 11, 547–559.

Koolhaas, J.M., Korte, S.M., de Boer, S.F., van der Vegt, B.J., van Reenen, C.G., Hopster, H., de Jong, I.C., Ruis, M.A., Blokhuis, H.J., 1999. Coping styles

in animals: current status in behavior and stress-physiology. Neurosci. Biobehav. Rev. 23, 925–935.

Korte, S.M., Koolhaas, J.M., Wingfield, J.C., McEwen, B.S., 2005. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci. Biobehav. Rev. 29, 3–38.

Korte-Bouws, G.A., Korte, S.M., de Kloet, E.R., Bohus, B., 1996. Blockade of corticosterone synthesis reduces serotonin turnover in the dorsal hippocampus of the rat as measured by microdialysis. J. Neuroendocrinol. 8, 877–881.

Korzan, W.J., Summers, C.H., 2004. Serotonergic response to social stress and artificial social sign stimuli during paired interactions between male *Anolis carolinensis*. Neuroscience 123, 835–845.

Korzan, W.J., Summers, T.R., Ronan, P.J., Summers, C.H., 2000. Visible sympathetic activity as a social signal in *Anolis carolinensis*: changes in aggression and plasma catecholamines. Horm. Behav. 38, 193–199.

Korzan, W.J., Summers, T.R., Summers, C.H., 2002. Manipulation of visual sympathetic sign stimulus modifies social status and plasma catecholamines. Gen. Comp. Endocrinol. 128, 153–161.

Korzan, W.J., Øverli, Ø., Forster, G.L., Watt, M.J., Höglund, E., Summers, C.H., 2004. Predicting social dominance. Comp. Biochem. Physiol. 137, S27 (Ref Type: Abstract).

Kotrschal, K., Hirschenhauser, K., Möstl, E., 1998. The relationship between social stress and dominance is seasonal in greylag geese. Anim. Behav. 55, 171–176.

Kruk, M.R., 1991. Ethology and pharmacology of hypothalamic aggression in the rat. Neurosci. Biobehav. Rev. 15, 527–538.

Kruk, M.R., Westphal, K.G., van Erp, A.M., van Asperen, J., Cave, B.J., Slater, E., de Koning, J., Haller, J., 1998. The hypothalamus: cross-roads of endocrine and behavioural regulation in grooming and aggression. Neurosci. Biobehav. Rev. 23, 163–177.

Kruk, M.R., Halász, J., Meelis, W., Haller, J., 2004. Fast positive feedback between the adrenocortical stress response and a brain mechanism involved in aggressive behavior. Behav. Neurosci. 118, 1062–1070.

Kuroda, Y., Watanabe, Y., Albeck, D.S., Hastings, N.B., McEwen, B.S., 1994. Effects of adrenalectomy and type I or type II glucocorticoid receptor activation on 5-HT_{1A} and 5-HT_2 receptor binding and 5-HT transporter mRNA expression in rat brain. Brain Res. 648, 157–161.

Larson, E.T., Summers, C.H., 2001. Serotonin reverses dominant social status. Behav. Brain Res. 121, 95–102.

Lay, D.C., Wilson, M.E., 2002. Development of the chicken as a model for prenatal stress. J. Anim. Sci. 80, 1954–1961.

Le Corre, S., Sharp, T., Young, A.H., Harrison, P.J., 1997. Increase of 5-HT_7 (serotonin-7) and 5-HT_{1A} (serotonin-1A) receptor mRNA expression in rat hippocampus after adrenalectomy. Psychopharmacology (Berl) 130, 368–374.

Lepage, O., Vilchez, I.M., Pottinger, T.G., Winberg, S., 2003. Time-course of the effect of dietary L-tryptophan on plasma cortisol levels in rainbow trout *Oncorhynchus mykiss*. J. Exp. Biol. 206, 3589–3599.

Lesch, K.P., Merschdorf, U., 2000. Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. Behav. Sci. Law 18, 581–604.

Lewis, D.A., Sherman, B.M., 1984. Serotonergic stimulation of adrenocorticotropin secretion in man. J. Clin. Endocrinol. Metab 58, 458–462.

Lightman, S.L., Windle, R.J., Julian, M.D., Harbuz, M.S., Shanks, N., Wood, S. A., Kershaw, Y.M., Ingram, C.D., 2000. Significance of pulsatility in the HPA axis. Novartis Found. Symp. 227, 244–257.

Lightman, S.L., Windle, R.J., Ma, X.M., Harbuz, M.S., Shanks, N.M., Julian, M.D., Wood, S.A., Kershaw, Y.M., Ingram, C.D., 2002. Hypothalamic-pituitary-adrenal function. Arch. Physiol. Biochem. 110, 90–93.

Liposits, Z., Phelix, C., Paull, W.K., 1987. Synaptic interaction of serotonergic axons and corticotropin releasing factor (CRF) synthesizing neurons in the hypothalamic paraventricular nucleus of the rat. A light and electron microscopic immunocytochemical study. Histochemistry 86, 541–549.

Luine, V.N., Spencer, R.L., McEwen, B.S., 1993. Effects of chronic corticosterone ingestion on spatial memory performance and hippocampal serotonergic function. Brain Res. 616, 65–70.

Marcucci, F., Giacalone, E., 1969. *N*-acetyl aspartic, aspartic and glutamic acid brain levels in aggressive mice. Biochem. Pharmacol. 18, 691–692.

Martinez, M., Calvo-Torrent, A., Herbert, J., 2002. Mapping brain response to social stress in rodents with c-*fos* expression: a review. Stress 5, 3–13.

Matter, J.M., Ronan, P.J., Summers, C.H., 1998. Central monoamines in free-ranging lizards: differences associated with social roles and territoriality. Brain Behav. Evol. 51, 23–32.

McEwen, B.S., de Kloet, E.R., Rostene, W., 1986. Adrenal steroid receptors and actions in the nervous system. Physiol. Rev. 66, 1121–1188.

Meddle, S.L., Romero, L.M., Astheimer, L.B., Buttemer, W.A., Moore, I. T., Wingfield, J.C., 2002. Steroid hormone interrelationships with territorial aggression in an Arctic-breeding songbird, Gambel's white-crowned sparrow, *Zonotrichia leucophrys gambelii*. Horm. Behav. 42, 212–221.

Meddle, S.L., Owen-Ashley, N.T., Richardson, M.I., Wingfield, J.C., 2003. Modulation of the hypothalamic-pituitary-adrenal axis of an Arctic-breeding polygynandrous songbird, the Smith's longspur, *Calcarius pictus*. Proc. Biol. Sci. 270, 1849–1856.

Melloni, R.H., Connor, D.F., Hang, P.T., Harrison, R.J., Ferris, C.F., 1997. Anabolic-androgenic steroid exposure during adolescence and aggressive behavior in golden hamsters. Physiol. Behav. 61, 359–364.

Mendelson, S.D., McEwen, B.S., 1991. Autoradiographic analyses of the effects of restraint-induced stress on 5-HT_{1A}, 5-HT_{1C} and 5-HT_2 receptors in the dorsal hippocampus of male and female rats. Neuroendocrinology 54, 454–461.

Mendelson, S.D., McEwen, B.S., 1992a. Autoradiographic analyses of the effects of adrenalectomy and corticosterone on 5-HT_{1A} and 5-HT_{1B} in receptors in the dorsal hippocampus and cortex of the rat. Neuroendocrinology 55, 444–450.

Mendelson, S.D., McEwen, B.S., 1992b. Quantitative autoradiographic analyses of the time course and reversibility of corticosterone-induced decreases in binding at 5-HT_{1A} receptors in rat forebrain. Neuroendocrinology 56, 881–888.

Meyer, W.N., Keifer, J., Korzan, W.J., Summers, C.H., 2004. Social stress and corticosterone regionally upregulate limbic *N*-methyl-D-aspartate receptor (NR) subunit type NR_{2A} and NR_{2B} in the lizard *Anolis carolinensis*. Neuroscience 128, 675–684.

Miczek, K.A., Tidey, J.W., 1989. Amphetamines: aggressive and social behavior. NIDA Res. Monogr. 94, 68–100.

Miczek, K.A., Weerts, E.M., DeBold, J.F., 1993. Alcohol, benzodiazepine-$GABA_A$ receptor complex and aggression: ethological analysis of individual differences in rodents and primates. J. Stud. Alcohol, Suppl. 11, 170–179.

Miczek, K.A., DeBold, J.F., van Erp, A.M., 1994a. Neuropharmacological characteristics of individual differences in alcohol effects on aggression in rodents and primates. Behav. Pharmacol. 5, 407–421.

Miczek, K.A., Weerts, E., Haney, M., Tidey, J., 1994b. Neurobiological mechanisms controlling aggression: preclinical developments for pharmacotherapeutic interventions. Neurosci. Biobehav. Rev. 18, 97–110.

Miczek, K.A., Maxson, S.C., Fish, E.W., Faccidomo, S., 2001. Aggressive behavioral phenotypes in mice. Behav. Brain Res. 125, 167–181.

Miczek, K.A., Fish, E.W., De Bold, J.F., De Almeida, R.M., 2002. Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and gamma-aminobutyric acid systems. Psychopharmacology (Berl) 163, 434–458.

Miczek, K.A., Covington III, H.E., Nikulina Jr., E.M., Hammer, R.P., 2004. Aggression and defeat: persistent effects on cocaine self-administration and gene expression in peptidergic and aminergic mesocorticolimbic circuits. Neurosci. Biobehav. Rev. 27, 787–802.

Mikics, E., Kruk, M.R., Haller, J., 2004. Genomic and non-genomic effects of glucocorticoids on aggressive behavior in male rats. Psychoneuroendocrinology 29, 618–635.

Millard, S.A., Gal, E.M., 1971. The contribution of 5-hydroxyindolepyruvic acid to cerebral 5-hydroxyindole metabolism. Int. J. Neurosci. 1, 211–218.

Millard, S.A., Costa, E., Gal, E.M., 1972. On the control of brain serotonin turnover rate by end product inhibition. Brain Res. 40, 545–551.

Moore, M.C., 1987. Circulating steroid hormones during rapid aggressive responses of territorial male mountain spiny lizards, *Sceloporus jarrovi*. Horm. Behav. 21, 511–521.

Moreira, P.S., Pulman, K.G., Pottinger, T.G., 2004. Extinction of a conditioned response in rainbow trout selected for high or low responsiveness to stress. Horm. Behav. 46, 450–457.

Munro, A.D., Pitcher, T.J., 1985. Steroid hormones and agonistic behavior in a cichlid teleost, *Aequidens pulcher*. Horm. Behav. 19, 353–371.

Neckers, L., Sze, P.Y., 1975. Regulation of 5-hydroxytryptamine metabolism in mouse brain by adrenal glucocorticoids. Brain Res. 93, 123–132.

Nelson, R.J., Chiavegatto, S., 2001. Molecular basis of aggression. Trends Neurosci. 24, 713–719.

Nephew, B.C., Romero, L.M., 2003. Behavioral, physiological, and endocrine responses of starlings to acute increases in density. Horm. Behav. 44, 222–232.

Nephew, B.C., Aaron, R.S., Romero, L.M., 2005. Effects of arginine vasotocin (AVT) on the behavioral, cardiovascular, and corticosterone responses of starlings (*Sturnus vulgaris*) to crowding. Horm. Behav. 47, 280–289.

O'Keane, V., Dinan, T.G., 1991. Prolactin and cortisol responses to D-fenfluramine in major depression: evidence for diminished responsivity of central serotonergic function. Am. J. Psychiatry 148, 1009–1015.

Orchinik, M., Murray, T.F., Moore, F.L., 1991. A corticosteroid receptor in neuronal membranes. Science 252, 1848–1851.

Orchinik, M., Murray, T.F., Franklin, P.H., Moore, F.L., 1992. Guanyl nucleotides modulate binding to steroid receptors in neuronal membranes. Proc. Natl. Acad. Sci. U. S. A. 89, 3830–3834.

Orchinik, M., Murray, T.F., Moore, F.L., 1994a. Steroid modulation of $GABA_A$ receptors in an amphibian brain. Brain Res. 646, 258–266.

Orchinik, M., Weiland, N.G., McEwen, B.S., 1994b. Adrenalectomy selectively regulates $GABA_A$ receptor subunit expression in the hippocampus. Mol. Cell. Neurosci. 5, 451–458.

Orchinik, M., Weiland, N.G., McEwen, B.S., 1995. Chronic exposure to stress levels of corticosterone alters $GABA_A$ receptor subunit mRNA levels in rat hippocampus. Brain Res. Mol. Brain Res. 34, 29–37.

Orchinik, M., Carroll, S.S., Li, Y.H., McEwen, B.S., Weiland, N.G., 2001. Heterogeneity of hippocampal $GABA_A$ receptors: regulation by corticosterone. J. Neurosci. 21, 330–339.

Ossowska, G., Klenk-Majewska, B., Szymczyk, G., 1997. The effect of NMDA antagonists on footshock-induced fighting behavior in chronically stressed rats. J. Physiol. Pharmacol. 48, 127–135.

Øverli, Ø., Harris, C.A., Winberg, S., 1999. Short-term effects of fights for social dominance and the establishment of dominant–subordinate relationships on brain monoamines and cortisol in rainbow trout. Brain Behav. Evol. 54, 263–275.

Øverli, Ø., Pottinger, T.G., Carrick, T.R., Overli, E., Winberg, S., 2001. Brain monoaminergic activity in rainbow trout selected for high and low stress responsiveness. Brain Behav. Evol. 57, 214–224.

Øverli, Ø., Kotzian, S., Winberg, S., 2002a. Effects of cortisol on aggression and locomotor activity in rainbow trout. Horm. Behav. 42, 53–61.

Øverli, Ø., Pottinger, T.G., Carrick, T.R., Overli, E., Winberg, S., 2002b. Differences in behaviour between rainbow trout selected for high- and low-stress responsiveness. J. Exp. Biol. 205, 391–395.

Øverli, Ø., Korzan, W.J., Höglund, E., Winberg, S., Bollig, H., Watt, M.J., Forster, G.L., Barton, B.A., Øverli, E., Renner, K.J., Summers, C.H., 2004a. Stress coping style predicts aggression and social dominance in rainbow trout. Horm. Behav. 45, 235–241.

Øverli, Ø., Korzan, W.J., Larson, E.T., Winberg, S., Lepage, O., Pottinger, T.G., Renner, K.J., Summers, C.H., 2004b. Behavioral and neuroendocrine correlates of displaced aggression in trout. Horm. Behav. 45, 324–329.

Packer, C., Collins, D.A., Sindimwo, A., Goodall, J., 1995. Reproductive constraints on aggressive competition in female baboons. Nature 373, 60–63.

Piazza, P.V., Le Moal, M., 1997. Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. Brain Res. Brain Res. Rev. 25, 359–372.

Pottinger, T.G., Carrick, T.R., 1999. Modification of the plasma cortisol response to stress in rainbow trout by selective breeding. Gen. Comp. Endocrinol. 116, 122–132.

Pottinger, T.G., Carrick, T.R., 2001. Stress responsiveness affects dominant-subordinate relationships in rainbow trout. Horm. Behav. 40, 419–427.

Ramenofsky, M., 1985. Acute changes in plasma steroids and agonistic behavior in male Japanese quail. Gen. Comp. Endocrinol. 60, 116–128.

Reneerkens, J., Piersma, T., Ramenofsky, M.R., 2002. An experimental test of the relationship between temporal variability of feeding opportunities and baseline levels of corticosterone in a shorebird. J. Exp. Zool. 293, 81–88.

Ricci, L.A., Grimes, J.M., Melloni, R.H., 2004. Serotonin type 3 receptors modulate the aggression-stimulating effects of adolescent cocaine exposure in Syrian hamsters (*Mesocricetus auratus*). Behav. Neurosci. 118, 1097–1110.

Ricci, L.A., Grimes, J.M., Knyshevski, I., Melloni, R.H., 2005a. Repeated cocaine exposure during adolescence alters glutamic acid decarboxylase-65 (GAD_{65}) immunoreactivity in hamster brain: correlation with offensive aggression. Brain Res. 1035, 131–138.

Ricci, L.A., Knyshevski, I., Melloni Jr., R.H., 2005b. Serotonin type 3 receptors stimulate offensive aggression in Syrian hamsters. Behav. Brain Res. 156, 19–29.

Roeling, T.A., Veening, J.G., Kruk, M.R., Peters, J.P., Vermelis, M.E., Nieuwenhuys, R., 1994. Efferent connections of the hypothalamic "aggression area" in the rat. Neuroscience 59, 1001–1024.

Romero, L.M., Dean, S.C., Wingfield, J.C., 1998. Neurally active stress peptide inhibits territorial defense in wild birds. Horm. Behav. 34, 239–247.

Saito, Y., Tsuzuki, K., Yamada, N., Okado, H., Miwa, A., Goto, F., Ozawa, S., 2003. Transfer of NMDAR2 cDNAs increases endogenous NMDARl protein and induces expression of functional NMDA receptors in PC12 cells. Mol. Brain Res. 110, 159–168.

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21, 55–89.

Sarnyai, Z., Sibille, E.L., Pavlides, C., Fenster, R.J., McEwen, B.S., Toth, M., 2000. Impaired hippocampal-dependent learning and functional abnormalities in the hippocampus in mice lacking $serotonin_{1A}$ receptors. Proc. Natl. Acad. Sci. U. S. A. 97, 14731–14736.

Schuett, G.W., Grober, M.S., 2000. Post-fight levels of plasma lactate and corticosterone in male copperheads, *Agkistrodon contortrix* (Serpentes, Viperidae): differences between winners and losers. Physiol. Behav. 71, 335–341.

Schuurman, T., 1980. Hormonal correlates of agonistic behavior in adult male rats. Prog. Brain. Res. 53, 415–420.

Siegel, A., Roeling, T.A., Gregg, T.R., Kruk, M.R., 1999. Neuropharmacology of brain-stimulation-evoked aggression. Neurosci. Biobehav. Rev. 23, 359–389.

Silverin, B., 1993. Territorial aggressiveness and its relation to the endocrine system in the pied flycatcher. Gen. Comp. Endocrinol. 89, 206–213.

Silverin, B., Baillien, M., Balthazart, J., 2004. Territorial aggression, circulating levels of testosterone, and brain aromatase activity in free-living pied flycatchers. Horm. Behav. 45, 225–234.

Sloman, K.A., Armstrong, J.D., 2002. Physiological effects of dominance hierarchies: laboratory artefacts or natural phenomena. J. Fish Biol. 61, 1–23.

Sloman, K.A., Montpetit, C.J., Gilmour, K.M., 2002. Modulation of catecholamine release and cortisol secretion by social interactions in the rainbow trout, *Oncorhynchus mykiss*. Gen. Comp. Endocrinol. 127, 136–146.

Smith, L.C., John-Alder, H.B., 1999. Seasonal specificity of hormonal, behavioral, and coloration responses to within- and between-sex encounters in male lizards (*Sceloporus undulatus*). Horm. Behav. 36, 39–52.

Summers, C.H., 2002. Social interaction over time, implications for stress responsiveness. Integr. Comp. Biol. 42, 591–599.

Summers, C.H., Greenberg, N., 1994. Somatic correlates of adrenergic activity during aggression in the lizard, Anolis carolinensis. Horm. Behav. 28, 29–40.

Summers, C.H., Larson, E.T., Summers, T.R., Renner, K.J., Greenberg, N., 1998a. Regional and temporal separation of serotonergic activity mediating social stress. Neuroscience 87, 489–496.

Summers, C.H., Risty, G., Keane, G., Hoffman, C.S., Mahmoodian, M., Renner, K.J., 1998b. Synergistic effects of corticosterone and progesterone on 5-HT release in the amygdala of estrogen primed rats. Abstr. - Soc. Neurosci. 24, 1195.

Summers, C.H., Larson, E.T., Ronan, P.J., Hofmann, P.M., Emerson, A.J., Renner, K.J., 2000. Serotonergic responses to corticosterone and testosterone in the limbic system. Gen. Comp. Endocrinol. 117, 151–159.

Summers, C.H., Summers, T.R., Moore, M.C., Korzan, W.J., Woodley, S.K., Ronan, P.J., Höglund, E., Watt, M.J., Greenberg, N., 2003a. Temporal patterns of limbic monoamine and plasma corticosterone response during social stress. Neuroscience 116, 553–563.

Summers, T.R., Matter, J.M., McKay, J.M., Ronan, P.J., Larson, E.T., Renner, K. J., Summers, C.H., 2003b. Rapid glucocorticoid stimulation and GABAergic inhibition of hippocampal serotonergic response: in vivo dialysis in the lizard *Anolis curolinensis*. Horm. Behav. 43, 245–253.

Summers, C.H., Forster, G.L., Korzan, W.J., Watt, M.J., Larson, E.T., Overli, O., Hoglund, E., Ronan, P.J., Summers, T.R., Renner, K.J., Greenberg, N., 2005a. Dynamics and mechanics of social rank reversal. J. Comp. Physiol. A Neuroethol. Sens. Neural. Behav. Physiol. 191, 241–252.

Summers, C.H., Korzan, W.J., Lukkes, J.L., Øverli, O., Höglund, E., Watt, M.J., Larson, E.T., Forster, G.L., Ronan, P.J., Summers, T.R., Renner, K.J., Greenberg, N., 2005b. Does serotonin influence aggression? Comparing regional activity before and during social interaction. Physiol. Biochem. Zool. 78, 679–694.

Suzuki, K., Koizumi, N., Hirose, H., Hokao, R., Takemura, N., Motoyoshi, S., 1998. Model of emotional stress in rats. Lab. Anim. Sci. 48, 353–356.

Sze, P.Y., Neckers, L., Towle, A.C., 1976. Glucocorticoids as a regulatory factor for brain tryptophan hydroxylase. J. Neurochem. 26, 169–173.

Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., Tsien, J.Z., 1999. Genetic enhancement of learning and memory in mice. Nature 401, 63–69.

Taravosh-Lahn, K., Delville, Y., 2004. Aggressive behavior in female golden hamsters: development and the effect of repeated social stress. Horm. Behav. 46, 428–435.

Tardiff, K., 1992. The current state of psychiatry in the treatment of violent patients. Arch. Gen. Psychiatry 49, 493–499.

Thompson, C.W., Moore, M.C., 1992. Behavioral and hormonal correlates of alternative reproductive strategies in a polygynous lizard: tests of the relative plasticity and challenge hypotheses. Horm. Behav. 26, 568–585.

Tokarz, R.R., 1987. Effects of corticosterone treatment on male aggressive behavior in a lizard (*Anolis sagrei*). Horm. Behav. 21, 358–370.

Tsagarakis, S., Navarra, P., Rees, L.H., Besser, M., Grossman, A., Navara, P., 1989. Morphine directly modulates the release of stimulated corticotrophin-releasing factor-4 1 from rat hypothalamus in vitro [published erratum appears in Endocrinology 1989 Dec; 125(6):3095]. Endocrinology 124, 2330–2335.

Urban, J.H., Miller, M.A., Dorsa, D.M., 1991. Dexamet asone-induced suppression of vasopressin gene expression in the bed nucleus of stria terminalis and medial amygdala is mediated by changes in testosterone. Endocrinology 29, 109–116.

van Hierden, Y.M., Korte, S.M., Ruesink, E.W., van, C.G., Engel, B., Korte-Bouws, G.A., Koolhaas, J.M., Blokhuis, H.J., 2002. Adrenocortical reactivity and central serotonin and dopamine turnover in young chicks from a high low feather-pecking line of laying hens. Physiol. Behav. 75, 653–659.

Van Praag, H.M., 1996. Faulty cortisol/serotonin interplay. Psychopathological and biological characterisation of a new, hypothetical depression subtype (SeCA depression). Psychiatry Res. 65, 143–157.

Vaux, A., Ruggiero, M., 1983. Stressful life change and delinquent behavior. Am. J. Community Psychol. 11, 169–183.

Vekovischeva, O.Y., Aitta-Aho, T., Echenko, O., Kankaanpaa, A., Seppala, T., Honkanen, A., Sprengel, R., Korpi, E.R., 2004. Reduced aggression tin AMPA-type glutamate receptor GluR-A subunit-deficient mice. Genes Brain Behav. 3, 253–265.

Watt, M.J., Forster, G.L., Joss, J.M., 2003. Steroid correlates of territorial behavior in male jacky dragons, *Amphibolurus muricatus*. Brain Behav. Evol. 61, 184–194.

Watt, M.J., Forster, G.L., Feng, N., Renner, K.J., Summers, C.H., 2004. Behavioral state influences temporal patterns of limbic monoamine activity during social stress. Abstr. - Soc. Neurosci. 30, 426.9.

Watt, M.J., Korzan, W.J., Summers, C.H., Forster, G.L., 2005. Rapid systemic responses to restraint stress differ between winners and losers of social interactions. Horm. Behav. 47, 133.

Watters, J.J., Swank, M.W., Wilkinson, C.W., Dorsa, D.M., 1996a. Evidence for glucocorticoid regulation of the rat vasopressin VIA receptor gene. Peptides 17, 67–73.

Watters, J.J., Wilkinson, C.W., Dorsa, D.M., 1996b. Glucocorticoid regulation of vasopressin V_{1A} receptors in rat forebrain. Mol. Brain Res. 38, 276–284.

Watters, J.J., Poulin, P., Dorsa, D.M., 1998. Steroid hormone regulation of vasopressinergic neurotransmission in the central nervous system. Prog. Brain Res. 119, 247–261.

Weiland, N.G., Orchinik, M., Tanapat, P., 1997. Chronic corticosterone treatment induces parallel changes in *N*-methyl-D-aspartate receptor subunit messenger RNA levels and antagonist binding sites in the hippocampus. Neuroscience 78, 653–662.

Winberg, S., Lepage, O., 1998. Elevation of brain 5-HT activity, POMC expression, and plasma cortisol in socially subordinate rainbow trout. Am. J. Physio1. 274, R645–R654.

Winberg, S., Nilsson, A., Hylland, P., Soderstom, V., Nilsson, G.E., 1997. Serotonin as a regulator of hypothalamic-pituitary-interrenal activity in teleost fish. Neurosci. Lett. 230, 113–116.

Winslow, J.T., Hastings, N., Carter, C.S., Harbaugh, C.R., Insel, T.R., 1993. A role for central vasopressin in pair bonding in monogamous prairie voles. Nature 365, 545–548.

Wommack, J.C., Taravosh-Lahn, K., David, J.T., Delville, Y., 2003. Repeated exposure to social stress alters the development of agonistic behavior in male golden hamsters. Horm. Behav. 43, 229–236.

Wommack, J.C., Salinas, A., Melloni Jr., R.H., Delville, Y., 2004. Behavioural and neuroendocrine adaptations to repeated stress during puberty in male golden hamsters. J. Neuroendocrinol. 16, 767–775.

Woodley, S.K., Malt, K.S., Moore, M.C., 2000. Neuroendocrine responses in free-living female and male lizards after aggressive interactions. Physiol. Behav. 71, 373–381.

Yang, E.J., Wilczynski, W., 2003. Interaction effects of corticosterone and experience on aggressive behavior in the green anole lizard. Horm. Behav. 44, 281–292.

Yau, J.L., Noble, J., Widdowson, J., Seckl, J.R., 1997. Impact of adrenalectomy on 5-HT_6 and 5-HT_7 receptor gene expression in the rat hippocampus. Brain Res. Mol. Brain Res. 45, 182–186.

Yodyingyuad, U., de la Riva, C., Abbott, D.H., Herbert, J., Keverne, E.B., 1985. Relationship between dominance hierarchy, cerebrospinal fluid levels of amine transmitter metabolites (5-hydroxyindole acetic acid and homovanillic acid) and plasma cortisol in monkeys. Neuroscience 16, 851–858.