Is dog domestication due to epigenetic modulation in brain?

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Abstract: Dogs (*Canis lupus familiaris*), derived from wolves (*Canis lupus*), are known as the first domesticated animal and dogs have been living in human environment for about 25.000 years. Today researchers tend to proclaim a self-domestication-process, but they are still figuring out, why and how this process started. During the Palaeolithic period, humans and wolves lived in similar structured family clans as cooperative hunters in the same ecological niche. Evolutionary continuity of mammalian brains enabled humans and wolves interspecific communication and social interaction which reduced stress and aggression during their frequently contacts as the first step of a natural domestication process. Domestication means decreased aggression and decreased flight distance concerning to humans. Therefore changes of the activity of the Hypothalamic-pituitary-adrenal (HPA) axis are suspected to be important during the domestication processes from wolf to dog. The hypothesis of Active Social Domestication (ASD) considers genetic selection as a necessary prediction but not a sufficient explanation of dog domestication. In addition dog domestication is suggested to be essentially an epigenetic based process that changes the interactions of the HPAaxis and the 5-Hydroxytryptamine (5-HT) system. The limbic brain regions such as hippocampus and amygdala play a key role in the mood control. They are sensitive to glucocorticoids and innerved by serotonergic projections. The HPAaxis and the 5-HT system are closely cross-regulated under physiological conditions. The activity of the HPAaxis is influenced thru an enhancement of the corpus amygdala and an inhibition thru the hippocampus. Hippocampal glucocorticoid receptor density (hGCR) is likely to affect its inhibitory effect on this system. Prosocial behaviour enhances epigenetically hGCR expression via increased serotonin and subsequently increased nerve growth factor levels binding on GRexon1;7promotorbloc inducing its demethylation and thus leading to decreased cortisol levels. Low cortisol levels increase social learning capability and promote the activity of the prefrontal cortex contributing to better executive function including better cognitive inhibition. Thus epigenetically decreased cortisol levels of less stressed human-associated wolf clans allowed them to extend their social skills to interactions with humans. Over time tame wolves could grow into domestic dogs able to emerge human directed behaviour.

Key Words: dog, wolf, domestication; stress-axis; epigenetics; coevolution.

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Today it is commonly accepted that dogs were domesticated as the first animal about 25.000 years ago (Thalman et al., 2013; Ovodov et al., 2011). But researchers are still figuring out, why and how this domestication process started. In the past it was common to follow the hypothesis founded by Lorenz (1967), who considered human hand reared wolf-pups as dog's ancestor. But even a hand reared wolf-pup taken during the first nine days of its live is as an adult wolf a potential risk for humans (Kubinyi et al., 2007) and it also needs a partner from the wild for reproduction. Therefore this hypothesis (Lorenz, 1967; Zimen, 1992) seemed rather unlikely and was dropped. Recent researchers tend to proclaim a self-domestication process. Coppinger (2001) argued, the waste dump was the place where dogs evolved. A population of wolves began to exploit the new ecological niche (Peterson et al., 2004) of scavenging human food remains and feces. Those wolves showed higher reproductive success and thus, from generation to generation they were selected to be more tolerant to humans as a kind of self-domestication

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process. But archaeologists proclaim, that waste dumps are a characteristic of modern times (Havilcek, 2015; Pichtel, 2005). In the Paleolithic period people used all material of their prey. Archaeologists only found Stone Age dumps with fragments from making stone tools (Havilcek, 2015; Rust, 1948). Nevertheless it is common sense that dog domestication began in the Upper Paleolithic period, but human settlement started first in the Neolithic period (Thalman et al., 2013; Shipman, 2015). Therefore the hypothesis of dog domestication at the waste dump appears rather unlikely and should also be dropped, although the idea of a self-domestication occurs still plausible. Brian Hare evolved a hypothesis of self-domestication concerning primates and dogs in which social and friendly behaviour is suggested to be in the focus of the self-domestication process (Hare et al., 2012).

Wolves are very social mammals living as hunters in family clans rearing their pups together (Mech, 1999). They hunt in cooperative groups and use refined social communication consisting of complex mimicry, joint attention and howling (Mech, 2009). Gray wolves have been living in Europe for hundred thousands of years, but Homo sapiens immigrated to Europe about 45.000 years before our time and invaded the ecological niche of ancient wolves (Shipman, 2015). In these ancient times individuals of Homo sapiens, called human in the following, also lived as cooperative hunter-gatherers in family clans raising their children together (Hawkes, 2003; Page et al., 2017). Wolves and humans hunted mammoth, rhinoceros and other large herbivores from the Pleistocene using cooperative hunting strategies (Shipman, 2015). As a result, wolves and humans lived in cohabitation but also in competition during the Palaeolithic period. As social mammals both species were skilled with basic social communication gestures based on evolutionary conserved similar brain structures (Berns, 2012; 2013) which enabled them to interact and communicate with each other (Heberlein et al., 2016; Darwin 1910). Thus, they came into contact. Thalmann et al. (2013) suggest an onset of dog's domestication approximately 18.800 to 32.100 years ago. Their study implies that "*domestic dogs are the culmination of a process that initiated with European hunter-gatherers and canids with whom they interact*".

There is evidence for fascinating confirmation about human partnership with early domesticated wolf-dogs soon after Neanderthals had disappeared. This alliance of two predator species allowed them an unprecedented degree of success in hunting large herbivores from the Pleistocene, and that it was a big evolutionary benefit for both (Shipman, 2015).

Neurobiology of human-wolf/dog communication

The evolutionary continuity of mammalian brains implies that basal brain systems like limbic system, stress axis and mirror neuron mechanism are evolutionary conserved in all mammalian brains (Ledoux, 2012; Gimpl & Fahrenholz, 2001; Reep et al., 2007; Ferrari, 2016). Mirror neuron mechanism is involved in empathy and mirror neurons start firing when both individuals are equipped with the same neuronal representation of an emotion or an action (Kilner & Lemon, 2013). Additional evidence suggests that mirror neurons are not inclusive to primates and humans. Today mirror neurons are experimentally verified in humans, primates and songbirds (Welberg, 2008) and it is reasonable to hypothesize that social mammals like wolves and dogs have mirror neurons, too (Ferrari, 2016). Humans` and wolves` similar learning experience should have created equal neuronal representations, coding the observed actions and emotions. Functional MRT studies proved that human mothers have similar brain activation in limbic brain regions when viewing their own child and their dog (Stoeckel et al., 2014). On the other hand dogs and humans show a similar physiological response to human infant crying (Yong & Ruffman, 2014). Empathy and pro-social behaviour is not only known for humans, but also for many other animals like rodents, wolves and dogs (Bartel et al., 2011; Romero et al., 2014; Joly-Mascheroni et al., 2008). Domestic dogs have the ability to yawn contiguously while watching human yawns and the contagiousness of human yawns in dogs correlate with the level of dog's social attachment to the yawning person (Romero et al., 2013). Romero's study (2013) demonstrates that dogs are capable of empathic abilities towards humans. Even wolves are vulnerable to contiguous yawning correlating with the level of social attachment within the pack (Romero et al., 2014). Further on it is commonly accepted that the neuropeptide oxytocin plays an important role in mammalian bonding, increasing empathy, social memory, trust and in-group behaviour (Lim & Young, 2006; Savaskan et al., 2008; Kosfeld et al., 2005). Nagasawa et al. (2015) show that gazing into each other's eye, a process mediated by the hormone oxytocin also exists between humans and their attached dogs. This mutual gazing increases oxytocin levels in both species indicating interspecific empathy. Even the reward system in brains of dogs and humans shows a similar functional mechanism. Functional MRT studies of awake unrestrained dogs indicated caudate activation in dog brains as a response to hand signals denoting reward versus no-reward similar to functional MRT-studies of human brains (Berns, 2012).

Because of the similar social behaviour like living in family clans (Mech, 1999; Hawkes, 2003; Page et al., 2017) and raising the off-spring together and because of using cooperative hunting strategies (Mech, 2009) in an identical environment (Shipman, 2015), humans and wolves should have had a similar learning experience in ancient times. Due to similar social behaviour and similar evolutionary conserved brain patterns (Reep et al., 2007) they should have been able to communicate with each other and thus, it was possible for both of them to become confident to each other (Range et al., 2014). We suppose that increased social contact between both species led to reduced stress and to improved pro-social behaviour and empathy (Beetz et al., 2012). From a neuro-chemistral perspective cortisol levels decreased and serotonin and oxytocin levels increased (Blume et al., 2008).

Genetic selection and domestication processes

Selection against aggression in mammals shows multiple equal effects in all domestic species concerning their morphology, behaviour, physiology and psychology, which is known as domestication syndrome (Hare et al., 2012). In domesticated species, the characteristic less aggressive and less fearful behaviour in combination with increased pro-social behaviour is accompanied by face shortening, reduced cranial capacity, reduced tooth-size, partial depigmentation, floppy ears and increased fertility (Trut et al., 2009). It is suggested that the domestication syndrome results from mild neural crest cell deficits during embryonic development where migration defects are particularly important (Wilkins et al., 2014). Neural crest cells arise from the neural tube shortly after its closing and they migrate throughout embryonic tissue where they differentiate into most of the peripheral nervous system as well as the facial skeleton and pigment cells. No genetic evidence indicates that the changes seen in domesticated animals are the result of single mutations (Wilkins et al., 2014). Polygenetic causation is suspected as a responsible mechanism. In addition the symptoms of domestication syndrome occur very rapidly.

The most well-known experiment concerning to canid domestication is the Siberian farm-fox-experiment with Siberian silver foxes (Balyaev, 1979). Having minimum but daily contact to humans, only low aggressive individuals at the age of seven month were chosen for further breeding. The control line was reared under identical conditions avoiding minimum daily contact to humans, and individuals were bred randomly. Within twenty to forty generations in the experimental group numerous features of domestication syndrome were observed. First, physiological changes including changes in the adrenal cortex, serotonergic and limbic systems related to a down regulation of the hypothalamic-pituitary-adrenal(HPA)axis, were identified. The brains of experimentally domesticated foxes exhibit elevated levels of serotonin and tryptophan hydroxylase relative to unselected control line (Popova et al., 1980; Kulikova et al., 1989; Hammer et al., 1992; Trut, 1999). Cortisol levels in domesticated foxes were also lower. They had less corticosteroid reactivity and changes in gene expression in the HPAaxis (Plyusina et al., 1991; Gulevich et al., 2004; Trut et al., 2009) compared to control group foxes. Second, individuals of the experimental fox population showed behavioural changes like tail wagging, submissive posturing and barking. Third, individuals of the experimental fox group showed morphological changes include floppy ears, piebald coats, curly and shortened tails (Trut, 1999). Fourth, cognitive changes in social problem solving skills improved in foxes of the experimental group (Miklosi et al., 2003; Hare et al., 2005). Finally, compared to control group individuals, spontaneous ability to use basic human communicative gestures had improved in experimental group foxes. Domesticated fox puppies were as skilled as dog puppies in using human communicative gestures (Hare et al., 2005).

It is commonly accepted that genetic polymorphism can modulate the function of evolutionary conserved complex mammalian brain systems like oxytocin system and serotonin system. Oxytocin is well known for its role in mammalian bonding (Lim & Young, 2006). Single nucleotide polymorphism (SNP) in oxytocin receptor gene in brain as well as in serotonin transporter (SERT) gene are known in humans, wolves and dogs (Kumsta et al., 2013; Kis et al., 2014; Oliva et al., 2016). Humans with SNPs in oxytocin receptor gene with homozygotes G allele are more social and friendly in general relationships, but they show no difference in closed relationship (Li et al., 2015). Dogs carrying G allele show lower proximity seeking (Kis et al., 2014; Oliva et al., 2016). Serotonin transporter 5-HTTLPR homozygotes L allele is associated with lower anxiety symptoms (Hariri, 2002). However, there might be many other unknown genetic variations influencing social behaviour. Gene expression changes in brains of domestic dogs compared to wild wolves are confirmed (Seatre et al., 2004; Axelsson et al., 2013). As a form of natural genetic selection and the first step of dogs` "self-domestication", we assume that less aggressive and less fearful ancient wolves had been the ones becoming more confident to humans (Hare et al., 2012). These less aggressive wolves gained a selective advantage because they were able to come into contact with humans more easily, eventually sharing hunting success (Thalman et al., 2013; Shipman, 2015). These human associated wolf clans formed behavioural cultures leading to genetic isolation (Wayne, 2014; Foote et al., 2016; Filatova et al., 2015). Coming into contact with humans, natural selection in wolves had played an important role long before intentional breeding by humans occurred (Hare et al., 2012).

Epigenetic Modulation of the HPAaxis

Genetic selection is a necessary prediction but not a sufficient explanation for domestication from wolf to dog. Concerning to the farm-fox experiment (Trut et al., 2009) first changes in experimental group foxes were seen in down regulation of the HPAaxis within a few generations. Therefore we consider that this results give evidence that domestication process is not only caused by genetic selection but also by epigenetic modulation of the HPAaxis.

Domestication means decreased flight distance and decreased sensory threshold chiefly concerning to humans causing less aggressive and less fearful behaviour (Benecke, 1994; Hare et al., 2012). Hence we have to work on the HPAaxis during domestication processes. We consider domestication is essentially an epigenetic based process of changing the interactions of the HPAaxis and the 5-hydroxytryptamine (5-HT) system.

The limbic brain regions such as hippocampus, amygdala and cingulate cortex play a key role in mood control (Kirsch et al., 2005; Kienast et al., 2008; Kosfeld & Fehr, 2005). They are sensitive to glucocorticoids and innerved by serotonergic projections. The activity of the HPAaxis is influenced thru an enhancement of the corpus amygdala and an inhibition thru the hippocampus. Hippocampal glucocorticoid receptor (hGCR) density is likely to affect its inhibitory effect on this system. Epigenetic input like DNA methylation is known to impact the regulation of hGCR expression (Buschdorf & Meaney, 2015). The HPAaxis and the 5-HT system are closely cross-regulated under physiological conditions (Lanfumey et al., 2008). If stress and therefore cortisol levels decrease, serotonin levels increase. And vice versa, increased serotonin levels leads to decreased cortisol levels. Lower cortisol and higher serotonin levels in brain promote pro- social behaviour, juvenilized social behaviour and learning ability whereas aggressive behaviour decreases (Murrin et al., 2007; Niehoff, 1999). Thus, changes in the interactions of the HPAaxis and the 5-HTsystem are of particular relevance when regarding the domestication processes of animals.

Deriving the hypothesis of the Active Social Domestication (ASD)

Experimental group foxes of the farm fox experiment first show changes in their adrenal cortex, serotonergic and limbic systems, which are related to a down regulation of the HPAaxis within only a few generations. The brains of experimentally domesticated foxes exhibit elevated levels of serotonin and tryptophan hydroxylase relative to unselected control line (Popova et al., 1980; Kulikova et al., 1989; Hammer et al., 1992; Trut, 1999). Cortisol levels in domesticated foxes were also lower. They had less corticosteroid reactivity and changes in gene expression in the HPAaxis (Plyusina et al., 1991; Gulevich et al., 2004; Trut et al., 2009) compared to control group foxes. These results are corresponding to epigenetic modulation of the HPAaxis due to social affection (Meaney & Szyf, 2005; Buschdorf & Meaney, 2015). We hypothesise that epigenetic modulation of the HPAaxis might be an important mechanism contributing to domestication and domestication syndrome. There is evidence in humans and rodents that parental care in form of social affection can affect endocrine and autonomic response to stress that endure into adulthood (Meaney & Szyf, 2005). Predictably, adult offspring of rat mothers, which showed increased pup licking and grooming (LG+), is less fearful. This offspring is equipped with significant increased hippocampal glucocorticoid receptor (hGCR) expression, enhancing glucocorticoid negative feedback sensitivity and decreasing corticotropin-releasing factor (CRF) levels. Whereas the offspring of stressed low licking rat mothers (LG-) is more fearful, showing decreased hGCR expression with high CRF levels. Cross-fostering the biological offspring of LG+ and LG- mothers reverses the phenotype, suggesting a direct relationship between variations in maternal care and development of the HPAaxis responses to stress. Stress responses in the adult rat are programmed early in life by maternal care and are associated with epigenomic marking (DNA methylation) of the hGCR 1,7 promotor. Even in human brains, a meaningful relationship between childhood abuse and epigenomic marking of the hGCR 1,7 promotor has been identified (McGowan et al., 2009). Due to evolutionary continuity of brains, the HPAaxis is established for millions of years (LeDoux, 2012) in the same function, therefore it is legal to predict explained epigenetic modulation of the HPAaxis in rodents (Meaney & Szyf, 2005) and humans (McGowan et al., 2009) as well as in wolves and in dogs.

Factors identified include down-regulation of hGCR expression by enhanced methylation of GCRexon1;7promotorbloc because of decreased social affection (McGowan et al., 2009). Social factors like licking and grooming enhance hGCR expression via increased serotonin, and subsequently increased NGF levels binding on GCRexon1; 7promotorbloc causing DNA demethylation. GCR density and thereby activity of the HPAaxis is determined in childhood (Meaney & Szyf, 2005). Low stress environment generates less stressed individuals, therefore maternal care improves. Due to the epigenetic modulation of the HPAaxis, the offspring of those less stressed mothers is again less fearful and less aggressive, in turn exposing improved maternal care. Cortisol levels decrease while cross regulated neurotransmitters and neuropeptids like serotonin and oxytocin increase. Epigenetic modulation of the HPAaxis leads to lower cortisol levels and might therefore also cause mild neural crest cell migration deficiency during embryonic development. Cortisol can cross the placenta, thus lower cortisol levels and higher serotonin levels of less fearful mothers might influence epigenetic modulation in embryonic development especially due to embryonic brain development (Ahmed et al., 2014; Trut et al., 2009). Further research is required and might give more information.

Because of this epigenetic modulation, individuals become less aggressive and less fearful, trust and in-group behaviour increase due to oxytocin effects (Kirsch et al., 2005; Kosfeld/Fehr, 2005). In the Paleolithic period individuals of wolf clans associated to human hunter-gatherers were less stressed because they were used to human presence and gained an evolutionary benefit (Thalman et al., 2013; Shipman, 2015). Hence from generation to generation epigenetic modulation of the HPAaxis decreased stress levels of human associated wolves more and more, and eventually the wild wolf became a tame wolf. But a tame wolf is not even a dog.

Nowadays it is commonly accepted that high cortisol levels inhibit the activity of prefrontal cortex and neural structures which are important for learning (Arai et al., 2009). Furthermore, the activity of the prefrontal cortex also plays an important role in glucocorticoid feedback inhibition of the HPAaxis. Low cortisol levels promote the function of the prefrontal cortex contributing to better executive function capability including better cognitive inhibition and improved social learning capability (McKlveen et al., 2013). Therefore, we suggest due to the hypothesis of the Active Social Domestication (ASD) that epigenetically decreased cortisol levels and increased serotonin levels enabled tamed and less fearful wolves a closer association to humans and better understanding of human social gestures. Emotional and cognitive empathy of tamed wolves could increase concerning to humans. The tame wolf became able to grow into a domesticated social dog capable of working together with humans in an active form of partnership. Dogs have learned to use human communicative and pointing gestures, and also developed complex human-analogue social behaviour (Marshall-Pescini et al., 2012; 2014). Compared to wolves, dogs possess a higher level of inhibitory control concerning to humans (Marshall-Pescini et al., 2015). Thus, this alliance of two predator species allowed them an unprecedented degree of hunting success during the Palaeolithic period and made it the first big evolutionary benefit of human-dog partnership (Shipman, 2015). Later on, dogs helped humans transporting materials, even tending their sheep and goats. Eventually wolf dogs integrated themselves in human social structures. Accepting humans as their preferred social binding partner (Range et al., 2013) tame wolf dogs became domestic dogs.

Summary

In addition to natural genetic selection, the hypothesis of Active Social Domestication from wolf to dog posits epigenetic modulation of HPAaxis caused by increased interspecific social affection (Meaney & Szyf, 2005; McGowan et al., 2009) as an important mechanism in the domestication process. We proclaim that sharing an identical ecological niche, wolves` and humans` similar social behaviour and cooperative hunting patterns (Shipman, 2015) enabled them interspecific communication due to the evolutionary continuity of their mammalian brains (Ledoux, 2012; Gimpl & Fahrenholz, 2001; Reep et al., 2007; Ferrari, 2016). Wolves with genetically disposed friendly behaviour and less fear are supposed to get in closer contact to human hunter-gatherers (Hare et al., 2012) during a cooperative hunt or while lingering near by the prey. Thus, interspecific interactions could improve. Being able to understand interspecifically the gestures of each other, individual bonding between wolves and humans could start (Range et al., 2014). Human associated wolves and human hunter-gatherers became familiar, behavioural cultures were formed (Wayne, 2014; Foote et al., 2016; Filatova et al., 2015; Avital & Jablonka, 2000) and genetic isolation of human associated wolf clan began (Wayne, 2014). Mutual empathy is assumed to have improved and thus, stress decreased. This means that epigenetic modulation via increased hGCR expression reduced the activity of the HPAaxis, maternal care and social affection could improve. Low cortisol levels increased the release of serotonin and oxytocin leading to a further grow of pro-social behaviour as well as social learning abilities (Beetz et al., 2012). Individual bonding between wolves and humans improved enhancing interspecific in-group behaviour related to both specimen. Thus, wild wolves became tame wolves. From generation to generation improved social learning abilities and increased inhibiting effect of the prefrontal cortex facilitated the domestication of tame wolves to domesticated dogs due to described epigenetic modulation of HPAaxis. Dogs are able to work together with humans in an active form of partnership. Dogs are integrated in human social structure. Dogs even prefer human bonding partners (Range et al., 2013).

Epigenetic modulation of the HPAaxis due to social affection has had an effect probably not only in wolves and dogs but also in humans. Today, social interactions between humans and dogs still reduce the activity of HPAaxis in both species and improve pro-social behaviour via increased oxytocin release (Beetz et al., 2012) as explained in the hypothesis of Active Social Domestication. Reducing stress as well as invigorating social learning abilities is known to be the reason of the benefit of dog facilitated therapy in medical and social treatment (Julius et al., 2014). Therefore humans` social and learning abilities are supposed to have improved during the Paleolithic period, too.

Discussion

Although the concept of the Active Social Domestication from wolf to dog is at present only a hypothesis, many scientific results do support it. We proclaim that epigenetic modulation of HPAaxis tries to fill the gap between natural selection and intentional breeding in dogs` domestication as a kind of self-domestication process. It has been proven that wolves and humans shared identic ecological niche and expressed same social and hunting behaviour (Mech, 1999; 2009). Shipman (2015) and Thalmann et al. (2013) described ancient interactions of humans and wolf-dogs when dogs were domesticated 18.800 - 32.100 years ago. The oxytocin and serotonin system as well as the HPAaxis are evolutionary conserved, both the hormones and their receptors are present in all mammal taxa (Ledoux, 2012; Gimpl & Fahrenholz, 2001). Furthermore evidence is provided that genetic variants of genes important for brain function (Axelsson et al., 2013) including mutations of the oxytocin gene may have played a role in the first step of natural selection from wolf to dog (Oliva et al., 2016; Hare et al., 2012). However, genetic polymorphisms and epigenetic mechanisms modulate the functions of complex brain systems in both species (Oliva et al., 2016; Meaney & Szyf, 2005). Epigenetic studies indicate that a less stress environment and higher social affection decrease cortisol levels via increased hGCR expression while increasing serotonin and oxytocin levels. Maternal care improves and thus the off spring shows less fearful and less aggressive behaviour (Meaney & Szyf, 2005; Mc Gowan et al., 2009). We suspect that these epigenetic mechanisms as well as natural genetic selection enabled wolves to grow into domestic dogs. During cohabitation of humans and their associated wolf clans, human-like social skills of first wolf-dogs emerged, such as following human referential gestures (Range & Viranyi, 2013), joint attention (Gamer et al., 2010; Nagasawa et al., 2015) and attachment to human owners (Prato-Previde et al., 2003). Until today, human-dog bonding decreases cortisol levels and increases oxytocin and serotonin levels in both species (Beetz et al., 2012).

The farm-fox experiment (Trut et al., 2009) is the most important experimental research supporting the hypothesis of the Active Social Domestication. Domestication syndrome occurs within a short period of only twenty generations. First, changes of experimental group foxes with little daily contact to humans were found in the HPAaxis, serotonin and oxytocin systems. This appears compatible to epigenetic modulations due to social affection. Later on, changes were identified concerning behavioural changes, than morphological changes and, even later on, changes in social problem solving. Domesticated fox puppies were as skilled as dog puppies in using human communicative gestures (Hare et al., 2005). Therefore, we consider these results as evidence that domestication process is not only caused by genetic selection, but also initiated by epigenetic changes of the HPAaxis. Stray dogs, not used to human presents in their critical period, 3-10 weeks of age, often show fear of humans which may override dog's cognitive capacity to use humans` social cues (Udell et al., 2010; Range & Viranyi, 2013). This may support the importance of epigenetic mechanisms in domestication processes.

Most of the previous theories assume intentional breeding by humans as the main mechanism of the domestication from wolf to dog (Lorenz, 1967; Zimen, 1992). But intentional breeding of wild wolves could not have been possible for humans living as hunter-gatherers 25.000 years ago without chains of steel or stables made of stone. Therefore, genetic selection caused by intentional breeding cannot be the main reason for initiating the first step of domestication from wolf to dog although it surely played an important role in further breeding of pedigree dogs. Contemporary theories of dog's domestication favour self-domestication processes (Coppinger, 2001; Morey, 1994; Hare et al., 2012). Beside natural selection we hypothesize epigenetic modulation of HPAaxis to play a key role in self-domestication processes, not only in dogs, but even in the domestication of other mammals and in human cultural evolution as well (Hare et al., 2012). Within a narrow time frame of dogs` domestication, archaeologists described a sudden further stage of human cultural development (Gamble et al., 2015). In the Aurignacien (approx. 35.000 - 26.000 years ago) first flutes, sculptures, cave paintings and javelin spins occurred. Modern humans started living in larger social groups, held together by their increased cultural practice. Even other mammals are known to live in larger groups due to inhabiting ecological niches with low stress factors. Florida Key deer (*Odocoileus virginianus clavium*) has increasingly encroached urban areas over the last 30 years showing higher body mass, higher fitness and they are living in larger social groups compared to those living farther away from urban areas (Harveson et al., 2007). Island vertebrates are known to be less aggressive and they are often living in larger social groups (Adler/Levins, 1994; Gray & Hurst, 1998). Darimont et al. (2014) describe low aggressive behaviour of island wolves consistent with a dietary niche. Diet is also known to effect epigenetic gene regulation of HPAaxis (Waterland & Jirtle, 2003). Therefore it is reasonable to discuss diet as an additional factor influencing domestication processes, especially concerning to a further stage of dog domestication when settlement and farming started in the Neolithic period. Then humans and their dogs started adaptation to starch-rich diet (Axelsson et al., 2013), thus tryptophane levels in brain increased leading to reduced aggression and better pro-social behaviour (Fernstrom & Wurtman, 1971; Chamberlain et al., 1987; Waterland & Jirtle, 2003).

Future research might strengthen the hypothesis of the Active Social Domestication while analysing cerebral methylation patterns in wolves and domestic dogs, most likely by comparing wild wolves versus human hand reared wolves as well as pet dogs versus stray dogs. Further research in neural crest cell migration deficits during embryonic development might also give evidence concerning epigenetic modulation due to cortisol levels. The main difficulty of the hypothesis of the Active Social Domestication is that dog domestication could not be repeated experimentally in the same way it happened.

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La domesticazione del cane è dovuta ad una modulazione epigenetica nel cervello?

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Sintesi

I cani (*Canis lupus familiaris*), sono considerati i primi animali ad essere stati addomesticati e vivono con l'uomo da almeno 25 mila anni. Oggi i ricercatori sostengono che la domesticazione sia da considerarsi un processo di auto-addomesticazione ma non è ancora chiaro come sia avvenuta. Durante il Paleolitico, uomini e lupi vivevano in famiglie strutturate come clan di cacciatori cooperativi, nella stessa nicchia ecologica. La continuità evolutiva che esiste tra i cervelli dei mammiferi ha reso possibile la comunicazione interspecifica e l'interazione sociale tra uomini e lupi, riducendo lo stress e l'aggressività durante i frequenti contatti tra le due specie e costituendo il primo passo di un processo di domesticazione naturale. La domesticazione implica una diminuzione dell'aggressività ed un a riduzione della distanza di fuga dall'essere umano. Per questo motivo, cambiamenti nell'attività dell'asse Ipotalamo-Ipofisi-Surrene (HPA) sono ritenuti essere molto importanti durante il processo di domesticazione del lupo che lo ha trasformato in cane.

L'ipotesi di una domesticazione sociale attiva considera la selezione genetica come un fattore predittivo ma non sufficiente per spiegare la domesticazione del cane. Inoltre si ritiene che la domesticazione del cane sia basata essenzialmente su un processo epigenetico che cambia le interazioni dell'asse HPA e del sistema serotoninergico.

Le regioni limbiche dell'encefalo, come l'ippocampo e l'amigdala, giocano un ruolo chiave nel controllo dell'umore. Esse sono sensibili ai glicocorticoidi e innervate da proiezioni neuronali serotoninergiche. L'asse HPA e il sistema serotoninergico sono strettamente interconnessi in condizioni fisiologiche. L'attività dell'asse HPA è influenzata da stimolazioni provenienti dal corpo dell'amigdala ed inibita dall'ippocampo. La densità dei recettori ippocampali di glicocorticoidi regola, verosimilmente, l'effetto inibitorio sul sistema.

Il comportamento pro-sociale stimola, epigeneticamente, l'espressione dei recettori ippocampali di glicocorticoidi in seguito ad un aumento della serotonina e conseguentemente si assiste ad un aumento del fattore di crescita del nervo, che si lega al GRexon1; 7, inducendo la sua demetilazione e quindi portando ad una riduzione dei livelli di cortisolo.

Ridotti livelli di cortisolo aumentano le capacità di apprendimento sociale e promuovono l'attività della corteccia prefrontale, migliorando le capacità operative e l'inibizione cognitiva. Perciò i ridotti livelli di cortisolo in famiglie di lupi meno stressate dalla presenza dell'uomo, hanno permesso loro di migliorare le capacità sociali nei confronti dell'essere umano. Col tempo questi lupi ammansiti sarebbero potuti trasformarsi in cani, in grado di mostrare comportamenti centripeti nei confronti delle persone.