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REVIEW

Neuropeptides as facilitators of domestication

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Abstract
Animal domestication was an important stage in the human history, which coincided with or probably even promoted the advent of a turning point at which part of the humankind switched from hunting and gathering to husbandry. The leading factor in evolutionary changes at the dawn of domestication was probably selection for behavior towards humans: first natural (as the animals were habituating to a new ecological niche close to humans), then nonconscious, artificial. Selection was supposed to work on the systems that regulate behavior by reducing stress response and aggression and by inducing an emotionally positive response to humans. A possible role of the neuropeptides adrenocorticotropic hormone (ACTH), oxytocin (OT), arginine vasopressin (AVP), and their receptors is in the reduction in stress response and in the shaping of domestic behavior. Effects of oxytocin on the behavior of domestic animals have been actively explored in the last 10 years, with special focus on the dog. The results obtained so far suggest that this neuropeptide is substantially important for human-canine interactions, together with sex, amount of aggression experienced, and other factors. The study of AVP demonstrated its importance in aggression in domestic animals. This work lends support to the hypothesis that a substantial factor in the shaping of domestic behavior and in the reduction in stress-response might be selection for an enhanced activity of the central OT system and a reduced activity of the central AVP system, which have effects on ACTH and social behavior.

Keywords Oxytocin · Arginine vasopressin · Adrenocorticotropic hormone · Domesticated animals · Behavior

Introduction

Human evolution is tightly linked to animal domestication. In the process of domestication, humans created a new environment for themselves, and that environment had a strong impact on every aspect of human life. Domesticated animals became an important source of food and hides, and among their other uses were transport and working. However, the dog—the first animal to have been domesticated and, therefore, the animal that tops any other domestic animal with its 15,000-year-long history—probably first appeared near hunters and was used for hunting (Guagnin et al. 2018; Freedman et al. 2014).

By far, the most important change that has ever occurred during animal domestication is tame behavior, which is not observed in the wild. Neuropeptides play an important role in the regulation of all classes of behavior, including aggressive behavior, affiliative behavior, and anxiety/fear. It is the change of these particular classes of behavior towards man that underlies tame behavior. Reduction in the reaction to stress appears to have been the most important stage of domestication. On their way towards tameness, animals stopped seeing man as a stressful agent, and it is possible that this was one of the mechanisms for decreasing aggression in domesticated animals towards man.

Domestication has been in the spotlight since Charles Darwin (Darwin 1868). However, the question as to what role neuropeptides have in domestication is not yet fully answered and is normally explored in relation to peripheral adrenocorticotropic hormone (ACTH) and, in the last 10 years, oxytocin (OT).

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Hypothalamic–pituitary–adrenal system, ACTH, and domestication

ACTH is an element of the hypothalamic–pituitary–adrenal (HPA) system, the activity of which is considered to be reduced in domesticated animals, which is reflected in reduced stress reactivity. However, the differences in corticosterone stress response between wild and domestic animals are included in the so-called domestication syndrome, which is essentially a list of traits observed in a large number domesticated animal species (Wilkins et al. 2014). However, direct comparisons of HPA activity between domesticated animals and their closest wild relatives are extremely limited and, as far as mammals are concerned, are mostly confined to pigs and guinea pigs; some avian exceptions are chicken and finch (Weiler et al. 1998; Künzl and Sachser 1999; Price 2002; Suzuki et al. 2014; Ericsson and Jensen 2016). The use of experimental domestication models developed through many years of selection first against aggression and then in favor of an increased emotionally positive response to humans in foxes and rats (tame foxes and tame gray rats) revealed an abrupt decrease in HPA axis variables (Plyusnina and Oskina 1997; Oskina et al. 2008; Trut et al. 2009). A decrease has been demonstrated for blood plasma ACTH and glucocorticoids, the width of the zona fasciculata, and the volumes of the nucleus and nucleolus of this zone (Plyusnina and Oskina 1997; Oskina et al. 2008; Trut et al. 2009). However, in the later stages of selection for tame and, conversely, aggressive behavior in rats, differences in corticosterone stress-response between these rat strains disappeared due to a reduction in this stress-response in aggressive gray rats (Prasolova et al. 2014; Herbeck et al. 2017a). By contrast, foxes still retain clear-cut differences in corticosterone response between tame, unselected, and aggressive individuals (Ovchinnikov et al. 2018).

It is rather difficult to be sure whether there is an association between stress and aggression towards man in modern dogs, because some dog breeds have been subjected to a secondary selection for aggressiveness and have been given a related training. Studies of German shepherd dogs differentiated experimental animals into fearful and aggressive groups, but showed no difference in saliva cortisol levels between them. However, a significant increase in cortisol levels after an aggression test with a human individual was observed only in the fearful group (Horváth et al. 2007), suggesting that aggression in the aggressive group is not associated with stress. Regrettably, there are no studies leading us to ultimately conclude that dogs have lower stress reactivity than wolves because of their different living conditions, and we therefore expect difficulty in laboratory experimentation. Living in captivity is by itself stressful for wolves. In this regard, it would be interesting to look at hybrids between a female dog and a male wolf: for such progeny, stressful maternal effects could not be a factor, but the genotype could. Regrettably, we are not aware of studies of this type.

The non-invasive technique now used in ecological studies for measuring corticosteroid metabolites in feces could be helpful in comparing ACTH activity between domesticated and wild animals in their natural habitats.

Studies of the hypophyseal expression of the *POMC* gene encoding a protein that is processed in the pituitary to form ACTH, β-endorphin and the melanocyte stimulating hormone, revealed lower mRNA levels in domesticated animals. This effect was demonstrated in foxes and chickens (Gulevich et al. 2004; Løtvedt et al. 2017). The importance of reduced ACTH on domestication is implied by the existence of two mechanisms found in the fox: not only downregulation of POMC expression, but also differences in pseudopodial formation implicated in the release of pituitary hormones (Hekman et al. 2018).

The reduced ACTH and glucocorticoid levels described could lead to reduction in the aggression and anxiety previously displayed to humans, both by experimental animals and by the ancestors of domesticated animals. However, it is not yet known how tame behavior—that is, a positive emotional bond between humans and domesticated animals, especially dogs—first came to the scene. One of the possible key mechanisms is a change of the central oxytocin system, which regulates both ACTH and social behavior (Neumann 2008; Neumann and Landgraf 2012).

It was confirmed by central administration of OT to animals (Windle et al. 2004) and intranasal administration to humans (Meinlschmidt and Heim 2007) that ACTH and glucocorticoid levels decreased in a manner depending on the level of OT administered. ACTH reduction takes place as corticotrophin-releasing hormone is reduced by OT (Jurek et al. 2015). Admittedly, earlier studies suggest that ACTH may be enhanced in response to CRH in the presence of OT in vitro (Gibbs et al. 1984). Along with its neuroendocrine effect on the HPA axis, OT produces a strong anxiolytic effect (Neumann and Landgraf 2012), which could also be an important factor for the ancestors of domesticated animals as they were becoming more and more familiar with a new ecological niche close to man.

The association between OT and ACTH in domesticated animals is poorly studied. Effects of OT on corticosteroids, which are the last in the production line operated by the HPA axis, have been explored somewhat better; however, data obtained are quite controversial. Intranasal administration of OT to neonatal pigs led to increased ACTH at a prepubescent age of 8 months (Rault et al. 2013). Administration of OT to neonatal rodents did not lead to any change in the HPA axis, but increased social behavior (Mogi et al. 2014). Adult tame gray rats used as an experimental domestication model did not show any change in corticosterone in response to stress following intranasal administration of OT for 5 days (Gulevich et al. under review). The use of the same administration schedule on gray rats that were, conversely, aggressive led to increased stressed-induced corticosterone levels (Gulevich et al. under review).

There are several interesting works on interactions between humans and dogs. During dog-owner interactions, blood oxytocin was reported to rise in both (Odendaal and Meintjes 2003; Rehn et al. 2014; Petersson et al. 2017). Blood levels of cortisol were decreased in the owners and were variously affected in the dogs: unaffected (Odendaal and Meintjes 2003; Mitsui et al. 2011), decreased (Rehn et al. 2014), or even increased (Handlin et al. 2011; Petersson et al. 2017). It was demonstrated in rodent experiments that an acute rise in oxytocin influences decreases only the stress-induced level of corticosteroids (Neumann 2008), and that is why the lack of changes in cortisol concentrations is not unexpected. Decreased blood levels of cortisol in the human and dog may not be associated with increased oxytocin or may be explained by some stress before the experiment, even though the experimenters did their best to keep it to a minimum (Rehn et al. 2014). The increase in cortisol levels in dogs (Petersson et al. 2017) following the increase in oxytocin levels is, on the one hand, consistent with early works by Gibbs et al. (1984); however, on the other hand, it may also have been induced by mild stress that appears during active prolonged interactions with the owner. Additionally, the amount of scratching and patting in that study correlated with cortisol levels (Petersson et al. 2017).

Nevertheless, the authors suggest that increased cortisol levels in that experiment were not associated with stress, for the dogs did not display stress-induced behavior. This is likely to be associated with a positive emotional excitement in anticipation of play, which has been demonstrated in dogs and in children (Flinn 2006; Horváth et al. 2008; Lewandowski et al. 2014).

Thus, most studies indicate that OT has an inhibitory effect on ACTH and stress; however, the number of studies addressing these relationships in domesticated animals is low and their results are contradictory in many respects; also, the statement that HPA activity is reduced in domesticated animals compared to their wild relatives is not sufficiently substantiated.

OT and domestication

OT and aggression Rodent studies revealed not only a relationship between oxytocin, ACTH and stress, but also down-regulation of aggressive behavior (Jurek and Newmann 2018). That was demonstrated, in particular, with male rats of the Groningen strain bred for 35 generations in captivity and showing rather a strong variation in intermale aggression (Calcagnoli et al. 2014). A negative correlation was found between aggressiveness and the amount of OT mRNA in the paraventricular nucleus (PVN) of the hypothalamus, and central administration of OT caused a dose-dependent decrease in aggression; the more aggressive the rats, the stronger the effect. Nevertheless, the amount of the OT receptor in the central amygdala and bed nucleus of the stria terminalis (BnST) was found to be positively correlated with aggressiveness. It is possible that a large amount of the OT receptor is what causes a more pronounced effect in more aggressive rats administered with OT into a ventricle (Calcagnoli et al. 2014). Female rats displayed basically the same effects of exogenous OT on the reduction in aggression not associated with maternal behavior; however, the factor 'genotype' was found, because OT administered to HAB rats noted for increased anxiety and aggression did not have any effect on these animals (de Jong et al. 2014). In Wistar rats, a correlation between aggressiveness and the amount of endogenous OT in PVN was found only in females (de Jong and Neumann 2017). This, however, may be associated not only with a sex-specific effect of OT, but also with the factor 'genotype', because Wistar rats show a weak variation in intermale aggression (de Boer et al. 2003). While exogenous oxytocin was found to suppress aggressive behavior in mice, they had increased aggressiveness following central administration of an OT receptor antagonist (Arakawa et al. 2015); however, data coming from animals with OT or its receptor knocked out are contradictory (for a review, see Jurek and Newmann 2018). In contrast to HAB rats (de Jong et al. 2014), aggressive gray rats had reduced aggressiveness following intranasal administration of OT for 5 days (Gulevich et al. under review). However, it should be noted that HAB rats are not just aggressive, they are too aggressive (Neumann et al. 2010).

It was quite a surprise that the tame gray rats used as the domestication model became more aggressive following intranasal administration of OT for 5 days (Gulevich et al. under review). Similar results were obtained from domesticated animals. A dog administered with OT intranasally may become less friendly in response to the owner's threatening behavior (Hernádi et al. 2015). Intranasal administration of OT to neonatal piglets led to increase in aggressive interactions under stressful conditions at an age of 17 days and 8 weeks (Rault et al. 2013). Heifers with high endogenous OT were observed to have increased numbers of both affiliative and aggressive interactions between them (Yayou et al. 2015). Enhanced aggression following central administration of OT was also observed in dominant males of the squirrel monkey (Winslow and Insel 1991a), and the chimpanzee had increased urine OT levels in inter-group conflicts (Samuni et al. 2017).

In dogs, no association has been found between basal levels of plasma oxytocin and levels of chronic aggression towards an unfamiliar dog or the aggressive response to a threatening human (MacLean et al. 2017). However, plasma levels of OT were found to be higher in a population of candidate assistance dogs than in a group of pet dogs (MacLean et al. 2017). The former group has for more than 40 years been under selection for friendliness and non-aggressive temperament. It is possible that OT level has had a role in the development of the friendly disposition the assistance dogs are known for; however, aggression displayed by some of them is associated with another system, the arginine vasopressinergic (AVP) system (MacLean et al. 2017). However, as MacLean et al. point out, the results of comparing two populations are in many ways preliminary and should be treated with caution, for the groups were not aligned by age, sex, and some other factors.

All the experiments cited report measuring peripheral concentrations of OT, which is a somewhat tricky measure of the activity of the OT system in the brain, because the release of OT into the blood (and then into the saliva or urine) is not always correlated with the local release of OT from axonal terminals in various parts of the brain (Knobloch et al. 2012; Grinevich et al. 2015, 2016).

Thus, the studies of the effects of OT on aggression provide contradictory results. Although results obtained from laboratory animals rather indicate reduction in aggression under the influence of OT, limited studies using domesticated animals, the gray rat as the domestication model, and apes indicate enhanced aggression under stressful conditions at high OT.

OT and affiliative behavior More unambiguous results come from those many studies on the role of oxytocin in affiliative behavior that have been conducted over the past 20 years on various diverse organisms (Ross and Young 2009; Bartz et al. 2011; Romero et al. 2014). This has relevance to rats' increased ability to discriminate between familiar and unfamiliar conspecifics following central administration of OT and decreased ability following administration of OT antagonists, which may have effects on the development of the social structure of the population and on the level of social aggression. The same effects were demonstrated for mice with the OT genes or OT receptor knocked out. Interestingly, the preference for non-social subjects was shown to remain unchanged (Ross and Young 2009; Song et al. 2016). However, OT may play a secondary role in memory and non-social learning (Jurek and Neumann 2018), and so, Rault et al. (2017) insist that the control in any experiment seeking to elucidate the role of OT in social behavior should be non-social. Some social behavior experiments with the monogamous prairie vole (*Microtus ochrogaster*) revealed an essential role of OT and OXTR in the preference to have a familiar sex partner, to make stable pairs, and to show an increased number of social contacts. It was therefore not surprising that a comparison between the brains of two vole species—the monogamous *prairie vole* (*Microtus ochrogaster*) and the polygamous mountain vole (*Microtus montanus*)—revealed a larger amount of the OT receptor in the monogamous species. However, affiliated behavior appears to be influenced by OT in a sex-specific manner, with a bias towards females (Ross and Young 2009). The chimpanzee that shared some food with a conspecific, no matter whether familiar or unfamiliar, was observed to have increased urinary OT. It was also demonstrated for the chimpanzee that OT promotes within-group cohesion during between-group conflicts (Wittig et al. 2014; Samuni et al. 2017). Some human experiments also suggest that administration of OT (normally sprayed in nasally) stimulates gazing, improves face perception, and potentiates the social emotional response (Bartz et al. 2011); however, other human studies suggest that placebo may cause social effects similar to those caused by oxytocin (Yan et al. 2018).

It has also been demonstrated that affiliative contacts (including sniffing, licking, gentle touching with the nose or paw, play bouts, and body contact) among dogs correlate with elevated endogenous OT in the urine, while intranasal administration of exogenous OT correlates with increased affiliative contacts. Additionally, oxytocin administration increased the frequency and duration of playful behavior in dogs (Romero et al. 2014, 2015). Playful behavior includes nipping, inhibited biting, play-chasing, mounting, play-fighting, and play-tackling. Nevertheless, the effect of intranasal administration of OT to piglets depended on their emotional state: affiliative contacts with conspecifics following administration of OT after a negative experience were increased and after a positive experience, decreased (Camerlink et al. 2016). As was mentioned above, increased endogenous plasma OT levels in heifers may be associated with affiliative as well as aggressive interactions (Yayou et al. 2015).

OT and domestic animal-human bonds Domesticated animals display affiliative behavior not only towards conspecifics, but also towards humans. The same is true of humans: they extend affiliative behavior that they display towards people to domesticated animals. It is possible that human empathy and affiliative behavior towards animals in other species arose long before animal domestication, because the chimpanzee was also observed to have empathy for other individuals in other species, humans, and baboons (O'Connell 1995; Phillips 2009). Additionally, the capacity to take care of young animals may have been the measure of the girls' future maternal care and may have been enhanced by sexual selection during anthropogenesis and given an evolutionary advantage in hunting due to acquiring the dog as a domestic animal (Bradshaw and Paul 2010). The past decade witnessed active research into finding associations between the activity of the central OT system in the modern dog and other domesticated species and their relationships with humans. Along with it, the response of the human OT system is being explored.

Some works show that human-canine contacts in the form of touching, initiating vocal cues, or even just gazing increase peripheral oxytocin both in the dog and man (Odendaal and Meintjes 2003; Rehn et al. 2014; Nagasawa et al. 2015). In the lambs, blood concentrations of OT were increased both by nursing and by making contact with humans. Moreover, in these lambs, the human presence caused an increase in the activity of OT neurons and several structures of the brain innervated by them (evidence from rat studies) and participating in the induction of emotions and social recognition (Nowak and Boivin 2015). The pig, with its one of the longest domestication history, was found to have increased OT concentrations in the spinal fluid following positive human interactions (Rault et al. 2017). This suggests an important role for oxytocin not only in affiliative intra-species bonding among rodents, apes, and humans, but also in contacts between domesticated animals and humans. Increased oxytocin levels were basically revealed when a dog was in contact with its owner rather than with an unfamiliar experimenter, suggesting that oxytocin in the dog participates only in the mechanisms of interaction with a familiar human. This is consistent with studies demonstrating a role of oxytocin not only in the reinforcement of intragroup affiliative behavior, but also probably in aggressive inter-group interactions (Samuni et al. 2017). Actually, this interpretation may turn out to be flawed, because all these studies used animals with established social relationships, living either in the house or in the farm side by side with experimenters for more than a year. This matter might probably be clarified by considering tame foxes that have minimum human contacts, but display a strong emotionally positive response to an unfamiliar experimenter (Trut et al. 2009).

Intranasal administration of oxytocin to dogs increases affiliative contacts between the dogs and behavior towards their owners: sniffing or licking their owners, the total amount of time dogs spent in close social proximity with their owners and gazing. Along with this, the owners showed a rise in urinary OT concentrations (Romero et al. 2014, 2015; Nagasawa et al. 2015, 2017). Gazing is an important social cue used by dogs in affiliative contacts with humans. The dingo is able to initiate gazing, although it is neither so frequent nor so lasting as in the domestic dog (Johnston et al. 2017). At the same time, tamed wolves do not seem to be able to initiate this communicative cue towards humans (Miklósi et al. 2003; Nagasawa et al. 2015). Apparently, the domestic dog's and dingo's ability to initiate gazing must be an important feature specific for human-canine bonding and acquired only in the course of domestication, an important mechanism of which could be increase in OT. It is a pity that no OT was measured in the dingo after gazing behavior, and the results provided by Nagasawa et al. (2015) (who suggest no increase in OT in the wolf) are widely criticized in the literature (Fiset and Plourde 2015; Kekecs et al. 2016).

An important feature that domesticated animals, especially dogs, possess and wild animals do not is the ability to accurately identify human guiding cues: puppies locate hidden food by looking where the human is looking or pointing to much more successfully than juvenile chimpanzees or juvenile wolves (Hare et al. 2012), and the pups of domesticated foxes perform better than those of wild foxes (Hare et al. 2005). It has been demonstrated that intranasal administration of OT improves the recognition of gestures that provide hints for locating hidden food (Oliva et al. 2015).

An interesting result came from an experiment in which the particular location of a dish depended upon whether the dish had some food in it or was empty: if the dish was placed between familiar objects, dogs administered with oxytocin tended to identify the dish as having food in it much more frequently. The effect was especially pronounced if there was an experimenter standing by the dish. It is possible that the effect of OT was due to inhibition of stress and anxiety within that particular social context (that is, making more eye contacts, perceiving verbal cues), which could ease tension and induce positive emotions (Kis et al. 2015).

Data shown above suggest that the OT system plays an important role in affiliative behavior displayed by domestic animals, especially dogs, towards humans and may be one of the most important mechanisms underlying fundamental change in animal behavior during domestication.

However, experiments with diverse dog breeds show the genotype specificity of the effects of oxytocin. Following intranasal administration of oxytocin, the border collie becomes able to make longer eye contact with an unfamiliar experimenter and the owner (Kovács et al. 2016b), which the Siberian Husky does not. These data may also be considered an argument in favor of a possible role of OT in positive or neutral interactions with unfamiliar people, not only with their owners. Additionally, it should be noted that the border collie is more human-oriented than the Siberian Husky (Kovács et al. 2016b). Additionally, the allele frequencies of the OT receptor are identical between the Siberian Husky and the wolf, but differ between them and the Border Collie (Kubinyi et al. 2017).

OT receptor polymorphism and domestic animal-human bonds In general, an association was found between *OXTR* and human-directed social behaviors. However, the details of the entire picture are that three single-nucleotide polymorphisms (SNPs) in the dog *OTXR* promoter are associated with the response towards humans. −213A/G is a SNP associated with the degree to which the dog is willing to interact both with a stranger and with the owner (dogs carrying the G allele are less willing to interact) (Kis et al. 2014). Two more SNPs, 19131A/G and rs8679684, are associated with the level of friendly behavior displayed by the dog in response to a stranger's passive or threatening behavior. However, in the German Shepherd and the Border Collie, the same alleles were associated with opposite types of behavior (Kis et al. 2014). Similar to the German Shepherd, the Golden Retrievers with the AA genotype of the SNP 19131AG have shorter latency to seek physical contact with their owner than GG individuals. Intranasal administration of OT increases contacts with the owner in AA dogs, but decreases in GG dogs (Persson et al. 2017). Other studies involving these and other *OXTR* SNPs also confirmed different effects on behavior, depending on the dog's breed (genotype) (Oláh et al. 2017;

Turcsán et al. 2017; Kovács et al. 2018). A relationship between OXTR SNPs with roughness was demonstrated in cats (Arahori et al. 2016). Additionally, it was demonstrated that these effects were also associated with *OXTR* SNPs and the owner's behavior (Kovács et al. 2018). However, no association was found in dogs between microsatellites at various distances from the OXTR gene and individual differences in the object-choice task (Oliva et al. 2016).

Differences in the frequencies of the SNPs −50C/G and rs8679682 were found between dogs and wolves (Bence et al. 2017). However, in the case of −50C/G, the C allele was more frequent not only in dogs than in wolves, but also in golden jackals compared to wolves. Curiously, rs8679682 was monomorphic for the C allele both in wolves and golden jackals, while in dogs (including the free-ranging Australian dingo and the Asian street pariah dog), the T allele was dominant (Bence et al. 2017). The effect of this SNP on the social behavior of the Border collie was demonstrated (Turcsán et al. 2017). Oliva et al. (2016) report on microsatellite markers close to *OXTR* that are significantly different between dogs and wolves. However, even so, these differences may be associated only with random differences between wolf populations that eventually gave rise to the modern wolves and modern dogs (Freedman et al. 2014). Persson et al. (2017) found no differences in the allele frequency of the SNP 19131AG between the Golden Retriever and the wolf, although this SNP was associated with the effect of endogenous and exogenous OT; however, the authors did not consider the exonic SNP rs8679682. By the way, the statement that *OXTR* is located in selective sweeps has yet to be confirmed (vonHoldt et al. 2010; Axelsson et al. 2013; Wang et al. 2013; Cagan and Blass 2016; Freedman et al. 2016; Marsden et al. 2016; Fam et al. 2018; Pendleton et al. 2018).

This implies that OT has a role in breed formation rather than in domestication. Nevertheless, differences in the promoter methylation of oxytocin receptor gene between male wolves and male Golden Retriever, as well as between the wolf and Siberian Husky in buccal samples (Banlaki et al. 2017). Another study (Cimarelli et al. 2017) found differences in the promoter methylation of oxytocin receptor gene in buccal samples in the wolf and border collie; additionally, the pattern of oxytocin receptor gene methylation was found to be associated with behavior in dogs when they were approached by a threatening human. However, these associations with behavior were sex-specific; additionally, available data on DNA methylation in buccal samples are only good for making discreet judgements of DNA methylation in the brain.

Effects of OT on domesticated animals depend on different factors While discussing data obtained from recent OT studies, we have to recognize some limitations that should be noted interpreting these data (Herbeck et al. 2017b; Rault et al. 2017). Increased OT levels in response to human contacts or increased contacts following administration of OT have mostly been recorded when the humans are owners, not unfamiliar experimenters (Rault 2016; Rault et al. 2017). Moreover, exogenous OT can reduce contacts with an unfamiliar experimenter (Persson et al. 2017) or induce aggression in response to threats from the owner (Hernádi et al. 2015), suggesting that OT becomes a part of interactions with a human provided that the human is familiar to the animal. However, this interpretation may be flawed, for all the works being overviewed used animals that had established social bonds, were living at home or animal farms and had for more than a year been in contact with people who stepped down as the experimenters. Apparently, the answer to this question could be found in the tame foxes that have little contact with humans, but show a strong emotionally positive response to unfamiliar experimenters (Trut et al. 2009).

Nevertheless, the fact that oxytocin responses to familiar and unfamiliar experimenters are different is consistent with the role shown for OT not only in the enhancement of within-group affiliative bonds, but probably also in between-group aggressive interactions (Samuni et al. 2017). Negative behavioral responses to unfamiliar humans are indicated by some human studies (Shamay-Tsoory et al. 2009; de Dreu et al. 2011). Even the research-inspiring fact that OT plays an important role only in monogamous but not polygamous voles lends support to the above assumption on different OT responses to familiar and unfamiliar experimenters. However, if this assumption is true, then OT should have mattered little early in domestication, in particular in the domestication of the dog, which may have probably been for long under proto-domestication, the process not only reinforcing social bonds, but destroying them. Free-living dogs are facultatively social. Feeding at dump sites does not require sociability and, moreover, rearing is completed much sooner in dogs than in wolves, probably suggesting that the activity of the OT system in mother-pup bonds is lower in dogs compared to wolves. Moreover, a comparison made by Nagasawa et al. (2015) between respective oxytocin values in the wolf and the dog (regrettably, individual data were provided only for the wolf) leads the conclusion that the basal OT level is higher in the wolf. Nevertheless, any individual level of endogenous OT does not seem to be directly associated with its effect on animal-human bonds. The experiments conducted by Romero et al. (2014) did not reveal significant correlation dogs' endogenous OT levels and affiliative behavior towards their owners or conspecifics; however, they revealed a negative association with the effect of exogenous OT on social proximity and a positive association with the affiliative behavior of the conspecific partner. Additionally, Petersson et al. (2017) reported that that dog owners with low oxytocin both before and during contacts touched their pets more frequently, while dogs with low endogenous OT received more stroking. On the other hand, the authors of an earlier work (Handlin et al. 2012) observed that dogs with the highest OT levels are kissed more frequently, the OT levels in the dogs correlating with those in their owners. An important point is sex-specific differences. Some works on domestic animals (dog, pig, cat) report stronger effects of the OT system, including OT receptor polymorphisms, on female than male behavior (Rault et al. 2013; Nagasawa et al. 2015, 2017; Oliva et al. 2015; Arahori et al. 2016; Kovács et al. 2016a; Turcsán et al. 2017), while others state that there are no gender differences (Romero et al. 2014; Persson et al. 2017). An opinion exists that the maternal behavior of domestic animals is not so good as that of their wild counterparts (Mignon-Grasteau et al. 2005). On the other hand, this does not apply to, for example, female pigs (Mignon-Grasteau et al. 2005). It is possible that the shaping of many types of social behavior is based—both evolutionarily and ontogenetically—on mother-infant bonding, with OT playing a key role in it (Decety et al. 2016). Consequently, affiliative behavior towards humans during domestication may be of similar origin, which probably explains sex-specific differences in OT effects across humans and rodents as well as dogs and other domestic animals. Charles Darwin (1872) noted: “A female terrier of mine lately had her puppies destroyed, and though at all times a very affectionate creature, I was much struck with the manner in which she then tried to satisfy her instinctive maternal love by expending it on me; and her desire to lick my hands rose to an insatiable passion. The same principle probably explains why dogs, when feeling affectionate, like rubbing against their masters and being rubbed or patted by them, for from the nursing of their puppies, contact with a beloved object has become firmly associated in their minds with the emotion of love.”

Thus, very little reliable information is available about the physiological and molecular differences of the OT system between wolves and dogs, let alone other domesticated animals and their wild relatives, suggesting its role in domestication. Nevertheless, some data, contradictory as they are, coming from experiments with domesticated animals suggest a key role for the OT system in domestication. The study of endogenous—at least peripheral—OT levels produces the most contradictory results and appears to hold the least promise for their comparative analysis between domestic animal and their wild relatives. However, an attempt to find out about differences in OT response to human contacts between domesticated dogs and socialized wolves (Nagasawa et al. 2015) appears intriguing. If it turns out the wolves have no such response, then it must be true that the mechanisms underlying affiliative behavior are multiple and, consequently, that social behavior of different animals had been evolving differently during domestication. On the other hand, the OT system is well known for its species-specific effects (Young 1999). This should be taken into account when comparing results of experimentation with, for example, dogs and pigs.

The most promising way to reach the answer is seen through making a neurobiological comparison of the OT system in the brain of domesticated and wild animals as well as studying the effect of exogenous OT on aggression and social behavior in domesticated animals, especially their wild relatives. Genetic studies say virtually nothing about differences in the OT gene or the OT receptor gene between domesticated and wild animals, but it may well turn out that there are no differences at the genetic level, but they can be revealed at others, from transcription factors and epigenetic marks to post-translation, or appear as modifications to the oxytocin signaling pathway.

AVP and domestication

Much less is known about the effects of AVP on domestic animals, as its interaction with ACTH in domestic animals has not been explored. However, it has been well demonstrated in model animals and humans that AVP stimulates the ACTH-response by acting directly via its receptors, V1a (AVPR1A) and V1b (AVPR1B), and plays an important role in the development of anxiety, depression, and aggression (Neumann and Landgraf 2012; Rotondo et al. 2016; Terranova et al. 2016). A limited number of works suggest a role for AVP in the formation of aggression in domestic animals aged 10–11 weeks. Experiments with pigs demonstrated a highly significant association between the *AVPR1B* SNP and aggressive behavior (Muráni et al. 2010). According to data on the Golden Retriever, separation-related behaviors are not associated with 42 SNPs within 500 kb of *AVPR1A* (van Rooy et al. 2016). Fam et al. (2018) published results suggesting that *AVPR1B* is under positive selection in the alpaca, guinea pig, chinchilla, and rabbit. In experiments with female pigs aged 8 weeks, aggressive animals were found to have more cells expressing *AVP* mRNA the medial amygdala, lateral septum (LS) and BnST, but not in PVN or in the supraoptic nucleus compared to non-aggressive animals (D'eath et al. 2005). A recent study by MacLean et al. (2017) is perhaps the first to have given experimental confirmation to the role of AVP in dogs’ aggressive behavior. It was demonstrated that pet dogs with chronic leash aggression towards conspecifics had higher total plasma AVP concentrations than did control dogs, no matter what breed or sex. Another experiment (MacLean et al. 2017) involved a population of candidate assistance dogs that had for more than 40 years been under selection for friendliness and non-aggressive temperament. In that population, individuals were identified with the most aggressive responses to a threatening stranger (MacLean et al. 2017). It was demonstrated that total plasma AVP concentrations were significantly higher in these dogs than in those that responded without aggression. However, no difference in plasma AVP was found between the population of candidate assistance dogs and a group of pet dogs (again, plasma OT levels were different). Apparently, AVP is an important mediator in dogs' aggressive responses; however, it is not so important at the time of secondary selection among dogs for friendly behavior as OT. At the same time, OT is not associated with aggression among dogs. It is possible that the balance between friendly and aggressive behavior lies in the ratio of OT- to AVP-ergic systems (Neumann and Landgraf 2012; MacLean et al. 2017). A comparison of hypothalamic *AVP* expression in the domestic chicken and its wild relative, however, showed higher values for the domestic chicken (Løtvedt et al. 2017).

A great body of rodent data suggests that AVP has an essential role in social behavior. In most experiments, administration of AVP to males in the parts of the brain called the anterior hypothalamus (AH) causes male aggression to increase, while administration of antagonists of its receptor V1a leads male aggression to decrease. As with OT, an essential role in AVP effects is with individual social experience: administration of AVP to the hypothalamus increases aggression in the hamsters that were housed individually, not as groups, and in the hamsters that had experienced encounters. It should be noted that testosterone promotes the synthesis of AVP, its binding to the receptor V1a and increased aggression following AVP administration (Delville et al. 1996). However, in Syrian hamsters, which follow a seasonal pattern of reproduction, AVP promotes increased aggression only within a long photoperiod, when the animals are sexually active (Caldwell and Albers 2004). As is known, the seasonal reproductive pattern is changed in most domesticated animals (Trut 1999), which leads to changes in the seasonal pattern of blood concentrations of testosterone (Osadchuk 1990; Haase 2000). Therefore, we can expect stronger AVP effects on aggression in domestic animals, and, therefore, yet another factor in selection against domestication. Nevertheless, data on the levels of sexual behavior and testosterone in wild and domestic animals are controversial. For example, domestic guinea pigs show higher basal levels of plasma testosterone and levels in courtship behavior than wild cavies, while no differences were found between wolves during the mating season and dogs kept in the same conditions (Haase 2000); tame foxes even showing decreased plasma testosterone concentrations (Osadchuk 1990).

At the same time, the AVP system has important roles in some other functions. For example, central administration of AVP to hamsters and squirrel monkeys increases the frequency of scent marking (Winslow and Insel 1991b). Oxytocin does not normally have this effect (Winslow and Insel 1991b; Albers and Bamshad 1999) or, as was demonstrated in mouse experiments, can even reduce scent marking (Arakawa et al. 2015). It should be noted that this behavior is more frequent in agonistic than non-agonistic contacts, both in rodents and in dogs (Cafazzo et al. 2012; Arakawa et al. 2015). However, AVP in rodents also plays a role in affiliative behavior, for it prolongs social recognition in mice and rats of both sexes (Albers 2012) and favors pair bonding in males of the monogamous prairie vole (Liu et al. 2001) and other social effects. Dominant male voles show a significantly higher level of AVP V1a receptor binding in the hypothalamus (Cooper et al. 2005), suggesting a role for AVP in developing hierarchical systems. However, cases are known where the effects of AVP were sex-dependent, as were those of OT. For example, AVP administration during early-life postnatal life enhances aggression in the male prairie vole, but not in females. Thus, if, during domestication, selection acts to weaken the central vasopressinergic system, it will be acting against not only anti-social effects that induce aggression, but also pro-social effects. It is possible that an enhancement of the activity of the oxytocinergic system could compensate in part or totally for this nuisance. Like the AVP system, this one plays an important role in social communication, social recognition, and pair bonding (see Ross and Young 2009). Additionally, recent studies in hamsters demonstrated that central administration of OT or AVP prolongs the time spent recognizing scent marks only due to binding with the OTR receptor rather than with V1a (Song et al. 2016). Studies in dogs demonstrated that the domestication process has remarkably changed social communication: dogs have developed no new cues unknown to wolves, but have changed the context of these cues (Bradshaw and Rooney 2017). Specific features of some domestic animals are probably reduced social bonding between conspecifics and promiscuity (Hale 1969; Coppinger and Coppinger 2002; Marshall-Pescini et al. 2017). Some researchers opine that the social structure of dogs has changed so much that the term 'dominance' does not apply to them anymore (Bradshaw et al. 2009). Reduction in social bonding is in many respects associated with habituation to a new ecological niche close to man and so living as packs becomes no longer vital. Unlike wolves, semi-wild dogs are facultatively social animals (Coppinger and Coppinger 2002). Recent comparative studies of behavior in wolves and dogs showed that a wolf performed better where a task required cooperation from two animals, ranks, and tight social bonds playing a key role (Marshall-Pescini et al. 2017). It appears likely that such sociobiological changes in the species under domestication might be associated with changes in the ratio between the OT- and AVP-ergic systems, which, according to Neumann and Landgraf (2012), may cause diverse effects on emotional and social behavior.

Conclusion

Selection for behavior towards humans, which is the main factor during domestication (Belyaev 1979), acted on a complex network of neuroendocrine, neurotransmitter, and neuropeptide systems regulating behavior. Modern studies have revealed crosstalk between social behavior, stress response systems, the central oxytocin system, and the vasopressinergic system in domesticated animals. It is possible that a reduction in stress response and aggression played an important role at the earliest stages of domestication and was largely due to the balance between OT and AVP, which, in turn, had effects on ACTH and aggressive behavior. Nevertheless, domesticated behavior, with its broad spectrum of emotionally positive responses to humans, can hardly be explained by a lack of stress and aggression. That is why selection for enhanced affiliative behavior regulated by the OT system may have been important at the next stage of domestication, which was essentially all about animal socialization. At present, experiments comparing domesticated animals and their wild relatives are regrettably scarce and still little is known about OT importance, even though the hypothesis of an important role of OT in the domestication mechanisms has been discussed for more than 10 years (Olmert 2009). It looks promising to explore the OT and AVP systems not only when comparing domesticated and aggressive animals, but also in experimental domestication models involving the silver fox and rodents, for they come from a single parental population, live in the same conditions, have not undergone secondary selection for economically valuable traits, and have not established social relationships with a particular person as the owner because of limited contacts (Trut et al. 2009). Administration of agonists and antagonists of OT and AVP and their receptors to domesticated animals and their non-domesticated relatives, followed by assessment of the stress response and the amount of change in behavior towards humans and conspecifics, as well as immunihistochemical and genetic comparisons, could probably shed light on how OT, AVP, and ACTH were interrelated during domestication.

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