Trends in Endocrinology & Metabolism

Special Issue: Advanced Themes in Endocrinology

Review

Endocrine Regulations in Human–Dog Coexistence through Domestication

Takefumi Kikusui,[1,2,*] Miho Nagasawa,[1,2] Kensaku Nomoto,[1,2] Sayaka Kuse-Arata,[1,2] and Kazutaka Mogi[1,2]

Endocrine system regulation is important for the maintenance of homeostasis; it controls hormonal functions in complex physiology and behavior and adaptations to social environments. Evidence indicates that for more than 35 000 years, dogs (*Canis familiaris*) have been domesticated through living with humans. For example, they have acquired human-like social skills, such as eye gazing and pointing gestures. These unique behaviors are, at least partially, regulated by hormones and are thought to have been genetically altered throughout domestication. Glucocorticoids affect social tolerance, while oxytocin facilitates social coordination and familiarity between individuals. We review historical and recent literature to facilitate an understanding of the roles of glucocorticoid and oxytocin functions in the human–canine coexistence dynamic established during domestication.

Highlights

Endocrine regulation plays pivotal roles in maintaining individual homeostasis, functioning from ancient organisms.

Endocrine pathways have expanded their functions to maintain social relationships, such as mother–infant relationship, cooperation, and inner-group favoritism.

The human–canine relationship, which has formed an interspecies coexistence for more than 35 000 years, is one of the most interesting models analyzing the social function of endocrine systems.

During the domestication process, the glucocorticoid and oxytocin functions played fundamental roles in the connection between dogs and humans.

The Human–Canine Relationship and Hormones

The human-canine relationship is a unique model where different species cohabit within the same group. Their cohabitation is thought to have begun 35 000–40 000 years ago, making the canine the oldest domesticated animal. Currently, the domestic dog is the animal that lives closest to humans. This habitation in adjacent niches that strongly influence each other is thought to have resulted in genetic and hormone function changes in both species.

Hormone secretion is modulated by the environment. For example, environmental stress activates glucocorticoid (GC) secretion to adjust behavior in response to a stressor, such as a natural enemy, by increasing glucose metabolism [1]. Hormones also regulate internal developmental changes, such as those that occur during sexual maturation. Considering the likely phylogenetic ancestry, hormones can moderate life-event mode shifts, from female to male, from juvenile to adult, from stable nutrition to starvation, and from resting to fighting [2]. Thus, hormones play a critical role in an individual's adjustment to their social environment, as well as developmental changes in epigenetics and phenotypic shape, the body, and nervous system, when adapting to environmental changes. This adaptive system maintains homeostatic responses within changing ecological circumstances and adaptive niches [3].

A candidate for the mechanism underlying the human–canine relationship involves hormonal changes in both humans and dogs, and these changes are proposed to have facilitated the cohabitation of humans and canines. In this review, we have focused on two major hormones, GC and oxytocin (OXT), and their roles in the functional adaptations between humans and canines.

Social Signal–Hormone–Behavior Circuit

Hormones have pivotal functions in regulating social interactions (Table 1; [4,5]). Within individuals, some hormones act on the nervous system and modulate the perception of social signals and changes in social behavior. Hormones also modulate the expression of social signals, such as pheromones (olfactory), vocalization (auditory), and facial and body posture (visual). It is of note that the secretion of these hormones is, in turn, regulated by brain functions, such that the perception of social signals, social status, and the conduction of social behavior, changes hormone secretion. Thus, there is a hormone–behavior circuit within individuals (Figure 1). In the context of social interaction, there are interindividual circuits, where social signals and behaviors are exchanged. The exchanges of the signals and expression of the behavior, as mentioned above, is regulated by hormones. For example, in mother–infant interactions in mice, affiliative interactions by pups, such as suckling and

[1]School of Veterinary Medicine, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 2525201, Japan

[2]https://sites.google.com/carazabu.com/lab-kaizai/ホーム/research?authuser=0

*Correspondence: kikusui@azabu-u.ac.jp

Glucocorticoid (GC)	Refs	Oxytocin (OXT)	Refs
Social behavior			
Maternal/caring			
Infant odor recognition (human) Mothers with higher cortisol concentrations were more attracted to their own infant's body odor	[80]	Maternal behavior (rat) Maternal care increased OXT activity and OXT blockade decreased maternal care	[81,82]
Maternal behavior (rat) GC enhanced maternal behavior	[83]	Maternal behavior (mouse) OXT and OXT receptor null mouse impaired in maternal behavior	[84]
Maternal contact (baboon) Mothers with higher prepartum cortisol levels showed higher levels of infant-directed affiliative behaviors	[85]	Alloparental behavior (mouse) Virgin female displaying alloparental behavior showed OXT activation and OXT blockade decreased alloparental care	[34]
Maternal carrying (marmoset) GC-treated mothers often inspected their infants under noise stress	[86]	Parenting (human) Maternal OXT was related to the amount of affectionate parenting behaviors	[87]
Aggression/outer-group conflict			
Aggression (dog) Aggressive dogs showed higher plasma concentrations of GC than nonaggressive dogs	[26]	Out-breed aggression (mouse) Male mice showed robust aggression toward out-breed males and OXT null mice did not show this phenotype	[88]
Aggression (acute, rat) Acute GC treatments increase aggressive behavior in rats	[89]	Territorial aggression (vole) Oxytocin had profound effects on the aggression of male prairie voles toward conspecifics	[90]
Aggression (acute, mouse) Escalated aggressive behavior was correlated to plasma GC and inhibition of GC reduced aggressive behavior	[91]	Racial discrimination (human) OXT creates intergroup bias, motivates in-group favoritism and out-group derogation	[46,47]
Dominance (human) When GC was high in males, higher testosterone decreased dominance and motivated lower status	[92]	Intergroup conflict (chimpanzee) Both sexes had high urinary OXT levels immediately before and during intergroup conflict	[46,51]
Negative intrusiveness (human) GC levels predicted negative intrusiveness in human mothers	[93]	Aggression (dog) OXT showed less friendly first reaction to stranger when the owner was approaching	[94]
Affiliation/inner group favoritism			
Positive interaction (human) Male with high cortisol responses to the stressor showed high ratings of close interactions with their partner	[95]	Social affiliation (review) OXT correlated with affiliative behavior and OXT treatment increased it	[96]

Table 1. Social Functions of Glucocorticoid and Oxytocin

(Continued on next page)

Glucocorticoid (GC)	Refs	Oxytocin (OXT)	Refs
Affiliation (human) Affiliation stress (fear of rejection) increased GC	[97]	Bonding (human) Higher OXT correlated with mother's bonding to infants.	[98]
Bonding (voles) GC facilitated pair-bonding in male, but not female monogamous prairie voles	[99]	Bonding (dog) Gaze attachment from dogs stimulated OXT secretion in the owner and OXT treatment in dogs increased gaze attachment and OXT secretion in the owner	[36,37]
		Affiliation (rhesus monkey) Human-raised monkey showed low OXT and affiliative behavior	[100]
Social tolerance/anxiety			
Social fear (fox) Domesticated foxes showed reduction of fear and GC secretion	[22,23]	Social anxiety (human) OXT attenuated amygdala reactivity to fear in generalized social anxiety disorder	[101]
Social distress (mouse) Social separation in juvenile enhanced GC secretion and induced life-long anxiety	[29]	Social anxiety (human) OXT treatment improved positive evaluations of appearance and speech performance.	[102]
Fear retrieval (human) GC promoted the reinstatement of fear and fear-related amygdala activation	[103]	Social anxiety (rodents, review) OXT activity in the brain was associated with an anxiolytic and prosocial, socially competent phenotype	[104]
Fear memory (human) GC influenced prefrontal brain activation during fear conditioning	[105]		
Social anxiety (human, review) GC suppressed hippocampal activation and enhanced amygdala activity with higher emotion	[106]		
Social reward/reinforcing effects			
Rewards (rats) Rats preferred a GC solution to tap water, developing self-administration	[107]	Socially reinforced learning (rhesus monkey) OXT treatment enhanced socially reinforced learning	[52]
Aggression rewarding (mouse) Escalated aggressive behavior was correlated to plasma GC and inhibition of GC reduced aggressive behavior	[91,108]	Socially reinforced learning (humans) OXT reduced performance of learning rewards, but not losses, from happy faces	[91,108]
Reward circuits (human) Reward learning in men is impaired under high GC	[109]	Social reward (mouse) OXT acted in nucleus accumbens and formed social rewarding	[76]

Table 1. *Continued*

(Continued on next page)

Glucocorticoid (GC)	Refs	Oxytocin (OXT)	Refs
Reward dependency (human) Risk for dependence and for relapse after quitting was associated with deficient GC reactivity to stressors	[110]	Social learning (mouse) OXT gene null mouse showed impairments in social memory	[111]
Empathetic response			
Empathy score (human) Higher levels of empathy corresponding to lower aggression levels at moderate and high cortisol levels	[112]	Empathetic responsiveness OXT facilitated emotional empathy in men	[59,60],
Emotional contagion (human, mouse) Blockade of GC facilitated emotional contagion in mice and humans	[31]	Helping/prosocial behavior (human) OXT infusion increased charitable donations OXT treatment increased trust behavior	[39,40]
Maternal emotional contagion (human) Mothers with great sympathy in response to cries had higher GC	[113,114]	Consolation behavior (vole) OXT acted on cingulate cortex and facilitated consolation behavior to pair-mate	[48]
Empathy score (human) Empathetic males and systemic-type females had high GC	[115]	Emotional reading (human) OXT improved performance on Reading the Mind in the Eyes Test	[116]
Cooperation/coordination			
Parent–infant synchronicity (human) GC was related to low levels of mother–infant synchrony	[117]	Parent–infant synchronicity (human) OXT in parents was associated with child's social engagement, affect synchrony, and positive communicative sequences between parent and child	[63]
Prosocial behavior (human) Acute social stress engaged in substantially more prosocial behavior with increase of GC	[118,119]	Cooperation (human) OXT promoted autistic patients to respond to others and exhibit more appropriate coordinated behavior	[118,119]
Trust behavior (human) Significant negative correlation between social stress-induced GC elevation and General Trust Scale	[120]	Pointing follow (dog) OXT treatment increased the accuracy of following to the human pointing gesture	[73]
Cooperation (fish) GC mediated cleaner wrasse switch from cooperation to cheating and tactical deception	[121]	Trust behavior (human) OXT treatment increased trust behavior	[40]
Group formation (squirrel monkey) Formation of male groups was correlated to GC levels and dominance status	[122]	Group coordination (chimpanzee) High OXT was correlated to the group coordination for hunting and patrolling	[46,51,52]

Table 1. *Continued*

pup calls, stimulate the maternal OXT system, with the accompanying enhancement of parenting behavior toward their offspring [6]. Maternal behaviors such as grooming stimulate the OXT system in pups, and they, in turn, seek more contact with the parent [6].

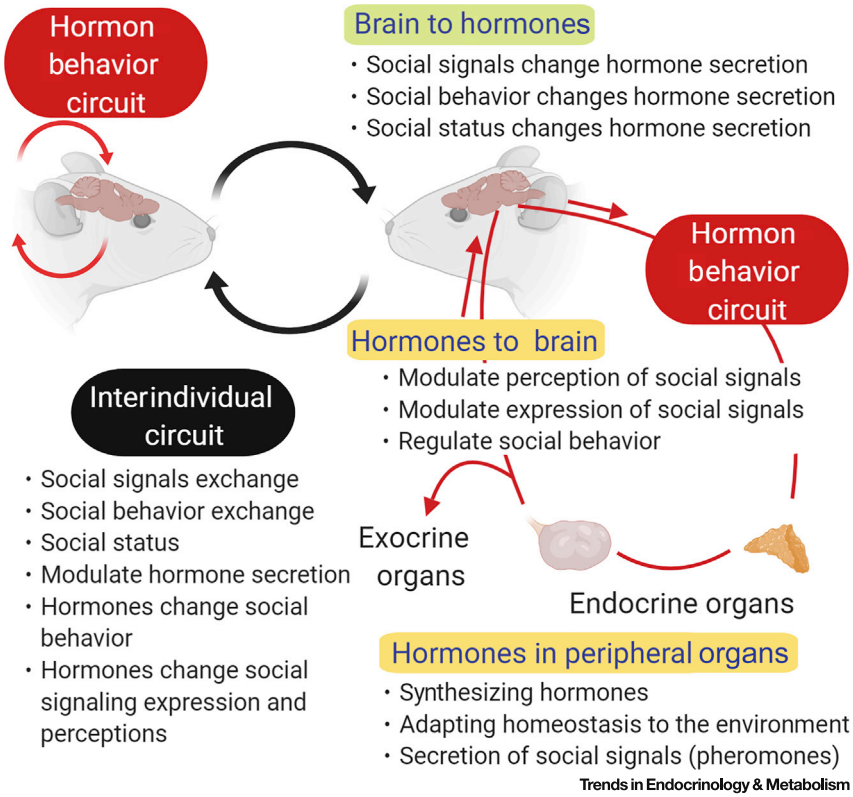

Figure 1. Social Signal–Hormone–Behavior Circuit.
Social behaviors are elicited by social signals, such as pheromones and vocal and visual signals. Interestingly, social signals are stimulated by hormones, such as glucocorticoid and oxytocin, and hormones can increase the sensitivity to and recognition of social signals. Hormones can also help induce specific social behaviors in individuals. We propose that hormones are the key regulators for individual interactions, especially with regard to sending and receiving social information and eliciting the appropriate social behaviors. This figure was created using BioRender (https://biorender.com/).

Similar hormone–behavior loops can be observed in female–male interactions and male–male aggression. Based on these findings, we hypothesize the existence of a social signal–hormone–behavior circuit (Figure 1). This interindividual circuit can be applied from dyads to larger groups in many types of social coordination that may involve conflict, including envy, and inequity aversion and cooperation. In the following paragraphs, we have briefly reviewed the social functions of GC and OXT and the social functions of these two hormones in human–canine interactions throughout domestication.

The Roles of GC in Social Signaling and Behavior

GC receptor (GR) systems in the brain regulate the negative aspects of social interactions. GRs are present in various brain regions, including the limbic system [7]. In the hippocampus, the GR acts to inhibit the hypothalamus–pituitary–adrenal (HPA) axis (negative feedback) and mitigates stress responses [7]. Prolonged social stress causes dysregulation of GR systems in the brain, as well as higher anxiety and depression-like symptoms [8,9]. In the hypothalamus, acute stimulation of GR can increase aggression toward an opponent [10].

Numerous previous studies have been conducted to reveal the relationship between social hierarchy and GC levels in group-living mammals. Low-ranking individuals in baboon troops experience greater stress from the threat of dominant individuals and thus have higher GC levels in their plasma

[11]. The increased levels of GC in subordinates suppresses reproductive behavior and aggression, making individuals less likely to challenge higher-ranking individuals, and fosters a stable hierarchy [12]. However, higher levels of GC in subordinate individuals are not observed in all social species. Among gray wolves (*Canis lupus*) in Yellowstone National Park, individuals of higher rank have higher levels of GC in their feces [13] and similar findings were reported for dwarf mongooses (*Helogale parvula*) [14] and African wild dogs (*Lycaon pictus*) [15]. In some of these species, there are high turnover rates of the highest-ranking individual in the social group, accompanied by constant threats from subordinates [12]. Creel demonstrated an interesting point: that the higher-ranked individuals had higher levels of basal GC in cooperative breeding species [14]. In cooperative species, it is proposed that some physiological costs might accompany the access to mates and resources that dominant individuals obtain [14]. Collectively, there is no clear, consistent explanation about the relationship between social rank and GC levels in group living animals; it depends on various social factors such as social rank, status, and breeding styles, as well as on individual differences.

The social function of GCs, such as social hierarchy and associated GC secretion, remains controversial. The physiological function of GC is to increase glucose (energy) metabolism for behavioral responses and this increase in glucose would be necessary for the social anxiety, aggression, and submissiveness responses of animals experiencing social stress and isolation [12]. Therefore, social vigilance leads to increases in GC, enhancing social anxiety and the fight–flight–freeze responses.

GC Response Changes in Domestication

The domestication of animals and plants by humans may be our most significant domination and utilization of nature [16]. Domestication involves the selection of traits that fundamentally alter wild species to make them more useful to humans. Usually, domesticated animals show weak survival ability [16]. For example, dogs have been selected for an ability to live and communicate with humans, while at the same time their fear and aggression toward humans has decreased [17]. Selection for tameness in domesticated animals often results in changes in development rates [18]. Developmental pathways in the embryonic period, such as neural crest cell development, are hypothesized to have triggered domestication and the unintentional emergence of domestication syndrome-related characters, such as piebald coat color and lop ears, reduced aggression/fear, and facilitation of reproduction (see Box 1) [19]. For many domesticated animals, nonseasonal breeding has replaced the seasonal breeding and gestation of their wild ancestors [20]. Charles Darwin was aware of these alterations in his writing on domestication in plants and animals [21].

A well-known example of domestication comes from studies of the silver fox (*Vulpes vulpes*) in Russia. There are well-documented reviews of the silver fox elsewhere [22,23], so we will only mention them here. Researchers in this experiment bred foxes that were not aggressive or fearful toward humans and were, in contrast, comfortable around humans. An unintended physical consequence was the appearance of piebald coat color and lop ears [22,23]. The domesticated foxes also displayed different endocrine development, especially in the GC system. They had reduced secretion of GC and exhibited greater exploratory behavior in, and behavioral and physiological tolerance to, new environments [22,23]. The exploratory and anxiety behaviors appeared to show negatively correlated effects and the GC changes can explain these changes.

Domesticated guinea pigs (*Cavia porcellus*) displayed less aggression and more socially tolerant behavior than their wild ancestor, the cavy [24]. At the same time, the activity of GC was distinctly reduced. Likewise, domesticated rats and some domesticated songbirds (passerines) also showed reduced GC levels [25]. It is likely that the wild ancestors of these species reacted to humans with high hormonal stress responses and fight–flight behaviors. In contrast, animals that live closely with humans need to mitigate these behaviors toward docility and tolerance but also reduce endocrine system responses. In domestic dogs, plasma GC levels were observed to be higher in those showing aggression toward family members than in nonaggressive dogs [26], suggesting that not only interspecific but also within-species comparisons and GC levels are associated with fight–flight behaviors.

Box 1. Concepts in Domestication and Socialization

Prosociality

Humans are highly prosocial animals and show various types of helping and affiliative behavior toward others; these behaviors can bring benefits to the recipients. In the field of comparative cognitive science, 'behaviors that benefit others' are regarded as prosocial behaviors. A similar term 'altruistic behavior' is defined as 'there is no immediate benefit to the conductor and only benefits to the other party'; strictly speaking, it is used only when the conducting behavior requires a cost. However, prosocial behavior is not necessary whether there is a cost or not. Therefore, prosocial behavior includes altruistic behavior. For example, allogrooming in rhesus monkeys is prosocial behavior, as it brings benefits to the recipients.

Mentalization

Mentalization, is referred to as 'holding mind in mind'. It is about paying attention to the mental state of oneself and others, thinking, examining, and feeling with the recognition of the mental state in mind. When we are paying attention to the emotions of ourselves and others, with or without being aware of our mental state, it is termed 'mentalization'. According to J.G. Allen and P. Fonagy *et al.* [123], the following mental statuses are the definitions of mentalizing: (i) to see ourselves from the outside and others from the inside; (ii) understanding misunderstanding; (iii) having mind in mind; and (iv) introspection for subjective self-construction: know yourself as others know you, but also know your subjective self (your experience).

Domestication Syndrome

Charles Darwin was aware of these alterations in his writing on the domestication in plants and animals and published a famous book '*The Variation of Animals and Plants under Domestication*' in January 1868. Variations in domesticated species confirmed his theory of the evolutionary origin of the species by natural selection, in contrast to the wild species. The domesticated species were genetically different from their original species through human selection. To date, the 'domestication syndrome', the variation of phenotypes in domesticated species, has been well documented. For example, common behavioral as well physiological changes are observed in domesticated animals. For example, depigmentation, floppy ears, reduced ears, shorter muzzles, smaller teeth, tameness, frequent reproductive cycle, and neotenous behavior.

Neural Crest Cell Hypothesis

As 'domestication syndromes' can be similar across different species, common mechanisms underlying domestication have been proposed. One hypothesis is the 'neural crest cell hypothesis'. Developmental pathways during the embryonic period, such as neural crest cell development, are hypothesized to have triggered domestication and the unintentional emergence of the domestication syndrome-related characters, such as piebald coat color and lop ears, reduced aggression/fear, and the facilitation of reproduction in domesticated animals. Neural crest is a vertebrate-specific structure that occurs in embryonic development. The neural crest cells released from this organ generate many cranial skeletons, melanocytes, ganglia, glial cells, and some hormone producing cells. Therefore, behavioral and physiological traits observed in domesticated animals can be explained as a direct consequence of the moderate changes in neural crest cells.

Under the pressures of domestication through time, alterations in the underlying genotypes were selected for [22,23].

Another important function of GC is the regulation of development. Maternal GC and GC in the early life stage affect cell and organ development, wherever GRs are found [27]. Peripheral embryonic precursors of melanocytes that control coat color were found to be correlated with GC levels in domesticated foxes [28]. In the brain, the hippocampus and prefrontal cortex have GRs and stimulation of them during development modulates lifelong social behavior, including social anxiety [29]. A decrease of GC in the developmental period may explain the phenotypic changes observed in several domesticated animal species.

We measured the basal levels of urinary cortisol in European dog breeds, wolves, and ancient dog breeds, which are genetically closer to wolves than the European breeds. The wolves were

hand-raised by professionals and well-habituated to humans. As expected, the wolves' cortisol was higher, compared with that of the dogs, and the ancient breeds showed higher cortisol compared with the European breeds (unpublished data). Wolves are fearful and not socially tolerant toward humans, but domestic dogs are very social toward humans [17]. These data suggest that, at the beginning of domestication, ancestral dogs that had lower GC and anxiety/fear responses to humans could approach human groups [17], that is, selection probably favored underlying genotypic variations in the ancestral population. GC regulation of social tolerance and nonfearful responses to humans may have been the most important turning point in the domestication of dogs [17].

Another important function of GC in the brain is increased neurogenesis in the hippocampus, which is related to increased learning and memory in domesticated foxes [30]. GC decreases social cognition and inhibits emotional contagion in mice and humans [31], suggesting that lower GC can enhance emotional interactions.

However, the suppression of GC secretion does not fully explain the behavioral changes in domesticated animals. Domesticated animals, especially dogs, need to understand and follow human verbal and nonverbal communication cues, and some species of domesticated animals show coordinated behavior in response to human commands [17]. Wheat *et al.* showed the expression of two dimensions of domestication-related behaviors, namely, stress and fearful reactions, and cooperation and playfulness, which were characterized into independent behaviors in modern dog breeds [32], suggesting that there are at least two biological mechanisms underlying the behavioral characteristics of domesticated animals. To achieve this change in phenotype and the underlying genotype, another hormone, OXT, comes to light in the evolutionary process of domestication.

OXT Roles in Social Signaling and Behavior

OXT, which was initially discovered as a maternal hormone acting in peripheral organs, also functions in the brain and regulates social behavior, anxiety, fear, and stress response [33]. Effects of anxiety reduction and inhibition of the HPA axis by OXT was demonstrated in rodents and humans and these effects were hypothesized to be related to social buffering [33]. If the subject is under stressful or anxious conditions, they will seek out bonded or affiliated partners. Being with partners increases OXT secretion and, in turn, reduces anxiety and stress response. OXT is secreted in the hypothalamus during parturition and plays a role in initiating maternal behavior in rodents [34]. In mouse pups, however, the OXT system in the brain enables attachment behavior, such as suckling and the emission of distress calls [35]. These biological functions of OXT were also observed in canines, macaques, and primates, including humans. The social function of OXT is therefore suggested to initiate and facilitate affiliations. In domesticated dogs, their affiliative interactions, such as sniffing, licking, and gentle touching, increased endogenous OXT secretions. In addition, intranasal OXT administration enhanced social contact and play behaviors [36]. Affiliations are not only intraspecies, nasal OXT administration to dogs can facilitate mutual gazing with the human owner [37], indicating that higher OXT is related to social affiliations between humans and canines. OXT is also correlated with allogrooming behavior toward troop members in several monkey species [38]. In humans, OXT enhances prosocial behaviors, such as charitable and trusting behaviors toward unfamiliar counterparts [39,40]. OXT moderates positive social interests and affiliations with the partner and decreases social distance in humans [41].

Interestingly, the agonistic effects of OXT were reported in different experimental contexts, in which the behavior toward the outgroup members was evaluated. For example, OXT exaggerates territorial and maternal aggression toward intruders in rodents [42]. In humans, OXT treatment increases social distancing toward strangers [43] and it enhances racial discrimination [44], suggesting that OXT acts to promote territorial defense. The actions of OXT that differ at first glance in social behavior, sometimes facilitating affiliations and sometimes enhancing agonistic behavior [44], may originate from the fundamental functions of OXT. As mentioned above, OXT is a hormone that ties family members [45]; in turn, it enhances aggression toward outside members to protect the family.

In groups or with family members, OXT acts to promote social coordination such as group hunting and in-group favoritism [46,47]. In the monogamous prairie vole (*Microtus ochrogaster*), selective aggression toward strangers to protect family members was regulated by OXT [45]. Consolation behavior toward a stressed partner was also accompanied by OXT activity in the anterior cingulate cortex in voles [48]. Human studies revealed similar functions; OXT enhances prosocial behavior and in-group favoritism (see Box 1) [47]. Activity in the OXT receptor gene and empathy-related brain activity correlated with racial in-group bias and enhanced ethnocentrism [46,47]. In research on wild animals, baseline secretions of OXT are related to some in-group behaviors. OXT in chimpanzees (*Pan troglodytes*) was secreted during social grooming, a behavior that is thought to be an indirect reciprocal behavior [49]. Not only has the association between basal secretion of OXT and social behavior been reported, but also the OXT response to social stimulation. Chimpanzees showed higher urinary OXT levels after a single food-sharing event compared with other types of social feeding and irrespective of previous social bond levels [50]. Urinary OXT levels in chimpanzees rise with the anticipation of intergroup conflict and participation in actual instances of conflict, but not during affiliative intragroup behaviors or with potential threats by rivals [46,51,52]. These observations from chimpanzees in the wild are comparable with those found in laboratory rodent models, strongly suggesting that these social functions of OXT have ancient roots in evolution. Taken together, these studies indicate that OXT regulation is key for the formation of a family-like social group, with close emotional bonds that include the protection of members from potentially dangerous outgroups and that OXT facilitates social recognition, cooperation, and competition in the defense of social resources against non-group members.

OXT Changes in Domestication

Decreases in GC levels can explain some aspects of human–dog coexistence, in that GC is associated with reduced social vigilance [17], but it does not fully support the social coordination found in human–dog interactions. In this sense, OXT appears to complement GC by enabling mostly positive social behavioral changes in domesticated animals, especially in dogs. However, few studies focus on the changes of OXT function in terms of canine domestication.

Darwin mentioned that humans have self-domesticated [53], in a sense, because of our self-awareness and capacity for conscious change [54]. It is hypothesized that changes in a wide range of cooperation and coordination were correlated with allomaternal care [55], which is modulated by the OXT system [34]. In humans, OXT receptors are abundant in the central nervous system, including the prefrontal cortex and orbitofrontal cortex [56], suggesting that OXT is related to higher brain functions regulated by the prefrontal cortex and orbitofrontal cortex. For example, manipulation of central OXT functions by nasal administration changes the prosociality [39], trust behavior to unknown people [40], and social norms [57]; furthermore, social coordination is facilitated by eye contact [58]. OXT treatment increases eye contact [59,60] and direct eye contact makes imitators respond faster than when the person they are imitating is looking away [61]. This effect is regulated by the medial prefrontal cortex [61]. In humans, eye contact enhances mentalization and facilitates joint attention (see Box 1) [61]. Eye contact plays an important part in the formation of emotional bonds [62], especially between parents and infants, with strong associations between the duration of infant–parent eye contact and the secretion of OXT [63].

Similar behavioral changes, such as the use of the eye gaze to exchange affiliative information and cooperation, have been observed in domesticated animals. An interesting point is that domesticated animals have acquired the use of eye gaze behaviors to communicate with humans, evidenced by goats and horses [64,65]. In wild species, such as monkeys and wolves [66], eye contact is used as a threatening signal [67]. Thus, the use of eye contact for affiliative and cooperative signal exchange is unique to domesticated animals. Especially in dogs, cooperation is important in hunting and guarding the human–dog cohabitats [68], which may also involve OXT functions. Dogs need to understand human social signals for successful performance of these tasks. In addition, dogs use eye contact for joint attention and problem solving [69]. These behaviors were not clearly observed in wolves, suggesting that genetic changes in the OXT system underlies these phenotypic behaviors. Compared

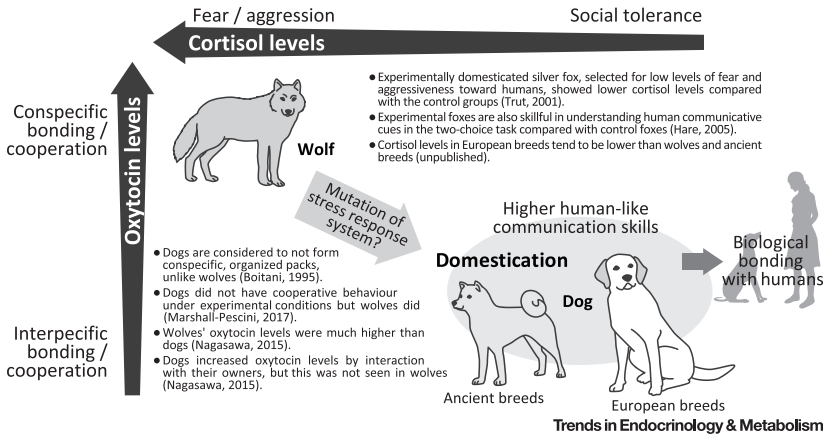

Figure 2. Role of Glucocorticoid (GC) and Oxytocin (OXT) on the Domestication and Coexistence of Dogs with Humans.

Wolves, the ancestors of domestic dogs, show higher baseline levels of GC and OXT, which are associated with higher social vigilance to humans and same species cooperation and coordination. In dogs, the decrease of GC secretion results in decreased social fear and anxiety and an increase in social tolerance toward humans, which supports the coexistence of dogs and human in the short term. OXT responses to the social signals of humans, such as eye contact, have been acquired in dogs and this OXT response can facilitate interspecies bonding and behavioral coordination for mutual benefits. (See [17,37].)

with those of wolves, the OXT receptor genes in dogs contained mutations [70] and these changes may be related to social coordination and eye contact behavior. In drug-detecting dogs, the OXT receptor genotype was related to the success rate of the dogs' training [71]. Similar results for OXT-related genetic variants and dog–human interactions were reported in dogs [72], implying that the OXT system in dogs is involved in coordinated behavior with humans. Supporting these findings, exogenous OXT applications to dogs improved their interpretation of directions to find hidden food [73]. Most likely, these effects are caused by the GC reduction and anxiolytic effects of OXT, which ameliorates tension and increases positive emotions [74]. Furthermore, gene polymorphisms in the OTR promoter region of dogs affect proximity-seeking toward an unfamiliar person, as well as the owner, and friendly behavior toward strangers [74].

Human–Canine Bonds and OXT

Humans often direct mutualistic or altruistic behaviors toward biological and nonbiological (or social) kin [75]. OXT is expected to both motivate and reward behaviors by activating certain regions of the brain and other organs [76]. This is an interesting phenomenon; the closed relationship can co-occur with OXT system activation even though there is no genetic relationship [37]. Humans even accept other species as though they were family members, providing defense, food, physical proximity, and shelter [77]. It is likely that such positive and affiliative relationships are accompanied by the activation of the brain OXT system. Nagasawa *et al*. discovered that dog owners showed increased OXT after a 30-minute interaction with their dogs [37]. In this experiment, eye contact from dogs to owners triggered the interactions and the duration of eye gaze was positively related to the increase of urinary OXT. Also, the owners showed an increase in caring behavior toward the dogs [78]. This affiliative contact from the owners to the dogs enhances OXT secretion in dogs, resulting in increased eye contact [37].

This OXT-mediated positive loop was not observed in wolves, suggesting that dogs have acquired this loop with humans during their domestication [37]. Interestingly, the baseline secretion of OXT in wolves was three times higher than that of dogs, suggesting that the baseline activity of the OXT system and OXT responses to social stimuli are not parallel in the two related species. While dogs have lower baseline OXT activity, they have acquired responses to social signals from humans.

Outstanding Questions

How can we conduct an empirical study to demonstrate the endocrine functions involved in domestication of dogs?

Is there a crosstalk between glucocorticoid and oxytocin regarding social behavior in domesticated animals?

How can we detect the genetic changes related to hormones involved in domestication?

Are there genetic impacts on human evolution by their coexistence with dogs?

The decline of basal activity can be related to interspecies bonding. With higher baseline OXT levels, wolves form a tight intragroup and intraspecies bond and they show well-organized social coordination with each other (intraspecies favoritism) [79], but they do not bond with humans. The two aspects of OXT system changes observed in the comparison of dogs and wolves need to be clarified in future studies. Moreover, GC and OXT affect each other, especially as OXT inhibits GC secretion; therefore, the interactions of these two hormones in the domestication process and the mutual relationships between humans and canines need to be elucidated in the future. It is also worthwhile to mention that the effects of GC and OXT on social behavior depend on social context and/or individuals. Therefore, detailed analysis of hormones and social behavior is crucial for further understanding (see Outstanding Questions).

Concluding Remarks and Future Perspectives

Higher social anxiety prohibits affiliations, behavioral coordination, and emotional interactions, both in inter- and intraspecies circumstances. As Hare and Tomasello proposed, the decreased functioning of the GC system in dogs is an underlying physiological mechanism for forming bonds and cooperative relationships between dogs and humans [17]. The functional changes in hormones through domestication are essential to both dogs and humans. This idea was first proposed as an example of convergent evolution between dogs and humans [17]. Humans have also been domesticated, at least partially, by their canine companions. For example, dogs may have helped human survival with hunting and night-time guarding, resulting in increased survival rates of humans despite the lack of the actual physical ability to survive in the wild. This can enhance the domestication of humans [68]. Recent genetic and archeological evidence suggests that human–canine coexistence has a prehistory of more than 35 000 years. Owing to the history of human–canine coexistence in some regions, it is possible that genetic changes have manifested in both species. Dogs have made humans human and humans have made dogs. The evidence supporting this hypothesis is too weak at present and future research in genetics, behavior, and archeology are required to provide more evidence for this hypothesis. The two hormones, GC and OXT, are key to understanding the neurobehavioral mechanisms underlying this long-standing mutualistic relationship (Figure 2).

Author Contributions

T.K., M.N., K.N., S.A., and K.M. were involved in the design and contributed to the write-up.

Acknowledgments

We thank all dogs, their owners, and laboratory members, especially Ms. S. Tomori and N. Hirayama who helped with the experiments. This study was supported in part by the Grant-in-Aid for Scientific Research on Innovative Areas (No. 4501, 4601, 25118007) from the Japan Society for the Promotion of Science, in Japan, and Japan Private University Branding Project (Azabu University).

References

1. Rabasa, C. and Dickson, S.L. (2016) Impact of stress on metabolism and energy balance. *Curr. Opin. Behav. Sci.* 9, 71–77
2. Ketterson, E.D. and Nolan, Jr. V. (1992) Hormones and life histories: an integrative approach. *Am. Nat.* 140, S3–S62
3. Taff, C.C. and Vitousek, M.N. (2016) Endocrine flexibility: optimizing phenotypes in a dynamic world? *Trends Ecol. Evol.* 31, 476–488
4. Adkins-Regan, E. (2005) Hormones and Animal Social Behavior (Princeton University Press)
5. Pfaff, D.W. (2002) Hormones, Brain and Behavior (Elsevier)
6. Nagasawa, M. *et al.* (2012) Oxytocin and mutual communication in mother-infant bonding. *Front. Hum. Neurosci.* 6, 31
7. Herman, J.P. *et al.* (2005) Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 29, 1201–1213
8. Pariante, C.M. and Miller, A.H. (2001) Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol. Psychiatry* 49, 391–404
9. Gregus, A. *et al.* (2005) Effect of repeated corticosterone injections and restraint stress on anxiety and depression-like behavior in male rats. *Behav. Brain Res.* 156, 105–114
10. Haller, J. (2014) The glucocorticoid/aggression relationship in animals and humans: an analysis sensitive to behavioral characteristics, glucocorticoid secretion patterns, and neural mechanisms. *Curr. Top. Behav. Neurosci.* 17, 73–109
11. Sapolsky, R.M. (1992) Neuroendocrinology of the Stress-Response (MIT Press), pp. 287–324

12. Sapolsky, R.M. (1992) Cortisol concentrations and the social significance of rank instability among wild baboons. *Psychoneuroendocrinology* 17, 701–709
13. Sands, J. and Creel, S. (2004) Social dominance, aggression and faecal glucocorticoid levels in a wild population of wolves, *Canis lupus*. *Anim. Behav.* 67, 387–396
14. Creel, S. (2001) Social dominance and stress hormones. *Trends Ecol. Evol.* 16, 491–497
15. Creel, S. (2005) Dominance, aggression, and glucocorticoid levels in social carnivores. *J. Mammal.* 86, 255–264
16. Kareiva, P. *et al.* (2007) Domesticated nature: shaping landscapes and ecosystems for human welfare. *Science* 316, 1866–1869
17. Hare, B. and Tomasello, M. (2005) Human-like social skills in dogs? *Trends Cogn. Sci.* 9, 439–444
18. Price, E.O. (1999) Behavioral development in animals undergoing domestication. *Appl. Anim. Behav. Sci.* 65, 245–271
19. Wilkins, A.S. *et al.* (2014) The "domestication syndrome" in mammals: a unified explanation based on neural crest cell behavior and genetics. *Genetics* 197, 795–808
20. Setchell, B.P. (1992) Domestication and reproduction. *Anim. Reprod. Sci.* 28, 195–202
21. Darwin, C. (2010) The Variation of Animals and Plants under Domestication (Cambridge University Press)
22. Trut, L. *et al.* (2009) Animal evolution during domestication: the domesticated fox as a model. *Bioessays* 31, 349–360
23. Trut, L.N. (1999) Early canid domestication: the farm-fox experiment: foxes bred for tamability in a 40-year experiment exhibit remarkable transformations that suggest an interplay between behavioral genetics and development. *Am. Sci.* 87, 160–169
24. Künzl, C. and Sachser, N. (1999) The behavioral endocrinology of domestication: a comparison between the domestic guinea pig (*Cavia apereaf. porcellus*) and its wild ancestor, the cavy (*Cavia aperea*). *Horm. Behav.* 35, 28–37
25. Suzuki, K. *et al.* (2012) Decreased fecal corticosterone levels due to domestication: a comparison between the white-backed munia (*Lonchura striata*) and its domesticated strain, the Bengalese finch (*Lonchura striata* var. *domestica*) with a suggestion for complex song evolution. *J. Exp. Zool. A Ecol. Genet. Physiol.* 317, 561–570
26. Rosado, B. *et al.* (2010) Blood concentrations of serotonin, cortisol and dehydroepiandrosterone in aggressive dogs. *Appl. Anim. Behav. Sci.* 123, 124–130
27. Fowden, A.L. *et al.* (2006) Intrauterine programming of physiological systems: causes and consequences. *Physiology* 21, 29–37
28. Oskina, I.N. *et al.* (2010) Role of glucocorticoids in coat depigmentation in animals selected for behavior. *Cytol. Genet.* 44, 286–293
29. Kikusui, T. *et al.* (2019) Early weaning increases anxiety via brain-derived neurotrophic factor signaling in the mouse prefrontal cortex. *Sci. Rep.* 9, 3991
30. Lindberg, J. *et al.* (2005) Selection for tameness has changed brain gene expression in silver foxes. *Curr. Biol.* 15, R915
31. Martin, L.J. *et al.* (2015) Reducing social stress elicits emotional contagion of pain in mouse and human strangers. *Curr. Biol.* 25, 326–332
32. Wheat, C.H. *et al.* (2019) Behavioural correlations of the domestication syndrome are decoupled in modern dog breeds. *Nat. Commun.* 10, 2422
33. Kikusui, T. *et al.* (2006) Social buffering: relief from stress and anxiety. *Philos. Trans. R Soc. Lond. B Biol. Sci.* 361, 2215–2228
34. Okabe, S. *et al.* (2017) Pup exposure facilitates retrieving behavior via the oxytocin neural system in female mice. *Psychoneuroendocrinology* 79, 20–30
35. Winslow, J.T. *et al.* (2000) Infant vocalization, adult aggression, and fear behavior of an oxytocin null mutant mouse. *Horm. Behav.* 37, 145–155
36. Romero, T. *et al.* (2014) Oxytocin promotes social bonding in dogs. *Proc. Natl. Acad. Sci. U S A* 111, 9085–9090
37. Nagasawa, M. *et al.* (2015) Social evolution. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. *Science* 348, 333–336
38. Ebitz, R.B. and Platt, M.M. (2014) An evolutionary perspective on the behavioral consequences of exogenous oxytocin application. *Front. Behav. Neurosci.* 7, 225
39. Barraza, J.A. *et al.* (2011) Oxytocin infusion increases charitable donations regardless of monetary resources. *Horm. Behav.* 60, 148–151
40. Kosfeld, M. *et al.* (2005) Oxytocin increases trust in humans. *Nature* 435, 673
41. Preckel, K. *et al.* (2014) Oxytocin facilitates social approach behavior in women. *Front. Behav. Neurosci.* 8, 191
42. Bosch, O.J. and Neumann, I.D. (2012) Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. *Horm. Behav.* 61, 293–303
43. Scheele, D. *et al.* (2012) Oxytocin modulates social distance between males and females. *J. Neurosci.* 32, 16074–16079
44. Bethlehem, R.A. *et al.* (2014) The oxytocin paradox. *Front. Behav. Neurosci.* 8, 48
45. Young, L.J. and Wang, Z. (2004) The neurobiology of pair bonding. *Nat. Neurosci.* 7, 1048–1054
46. Samuni, L. *et al.* (2018) Reward of labor coordination and hunting success in wild chimpanzees. *Commun. Biol.* 1, 138
47. De Dreu, C.K. *et al.* (2011) Oxytocin promotes human ethnocentrism. *Proc. Natl. Acad. Sci. U S A* 108, 1262–1266
48. Burkett, J.P. *et al.* (2016) Oxytocin-dependent consolation behavior in rodents. *Science* 351, 375–378
49. Crockford, C. *et al.* (2013) Urinary oxytocin and social bonding in related and unrelated wild chimpanzees. *Philos. Trans. R Soc. Lond. B Biol. Sci.* 280, 20122765
50. Wittig, R.M. *et al.* (2014) Food sharing is linked to urinary oxytocin levels and bonding in related and unrelated wild chimpanzees. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 281, 20133096
51. Samuni, L. *et al.* (2017) Oxytocin reactivity during intergroup conflict in wild chimpanzees. *Proc. Natl. Acad. Sci. U S A* 114, 268–273
52. Parr, L.A. (2014) Intranasal oxytocin enhances socially-reinforced learning in rhesus monkeys. *Front. Behav. Neurosci.* 8, https://doi.org/10.3389/fnbeh.2014.00278
53. Darwin, C. (1874) The Descent of Man, and Selection in Relation to Sex (John Murray)
54. Hare, B. *et al.* (2012) The self-domestication hypothesis: evolution of bonobo psychology is due to selection against aggression. *Anim. Behav.* 83, 573–585
55. Burkart, J.M. *et al.* (2014) The evolutionary origin of human hyper-cooperation. *Nat. Commun.* 5, 4747
56. Meyer-Lindenberg, A. *et al.* (2011) Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat. Rev. Neurosci.* 12, 524
57. Radke, S. and De Bruijn, E.R. (2012) The other side of the coin: oxytocin decreases the adherence to fairness norms. *Front. Hum. Neurosci.* 6, 193

58. Xu, S. *et al.* (2018) The effect of eye contact is contingent on visual awareness. *Front. Psychol.* 9, 93
59. Guastella, A.J. *et al.* (2010) Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol. Psychiatry* 67, 692–694
60. Hurlemann, R. *et al.* (2010) Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *J. Neurosci.* 30, 4999–5007
61. Cañigueral, R. and Hamilton, A.F.C. (2019) The role of eye gaze during natural social interactions in typical and autistic people. *Front. Psychol.* 10, 560
62. Farroni, T. *et al.* (2002) Eye contact detection in humans from birth. *Proc. Natl. Acad. Sci. U S A* 99, 9602–9605
63. Feldman, R. *et al.* (2011) Maternal and paternal plasma, salivary, and urinary oxytocin and parent–infant synchrony: considering stress and affiliation components of human bonding. *Dev. Sci.* 14, 752–761
64. Ringhofer, M. and Yamamoto, S. (2017) Domestic horses send signals to humans when they face with an unsolvable task. *Anim. Cogn.* 20, 397–405
65. Nawroth, C. *et al.* (2016) Goats display audience-dependent human-directed gazing behaviour in a problem-solving task. *Biol. Lett.* 12, 20160283
66. Fox, M.W. (1970) A comparative study of the development of facial expressions in canids; wolf, coyote and foxes. *Behaviour* 36, 49–73
67. Emery, N.J. (2000) The eyes have it: the neuroethology, function and evolution of social gaze. *Neurosci. Biobehav. Rev.* 24, 581–604
68. Serpell, J. (1995) The Domestic Dog: Its Evolution, Behaviour, and Interactions with People (Cambridge University Press)
69. Miklosi, A. *et al.* (2003) A simple reason for a big difference: wolves do not look back at humans, but dogs do. *Curr. Biol.* 13, 763–766
70. Tonoike, A. *et al.* (2016) The frequency variations of the oxytocin receptor gene polymorphisms among dog breeds. *J. Azabu Univ.* 27, 11–18
71. Konno, A. *et al.* (2018) Effect of canine oxytocin receptor gene polymorphism on the successful training of drug detection dogs. *J. Hered.* 109, 566–572
72. Kovács, K. *et al.* (2018) Dog-owner attachment is associated with oxytocin receptor gene polymorphisms in both parties. A comparative study on Austrian and Hungarian border collies. *Front. Psychol.* 9, 435
73. Oliva, J.L. *et al.* (2015) Oxytocin enhances the appropriate use of human social cues by the domestic dog (*Canis familiaris*) in an object choice task. *Anim. Cogn.* 18, 767–775
74. Kis, A. *et al.* (2015) Oxytocin induces positive expectations about ambivalent stimuli (cognitive bias) in dogs. *Horm. Behav.* 69, 1–7
75. Clutton-Brock, T. (2009) Cooperation between non-kin in animal societies. *Nature* 462, 51
76. Dölen, G. *et al.* (2013) Social reward requires coordinated activity of accumbens oxytocin and 5HT. *Nature* 501, 179–184
77. Rook, D. (2018) For the love of Darcie: recognising the human–companion animal relationship in housing law and policy. *Liverpool Law Rev.* 39, 29–46
78. Nagasawa, M. *et al.* (2009) Dog's gaze at its owner increases owner's urinary oxytocin during social interaction. *Horm. Behav.* 55, 434–441
79. Marshall-Pescini, S. *et al.* (2018) A task-experienced partner does not help dogs be as successful as wolves in a cooperative string-pulling task. *Sci. Rep.* 8, 16049
80. Fleming, A.S. *et al.* (1997) Cortisol, hedonics, and maternal responsiveness in human mothers. *Horm. Behav.* 32, 85–98
81. Fahrbach, S.E. *et al.* (1985) Possible role for endogenous oxytocin in estrogen-facilitated maternal behavior in rats. *Neuroendocrinology* 40, 526–532
82. Van Leengoed, E. *et al.* (1987) Inhibition of post-partum maternal behaviour in the rat by injecting an oxytocin antagonist into the cerebral ventricles. *J. Endocrinol.* 112, 275–282
83. Rees, S.L. *et al.* (2004) The effects of adrenalectomy and corticosterone replacement on maternal behavior in the postpartum rat. *Horm. Behav.* 46, 411–419
84. Takayanagi, Y. *et al.* (2005) Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. *Proc. Natl. Acad. Sci. U S A* 102, 16096
85. Bardi, M. *et al.* (2004) The role of the endocrine system in baboon maternal behavior. *Biol. Psychiatry* 55, 724–732
86. Saltzman, W. and Abbott, D.H. (2009) Effects of elevated circulating cortisol concentrations on maternal behavior in common marmoset monkeys (*Callithrix jacchus*). *Psychoneuroendocrinology* 34, 1222–1234
87. Gordon, I. *et al.* (2010) Oxytocin and the development of parenting in humans. *Biol. Psychiatry* 68, 377–382
88. Hattori, T. *et al.* (2015) Impairment of interstrain social recognition during territorial aggressive behavior in oxytocin receptor-null mice. *Neurosci. Res.* 90, 90–94
89. Mikics, É. *et al.* (2004) Genomic and non-genomic effects of glucocorticoids on aggressive behavior in male rats. *Psychoneuroendocrinology* 29, 618–635
90. Winslow, J.T. *et al.* (1993) Oxytocin and complex social behavior: species comparisons. *Psychopharmacol. Bull.* 29, 409–414
91. Fish, E.W. *et al.* (2005) Escalated aggression as a reward: corticosterone and GABA A receptor positive modulators in mice. *Psychopharmacology (Berl)* 182, 116–127
92. Mehta, P.H. and Josephs, R.A. (2010) Testosterone and cortisol jointly regulate dominance: evidence for a dual-hormone hypothesis. *Horm. Behav.* 58, 898–906
93. Mills-Koonce, W.R. *et al.* (2009) Psychophysiological correlates of parenting behavior in mothers of young children. *Dev. Psychobiol.* 51, 650–661
94. Hernádi, A. *et al.* (2015) Intranasally administered oxytocin affects how dogs (*Canis familiaris*) react to the threatening approach of their owner and an unfamiliar experimenter. *Behav. Processes* 119, 1–5
95. Berger, J. *et al.* (2016) Cortisol modulates men's affiliative responses to acute social stress. *Psychoneuroendocrinology* 63, 1–9
96. Bartz, J.A. and Hollander, E. (2006) The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior. *Horm. Behav.* 50, 518–528
97. Wirth, M.M. and Schultheiss, O.C. (2006) Effects of affiliation arousal (hope of closeness) and affiliation stress (fear of rejection) on progesterone and cortisol. *Horm. Behav.* 50, 786–795
98. Kendrick, K.M. (2000) Oxytocin, motherhood and bonding. *Exp. Physiol.* 85, 111S–124S
99. DeVries, A.C. *et al.* (1996) The effects of stress on social preferences are sexually dimorphic in prairie voles. *Proc. Natl. Acad. Sci. U S A* 93, 11980–11984
100. Winslow, J.T. *et al.* (2003) Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. *Neuropsychopharmacology* 28, 910–918

101. Labuschagne, I. *et al.* (2010) Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. *Neuropsychopharmacology* 35, 2403–2413
102. Guastella, A.J. *et al.* (2009) A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. *Psychoneuroendocrinology* 34, 917–923
103. Kinner, V.L. *et al.* (2018) Cortisol increases the return of fear by strengthening amygdala signaling in men. *Psychoneuroendocrinology* 91, 79–85
104. Neumann, I.D. and Slattery, D.A. (2016) Oxytocin in general anxiety and social fear: a translational approach. *Biol. Psychiatry* 79, 213–221
105. Stark, R. *et al.* (2006) Influence of the stress hormone cortisol on fear conditioning in humans: evidence for sex differences in the response of the prefrontal cortex. *Neuroimage* 32, 1290–1298
106. Erickson, K. *et al.* (2003) Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neurosci. Biobehav. Rev.* 27, 233–246
107. Deroche, V. *et al.* (1993) Rats orally self-administer corticosterone. *Brain Res.* 622, 315–320
108. Clark-Elford, R. *et al.* (2014) The effects of oxytocin on social reward learning in humans. *Int. J. Neuropsychopharmacol.* 17, 199–209
109. Kinner, V.L. *et al.* (2016) Cortisol alters reward processing in the human brain. *Horm. Behav.* 84, 75–83
110. Lovallo, W.R. (2006) Cortisol secretion patterns in addiction and addiction risk. *Int. J. Psychophysiol.* 59, 195–202
111. Ferguson, J.N. *et al.* (2000) Social amnesia in mice lacking the oxytocin gene. *Nat. Genet.* 25, 284–288
112. Pascual-Sagastizabal, E. *et al.* (2019) Testosterone and cortisol modulate the effects of empathy on aggression in children. *Psychoneuroendocrinology* 103, 118–124
113. Stallings, J. *et al.* (2001) The effects of infant cries and odors on sympathy, cortisol, and autonomic responses in new mothers and nonpostpartum women. *Parenting* 1, 71–100
114. Sethre-Hofstad, L. *et al.* (2002) Attunement of maternal and child adrenocortical response to child challenge. *Psychoneuroendocrinology* 27, 731–747
115. Nakayama, Y. *et al.* (2007) Sex differences in the relationship between cortisol levels and the empathy and systemizing quotients in humans. *Neuro Endocrinol. Lett.* 28, 445–448
116. Domes, G. *et al.* (2007) Oxytocin improves "mind-reading" in humans. *Biol. Psychiatry* 61, 731–733
117. Gordon, I. *et al.* (2010) Oxytocin, cortisol, and triadic family interactions. *Physiol Behav.* 101, 679–684
118. von Dawans, B. *et al.* (2012) The social dimension of stress reactivity: acute stress increases prosocial behavior in humans. *Psychol. Sci.* 23, 651
119. Andari, E. *et al.* (2010) Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proc. Natl. Acad. Sci. U S A* 107, 4389–4394
120. Takahashi, T. *et al.* (2005) Interpersonal trust and social stress-induced cortisol elevation. *Neuroreport* 16, 197–199
121. Soares, M.C. *et al.* (2014) Cortisol mediates cleaner wrasse switch from cooperation to cheating and tactical deception. *Horm. Behav.* 66, 346–350
122. Mendoza, S.P. *et al.* (1978) The physiological response to group formation in adult male squirrel monkeys. *Psychoneuroendocrinology* 3, 221–229
123. Allen J.G. and Fonagy P., eds. The Handbook of Mentalization-based Treatment. *John Wiley & Sons*, 2006.