JIVS Journal of Istanbul Veterinary Sciences

Understanding canine aggression: Neurobiological insights for a complex behavior

Gökçen Güvenç Bayram[1], Zeynep Semen[2]

1. Dokuz Eylul University, Faculty of Veterinary Medicine, Department of Physiology, Izmir, Turkey**. 2.** Dokuz Eylul University, Faculty of Veterinary Medicine, Department of Biochemistry, Izmir, Turkey. Güvenç Bayram, G. ORCID: 0000-0002-1413-3651 ; Semen, Z. ORCID: 0000-0002-7722-5772

Review Article

Volume: 7, Issue: 2
August 2023
Pages: 68-79

Article History

Received: 29.03.2023
Accepted: 18.07.2023
Available online: 15.08.2023

ABSTRACT

The relationship between humans and dogs, as the first domesticated animals, exemplifies a significant aspect of human-animal interaction. During domestication, dogs have undergone behavioral changes to establish closer bonds with humans. However, certain dogs face challenges in fully adapting to their new environment, leading to behavioral disorders such as aggression. One of the most prevalent and dangerous behavioral problems in dogs is aggression, which poses risks to both humans and the dogs themselves, sometimes resulting in euthanasia. Canine aggression can arise from various medical and non-medical factors, including physical problems, endocrine system disorders, infectious diseases, central nervous system diseases, hereditary conditions, as well as racial or personal differences. Evaluating aggression based solely on species, breed, and sex characteristics is insufficient. Accurate diagnosis of aggressive behavior requires integrating findings from diverse diagnostic methods, including serum biochemistry, hormone analysis, urinalysis, electroencephalography, radiography, magnetic resonance tests, and behavioral assessments. However, to gain a comprehensive understanding of canine aggression, it is essential to consider the underlying pathophysiological processes and neurobiology. The management of aggressive behavior in dogs necessitates the implementation of diverse treatment strategies aimed at preventing the manifestation of undesirable behaviors. Within the realm of medical interventions, neutering and pharmacotherapy have emerged as prominent approaches. Neutering has shown effectiveness in mitigating aggression among dogs exhibiting aggressive tendencies. On the other hand, pharmacotherapy involves the utilization of complementary and suppressive pharmacological agents that target primary and intermediate components within the mechanisms underlying aggression. These components encompass neurotransmitter/neuromodulator substances, peptides, enzymes, and hormones, all of which contribute to the pathophysiological processes of aggression. Through the modulation of these factors, pharmacotherapy seeks to offer a comprehensive treatment approach for addressing aggressive behavior in dogs. This review aims to investigate the neurobiological basis of aggression in dogs, considering the underlying pathophysiological processes and the role of neurotransmitter/neuromodulator substances, neuropeptides, peptides, enzyme systems, and hormones. Accurate diagnosis and understanding of canine aggression are crucial for the development of effective medical and alternative treatment methods.

Keywords: aggressive behavior, canine aggression, dangerous dog breeds, serotonin, dopamine, oxytocin.

DOI: https://doi.org/10.30704/http-www-jivs-net.1272983

To cite this article: Güvenç Bayram, G., Semen, Z. (2023). Understanding canine aggression: Neurobiological insights for a complex behavior. ***Journal of Istanbul Veterinary Sciences, 7*(2),** 68-79. **Abbreviated Title*:* J. İstanbul vet. sci.**

Introduction

The concept of domestication, which involves the process of animals adapting to the settled life of humans, has a long history reaching back to prehistoric times and has played a vital role in forging a closer relationship between humans and the natural world (Siddiq, 2019). Among the many domesticated animals, dogs hold a special place as the first to be domesticated, dating back approximately 14,000 years. The enduring nature of our social interactions with dogs, spanning from ancient times to the present, serves as a fundamental exemplification of the profound bond between humans and animals. Throughout history, dogs have held multifaceted roles in both natural environments

***Corresponding Author:** Gökçen Güvenç Bayram
E-mail: gokcen.guvencbayram@deu.edu.tr

and human societies. Their companionship and contributions have solidified their status as one of the most prominent illustrations of human-animal interaction. Notably, certain qualities exhibited by dogs, such as loyalty, trainability, obedience, and harmony, have made them valuable assets in the process of image acquisition and socialization of individuals within society (Batmaz, 2021).

The most common behavioral disorder in dogs: Dominant aggression (Dominance-related aggression)

Observable movements in living organisms are known as behavior (Landsberg, 1990). Animal behavior is a complex phenomenon that encompasses survival behaviors developed by animals in response to their natural environment (Odendaal, 1997). Dogs, in particular, have undergone behavioral changes compared to their wolf ancestors due to their adaptability, allowing them to be closer to humans during domestication (Siddiq, 2019). However, dogs have not fully adapted to their new environment biologically within a short period, leading to internal conflicts between their internal structures and the new environment, resulting in stress, aggression, anxiety, and depression-like behaviors (Dodurka, 1999; Dodurka, 2001). Undesirable behavior exhibited by dogs is often labeled as behavioral disorders by humans (Overall, 1997). These behavioral disorders in dogs can manifest due to various factors, including genetic diseases, developmental challenges, breed-specific behaviors, social environment issues, adaptation strategies, and environmental adaptation disorders (Odendaal, 1997). The prevalence of certain behavioral disorders, such as aggression, fear, attention-seeking behaviors, loneliness, anxiety, environmental pollution, neglect of puppies, social withdrawal, destructive behaviors, digging, maternal cannibalism and coprophagia, contributes significantly to the abandonment of dogs in shelters (Feddersen-Petersen, 1990; Jagoe, 1994; Askew, 1996; Odendaal, 1997; Dodurka, 2005; Kwan and Bain, 2013). These behavioral problems not only pose challenges for dog owners but also serve as major reasons for relinquishment to shelters.

Aggression is a prevalent and hazardous behavioral problem in dogs that can lead to harm to humans and euthanasia of dogs (Houpt and Reisner, 1995; Horwitz, 2000). It is most commonly observed in intact male dogs and later in non-neutered female dogs, and neutering has been shown to reduce aggression in both sexes (Beaver, 1992). Aggression in dogs can have medical origins, including physical problems, endocrine system disorders, infectious diseases, central nervous system disorders, and hereditary diseases (Chapman and Voith, 1990; Landsberg, 1990; Dodman et al., 1996a). In addition to disease-related causes, racial or personal differences have also been found to influence aggression in dogs (Zapata et al., 2016).

Research utilizing behavioral tests, such as the Canine Behavioral Assessment and Research Questionnaire (C-BARQ), has revealed that dog aggression varies across species. Dogs were categorized based on aggression towards their owners, unfamiliar individuals, and other dogs. Dogs known for their friendly characteristics tend to display slight aggression towards strangers and other dogs, while dogs with more robust temperaments, including pit bulls, exhibit more pronounced aggression (Duffy et al., 2008). However, a study conducted in 2011 reported that pit bulls adopted from shelters did not show higher aggression compared to other species (MacNeil-Allcock et al., 2011). Another study investigating the degree of aggression based on scar size in pit bulls rescued from dog fighting, a breed often associated with aggression and euthanasia, found that animals with larger scar areas displayed higher levels of aggression. The study also reported that male pit bulls exhibit more aggression than females. Nonetheless, bite marks alone are insufficient to fully understand an animal's aggression, and behavioral tests should also be conducted (Miller et al., 2016). Instead of evaluating canine aggression solely based on species, breed, and sex characteristics, it is important to address the pathophysiological processes and neurobiology underlying aggression. Additionally, supporting these findings with results obtained from behavior observation and tests is essential for accurate diagnosis (Overall, 1997).

Studies utilizing behavioral tests, such as the Canine Behavioral Assessment and Research Questionnaire (C-BARQ), have shed light on the variability of dog aggression. Duffy et al. (2008) conducted a study where aggression in dogs was categorized based on species, including aggression towards the owner, aggression towards unfamiliar individuals, and aggression towards other dogs. The results showed that dogs known for their friendly characteristics exhibited slight aggression towards strangers and other dogs, while dogs with more robust temperaments, such as pit bulls, displayed more pronounced aggression. However, MacNeil-Allcock et al. (2011) reported that pit bulls adopted from shelters did not show higher levels of aggression compared to other species. Another study focused on investigating aggression levels based on scar size in pit bulls, a breed often associated with aggression and then euthanasia. The study demonstrated that pit bulls with larger scar areas displayed higher aggression levels. Furthermore, the study reported that male pit bulls exhibited more aggression than females. However, it is important to note that bite marks alone are insufficient to fully understand an animal's aggression, and behavioral tests should also be conducted (Miller et al., 2016). Therefore, evaluating canine aggression should not solely rely on species, breed, and sex characteristics, but should also consider the underlying pathophysiological processes and neurobiology of aggression (Overall, 1997).

Aggression in dogs can be classified into different types based on various reasons, including aggression for fear and self-defense, territorial aggression, herd aggression, racial and hereditary factors, aggression during the socialization period, aggression resulting from diseases, dominant aggression, and aggression of unknown origin (Askew, 1996; Feddersen-Petersen, 1990; Jagoe, 1994; Noyan, 2007). Among these types, dominant aggression is the most common and occurs independently of breed, gender, and age characteristics (Reisner et al., 1994; Dodman et al., 1996b; Uchida et al., 1997; Odore et al., 2020). Studies have found that the majority of dogs diagnosed with dominant aggression are young male dogs and purebreds, with bull terriers being one of the breeds associated with a higher incidence of dominant attacks (Blacksaw, 1991; Uchida et al., 1997).

Diagnosing dominant aggression may involve behavioral tests as well as additional methods such as serum biochemistry, hormone analysis, urine analysis, electroencephalography, radiography, and magnetic resonance tests (Landsberg, 1990; Serpell and Hsu, 2005; MacNeil-Allcock et al., 2011). Behavioral tests encompass various criteria for identifying dogs predisposed to dominant aggression. These criteria include prolonged eye contact with the dog, performing painless procedures such as grooming, nail clipping, and ear cleaning, withholding food from the dog, passing by while the dog is eating, adding food to the bowl while eating, attempting to pick up the dog, physically arousing the dog, physical contact such as lifting and hugging, carrying out therapeutic procedures, physical punishment, verbal stimulus as punishment, leash handling including putting on/off and pulling, walking next to the dog in a confined space, testing responsiveness to commands, physical contact of a stranger with loved ones, and a stranger approaching the dog. Dogs that display an aggressive attitude towards at least five of these criteria are classified as predisposed to dominant aggression (Landsberg, 1990; O'Farrell, 1992; Dodman et al., 1996a; Serpell and Hsu, 2005; MacNeil-Allcock et al., 2011).

Breed differences in dog aggression: The assessment of breed differences in dog aggression is often based on sources like bite statistics, behavior clinic reports, and expert opinions. However, relying solely on these sources can be misleading due to biases and racial stereotypes, as they may disproportionately associate higher aggression risks with larger or physically stronger breeds. In order to obtain more reliable information about breed-specific aggression, a study was conducted using the Canine Behavioral Assessment and Research Questionnaire (C-BARQ) to evaluate the behaviors of over 30 breeds of dog in response to various stimuli and situations (Hsu and Serpell, 2003; Duffy et al., 2008). The findings from this study revealed significant variations in aggression among dogs towards strangers, owners, and other dogs. Eight breeds, namely Dachshund, English Springer Spaniel, Golden Retriever, Labrador Retriever, Poodle, Rottweiler, Shetland Sheepdog, and Siberian Husky, showed similar rankings in terms of aggression towards strangers, other dogs, and their owners, respectively. Breeds such as Chihuahuas and Dachshunds scored above average for aggression towards humans and other dogs. Akitas and Pit Bull Terriers exhibited high levels of aggression specifically towards a particular target, such as other dogs. Overall, dogs tend to display aggression primarily towards other dogs, followed by unfamiliar individuals and their owners (Duffy et al., 2008).

Certain breeds showed a propensity for aggressive behavior towards humans. For instance, Dachshunds, Chihuahuas, and Jack Russell Terriers displayed aggressive tendencies towards both strangers and their owners (Liinamo et al., 2007). Australian Cattle Dogs exhibited higher aggression towards foreigners, while American Cocker Spaniels and Beagles showed aggression towards their owners. Notably, more than 20% of Akitas, Jack Russell Terriers, and Pit Bull Terriers exhibited highly aggressive behavior towards unfamiliar dogs. On the other hand, Golden Retrievers, Labrador Retrievers, Bernese Mountain Dogs, Brittany Spaniels, Greyhounds, and Whippets were among the breeds that demonstrated the least aggression towards both humans and other dogs (Duffy et al., 2008).

Legal regulation regarding dogs in the aggressive breed category in Türkiye: The choice of pets often reflects the preferences and personality traits of individuals. Pitbull breeds, characterized by their muscular and robust bodies, are favored as pets by certain segments of society due to their agility, bravery, protectiveness, and loyalty. However, in other circles, they are considered breeds to be avoided (Stepherd, 2018; Batmaz, 2021). Pitbulls originated in England through the crossing of Terrier and Bulldog dogs. The Pitbull breeds known today include the American Pitbull Terrier, the American Bulldog, the American Staffordshire Terrier, and the Staffordshire Bull Terrier. Over time, Pitbulls have been utilized in various domains. Their warrior-like and aggressive traits made them initially popular in blood sports such as Dog Fighting, Cock Fighting, Gladiator Fights, Hunting, and Bullfighting. They also became symbolic of America during the 1st and 2nd World Wars. While they can be beneficial as "nanny dogs" due to their loyalty, obedience, affection, and protectiveness, Pitbulls have garnered negative attention in society due to their historical involvement in illegal fights and media coverage highlighting Pitbull-related incidents (Gunter et al., 2016; Kogan et al., 2019; Batmaz, 2021).

In Turkey, the Animal Protection Law No. 5199, enacted in 2004, prohibits the production, adoption, rehoming, housing, feeding, exchange, display, gifting, and sale of Pitbulls (Resmi Gazete, 01.07.2004). In 2021, the Law on the Amendment of the Animal Protection Law and the Turkish Penal Code was published in the Official Gazette. As per Article 14/1 of this law, individuals engaged in the aforementioned activities are subject to administrative fines. The same article also forbids the transportation of "dangerous" animals registered before January 14, 2022, without a registration certificate, muzzle, and collar, as well as their entry into public areas and children's playgrounds/parks. In case of continued violations, the animals are confiscated, and an administrative fine is imposed, with the animals being taken to the nearest municipality shelter (Resmi Gazete, 14.07.2021).

The role of neuromodulators, neurotransmitters, and neuropeptides in canine aggression: In the treatment of dogs with dominant aggression, various strategies can be employed to prevent the display of undesirable behaviors. Behavioral treatments play a crucial role in reducing and eliminating aggression (Landsberg, 1990; Askew, 1996; Houpt et al., 1996; Uchida et al., 1997; Yeon et al., 1999; Dodman et al., 2006c; Odore et al., 2020). Additionally, medical treatment methods such as neutering and pharmacotherapy are utilized (Askew, 1996; Landsberg et al., 1997). Neutering has been shown to help decrease aggression in dogs with dominant behavior (Askew, 1996; Kuhne, 2012). On the other hand, pharmacotherapy involves the use of pharmacological agents that target neurotransmitter/ neuromodulator substances, peptides, enzymes, and hormones involved in the pathophysiological processes of aggression, aiming to complement and suppress these mechanisms (Dodman et al., 1996a; Reisner et al., 1996; Landsberg et al., 1997; Overall, 1997; Pineda et al., 2014; Notari et al., 2015; Niyyat et al., 2018). To further advance current medical and alternative treatment approaches, it is crucial to elucidate the underlying mechanisms and pathways involved in canine aggression, as well as the roles of neurotransmitter/neuromodulator substances, neuropeptides, peptides, enzyme systems, and hormonal control pathways in these processes.

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that plays a vital role in various physiological processes, including the modulation of neuropsychological functions, cardiovascular and respiratory control, gastrointestinal motility, regulation of food intake and energy balance, and urogenital system modulation (Rapport et al. 1948; Roth, 2007). The central and peripheral nervous systems have identified 15 receptors associated with serotonin. Serotonin and its receptors are involved in regulating all brain functions within the central nervous system. Serotonergic neurons, which express serotonin in the raphe nucleus of the brainstem, significantly contribute to the development of behavior in humans and animals through their projections to the cortex, limbic system, midbrain, and hindbrain. The serotonergic system manages behavioral and neuropsychological processes such as mood, perception, reward/punishment, anger, aggression, appetite, memory, and libido. Dysregulation of this system can lead to psychological and neurological disorders (Berger et al., 2009).

Compared to other neurotransmitters, the serotonergic system is the most consistently active neurotransmission system involved in neurobiological mechanisms underlying aggressive behaviors (Miczek et al., 2002 and 2007; Takahashi et al., 2011). Low levels of serotonin/serotonin metabolites and imbalances in the expression of serotonin receptors are key factors contributing to aggression. Additionally, the serotonergic system interacts with other neurotransmitter and neuromodulator substances, amino acids, steroids, and peptides in the central nervous system, further influencing aggression (Takahashi et al., 2012).

Neurotransmitter substances like glutamate and γ-Aminobutyric Acid (GABA), known for their high functional properties in the brain, directly modulate serotonergic neurons. They exhibit increased expression in regions where serotonin neurons are localized, and GABAergic and Glutamatergic receptors are present in regions where the serotonergic system projects (Takahashi et al., 2012). Corticotropin-releasing factor (CRF) immunoreactive fibers and CRF receptors in the dorsal raphe nucleus also play a crucial role in modulating serotonin neurons related to aggression (Quadros et al., 2009a and 2009b). Arginine vasopressin (AVP), oxytocin, and their respective receptors are responsible for the regulation of serotonergic neurons involved in aggressive behavior. Monoamine oxidase (MAO), the adrenergic system, dopaminergic system, neuropeptide Y (NPY), tryptophan, brain-derived neurotrophic factor (BDNF), and neuronal nitric oxide synthase (NOS) are additional factors that directly or indirectly influence the effectiveness of the serotonergic system in aggressive behaviors (Takahashi et al., 2012).

Studies conducted in humans and various animal species have revealed a relationship between aggressive behavior and serotonin (Kırlı, 2000; Lesch and Merschdorf, 2000; Almeida-Montes et al., 2000). Individuals exhibiting high levels of aggression often have lower levels of serotonin and serotonin metabolites, as well as alterations in the expression of serotonin receptors (Miczek et al., 2002). Research conducted on different dog breeds has reported lower levels of serotonin in serum (Çakıroğlu et al., 2007), cerebrospinal fluid (Reisner et al., 1996), and urine (Wright et al., 2012) in aggressive dogs compared to non-aggressive dogs. Treatment methods that increase serotonin levels in the brain, such as selective serotonin reuptake inhibitors, have shown to reduce aggression in both humans and animals (Bacqué-Cazenave et al., 2020).

Dopamine

Dopamine (3-hydroxy thiamine), a neurotransmitter belonging to the catecholamine family, is synthesized in both the central nervous system and the periphery. Its effects are mediated through specific receptors expressed in both central and peripheral regions (Hansen and Manahan-Vaughan, 2012). The dopaminergic system plays a vital role in modulating various behaviors, including motor control, motivation, reward/punishment, cognitive function, maternal instinct, and reproduction. Imbalances in dopaminergic signaling pathways have been implicated in neurodegenerative disorders. Furthermore, dopamine and its receptors are involved in the pathophysiology and psychopharmacology of neuropsychiatric conditions such as schizophrenia and attention deficit hyperactivity disorder (O-Klein et al., 2019). Although research on the dopaminergic system in aggression is limited compared to the serotonergic system, it has been shown to have a significant impact on aggression development (Rosell and Siever, 2015). There is an inverse relationship between dopamine synthesis capacity, particularly in the midbrain and striatum, and the frequency of aggressive responses. Additionally, midbrain dopamine storage capacity has been found to be negatively correlated with aggression-related behaviors (Hall et al., 2012). Pharmacologically induced increases in dopamine levels have been associated with heightened aggressive behaviors (Almeida et al., 2005). Yu et al. (2014) demonstrated that aggression is augmented by increased activity in dopaminergic neurons, and genetic and pharmacological factors influencing dopamine and serotonin signaling can modulate monoaminergic functions known to impact aggression, potentially altering the risk of aggressive and emotional dysfunctions.

Pharmacotherapeutic agents targeting dopaminergic receptors, such as the dopamine D2 receptor antagonist haloperidol, have long been used to mitigate human aggression. Haloperidol has shown efficacy in treating aggressive behavior in children and adolescents with psychotic disorders and Parkinson's behavior disorders (Glazer and Dickson, 1998; Fitzgerald, 1999; Kennedy et al., 2001; Beauchaine et al., 2000; Diederich et al., 2003; Masi, 2004). Preclinical studies have also implicated dopamine D1, D2, and D3 receptors in the modulation of aggression (Tidey and Miczek, 1992a and 1992b; Sanchez et al., 1993; Miczek et al., 2002 and 2004). In a study on defense-based aggression in cats, D2 receptors were found to play a role, and the stimulation of D2 receptors in the medial preoptic area and anterior hypothalamus, regions associated with defensive behaviors, facilitated the expression of emotional defense behavior (Sweidan et al., 1991).

Oxytocin

Oxytocin, a neuropeptide acting as both a neurotransmitter in the central nervous system and a hormone in the peripheral circulation, is involved in various social behaviors, including maternal-offspring bonding and pair bonding (Churchland and Winkielman, 2012). It is primarily synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior lobe of the pituitary gland, where it is released into the peripheral circulation to facilitate uterine contractions during birth process and milk expulsion during breastfeeding (Insel, 2010). In the central nervous system, oxytocin exerts its effects by being released from neurons extending from the paraventricular nucleus to the amygdala, hippocampus, and nucleus accumbens. The oxytocin receptor (OXTR), the sole receptor identified so far, exhibits a sex- and species-specific distribution in both the central and peripheral nervous systems. Variations in OXTR expression and activation contribute to individual differences in the oxytocin system (Buisman-Pijlman et al., 2014).

Oxytocin has been implicated in numerous psychiatric disorders, including autism, schizophrenia, mood disorders, generalized anxiety disorder, social phobia, post-traumatic stress disorder, obsessive-compulsive disorder, attention deficit hyperactivity disorder, aggression, suicidal tendencies, eating disorders, and personality disorders (Ishak et al., 2011). Studies have reported lower plasma oxytocin levels, particularly in females, associated with depression-like behaviors (Frasch et al., 1995; Ozsoy et al., 2009). Furthermore, oxytocin infusion has been shown to increase serotonin release in the raphe nucleus, the central site of action for selective serotonin reuptake inhibitors (Yoshida et al., 2009). Turan et al. (2013) found oxytocin levels to be higher in patients with bipolar disorder during manic episodes compared to depressive episodes and remissions. Acute stress and fear situations activate the oxytocin system, resulting in elevated oxytocin levels in both the central nervous system and peripheral tissues (Engelmann et al., 2004; Neumann, 2007). While chronic anxiety disorder and plasma oxytocin levels were positively correlated in women, an inverse relationship was observed in men (Holt-Lunstad et al., 2011; Weissman et al., 2013). Acute administration of oxytocin has also been shown to reduce anxiety (de Oliveira et al., 2012).

Animal studies with inactivated oxytocin genes/ receptors have demonstrated changes in social and aggressive behaviors (Takayanagi et al., 2005). In humans, lower levels of oxytocin measured in the cerebrospinal fluid have been associated with higher lifetime aggression scores, although no significant association was found with personality disorders (Lee et al., 2009). Polymorphism in the oxytocin receptor gene has been linked to aggressive behaviors observed in childhood (Beitchman et al., 2012), suggesting a potential role for oxytocin in the etiology of aggression.

Gamma-Aminobutyric Acid (GABA)

GABA (gamma-aminobutyric acid) is a neurotransmitter synthesized from its precursor substance, L-glutamate, through decarboxylation mediated by the enzyme glutamate decarboxylase (Wassef et al., 2003). It serves as the primary inhibitory neurotransmitter in the central nervous system of mammals (Gou et al., 2012). GABAergic neurons have widespread projections throughout the brain and exert regulatory effects on various physiological mechanisms. Three types of GABA receptors have been identified: GABAA, GABAB, and GABAC (Wassef et al., 2003).

The involvement of GABA in the pathophysiology of aggression is predominantly associated with its inhibitory function (Miczek et al., 2003). Activation of GABAA receptors is known to decrease aggressive behavior, while positive modulators can exacerbate aggression. Conversely, GABAB receptors are directly linked to increased aggression. Pharmacological activation of GABAB receptors in the dorsal raphe nucleus (DRN) leads to heightened aggressive behavior (Takahashi et al., 2010a). Serotonergic neurons in the DRN play a crucial role in serotonin regulation, and the interplay between GABA and serotonin is critical in aggression development. Numerous studies have demonstrated that high expression of GABAA and GABAB receptors in the DRN regulates serotonin levels (Takahashi et al., 2010a and 2010b). Activation of GABAergic receptors on serotonergic neurons can elevate serotonin levels in the medial prefrontal cortex. Conversely, GABA receptors in the medial raphe nucleus (MRN) do not exert a similar effect on aggression, indicating distinct roles of serotonin neurons in the MRN and DRN in aggression development (Mokler et al., 2009). Furthermore, GABAA receptors located in the lateral septum are involved in maternal aggression in females (Lee and Gammie, 2009). Further research is necessary to fully comprehend the intricate roles of GABA in the development of aggressive behaviors. However, existing studies support GABA receptors as valid therapeutic targets for the regulation of aggressive behavior.

Thyroid hormones

Thyroid hormones (THs) play a crucial role in maintaining energy homeostasis and regulating the metabolic stages necessary for growth and development (Cheng et al., 2010; Brent, 2012). Thyrotropin-releasing hormone (TRH) is produced by neurons in the paraventricular nucleus of the hypothalamus and released from hypothalamic nerve projections known as the median eminence. As a hypophysiotropic hormone, TRH stimulates the synthesis and release of thyroid-stimulating hormone (TSH, Thyrotropin) from the adenohypophysis (Fekete and Lechan, 2014). Several factors, including kidney failure, fasting, insomnia, depression, cortisol, and growth hormone, can influence TSH secretion (Jackson, 1982; Gary et al., 1996). The target organ of TSH is the thyroid gland, where the synthesis and secretion of thyroid hormones, thyroxine (T4) and triiodothyronine (T3), occur within follicles (van der Spek et al., 2017).

Hyperthyroidism, characterized by excessive secretion of thyroid hormones, is associated with weight loss due to an increased metabolic rate, lower cholesterol levels, heightened lipolysis, and gluconeogenesis. In contrast, hypothyroidism, resulting from the under-secretion of thyroid hormones, leads to weight gain due to a decreased metabolic rate, elevated cholesterol levels, reduced lipolysis, and decreased gluconeogenesis (Motomura and Brent, 1998; Brent, 2012). Thyroid hormones have significant effects on the development of the central nervous system, its functional processes, and behavioral characteristics (Bernal, 2005).

Studies have demonstrated that thyroid hormones regulate oxytocin and arginine vasopressin, essential factors involved in the regulation of behaviors such as sociability, aggression, and maternal behavior (Ferguson et al., 2000; Choleris et al., 2003; Bielsky and Young 2004; Bielsky et al., 2004 and 2005; Crawley et al., 2007; Yu et al., 2016). Decreased thyroid function has been associated with decreased neurotransmitter levels in the brain (Ito et al., 1977; Whybrow and Prange, 1981; Henley and Koehnle 1997; Mano et al., 1998), and it was concluded that thyroid hormones are required for the synthesis of neurotransmitters that are actively involved in behavioral processes and aggression (Bernal and Nunez 1995; Vara et al., 2002). Similarly, thyroid hormone function is closely linked to the dopaminergic and serotonergic systems in the brain (Henley et al., 1991; Henley and Valdic, 1997; Bauer et al., 2002; Strawn et al., 2004).

Hypothyroidism-induced aggression has been reported in dogs in numerous studies (Beaver, 1999; Beaver and Haug, 2003; Mertens and Dodman, 2003). Hypothyroidism is thought to contribute to approximately 1.7% of aggressive behavior, which may occur even in the absence of lethargy, weight gain, and other characteristic clinical signs (Beaver, 1983 and 1999; Juarbe-Diaz, 2002). In dogs, aggression has been associated with increased concentrations of thyroglobulin autoantibody (TgAA) along with T4 and TSH concentrations (Graham et al., 2004). Some dogs with hypothyroidism exhibit a paradoxical response of excitement and aggressive behavior. The aggressive behaviors resemble those displayed in situations of dominance or fear-related aggression and can occur without other typical signs of hypothyroidism (Aronson, 1998; Beaver, 1999). Hypothyroidism in dogs may also manifest as lethargy, mental dullness, intolerance to cold and exercise, decreased libido, cognitive dysfunction, behavioral abnormalities, and aggression (Camps et al., 2019). Treatment with L-thyroxine or levothyroxine supplementation has been reported to alleviate polyneuropathy and aggressive behaviors in a dog exhibiting such symptoms (Indrieri, 1987). Additionally, it has been shown that behavioral expressions displaying aggressive behaviors toward the owner in dogs with hypothyroidism decrease following treatment (Beaver and Haug, 2003).

Conclusion

Studying aggressive behavior presents a significant challenge due to the complex and multifaceted activities of neurotransmitters involved, which are still under investigation. Establishing causal links between these neurotransmitters and aggression is highly challenging, as their interactions often involve other neurotransmitters, neuromodulators, neuropeptides, or hormones. While there are numerous instances where different neurotransmitters are implicated in aggressive behaviors, understanding the precise mechanisms by which these neurotransmitters function in the majority of animal models used for studying aggression remains unclear. Understanding how individuals of a particular breed respond to their competitors is crucial before socializing them and interacting with humans and highlights the continuing importance of studying aggressive behavior in dogs. Traditional therapeutic approaches have sometimes hindered progress in understanding the multifactorial mechanisms underlying aggression. However, the application of innovative techniques, such as epigenetic research methods, holds promise for gaining deeper insights into how environmental changes influence and promote aggressive behavior. By investigating changes in methylation patterns associated with aggression and exploring genes related to neurotransmitter receptors or transporters, we can significantly contribute to elucidating the causes of heightened aggression and identifying novel targets for aggression prevention and treatment.

Gaining knowledge about the functioning of each neurotransmitter and their interplay in situations of increased aggressive behavior triggered by various factors will facilitate the development of interventions for pathological aggression. By delving into the intricate mechanisms and relationships among neurotransmitters, we can better understand how aggressive behavior manifests and explore potential avenues for managing and mitigating aggression.

References

Almeida, R. M. M., Ferrari, P. F., Parmigiani, S., Miczek, K. A. (2005). Escalated aggressive behavior: Dopamine, serotonin and GABA. *European Journal of Pharmacology*, *526*, 51–64.

Almeida-Montes, L. G., Valles-Sanchez, V., Moreno-Aguilar, J. (2000). Relation of serum cholesterol, lipid, serotonin and tryptofhan levels to severity of depression and to suicide attempts. *Journal of Psychiatry and Neuroscience, 25* (4), 371-377.

Aronson, L. (1998). *Systemic causes of aggression and their treatment. In Psychopharmacology of Animal Behavior Disorders. Eds* N. H. Dodman, L. Shuster. Oxford, Blackwell Science, 88-92.

Askew, H. R. (1996). *Treatment of Behavior Problems in Dogs and Cats*. Blackwell Science, Oxford.

Bacqué-Cazenave, J., Bharatiya, R., Barrière, G., Delbecque, J. P., Bouguiyoud, N., Giovanni, G., Cattaert, D., Deurwaerdère, P. (2020). Serotonin in Animal Cognition and Behavior. *International Journal of Molecular Sciences, 21*(5), 1649.

Batmaz, T. (2021). *Toplumsal Cinsiyet Bağlamında Evcil Hayvan Besleme Davranışı Olarak Pitbull Tercihi*, 9. Türkiye Lisansüstü Çalışmalar Kongresi Bildiriler Kitabı – IV, 325-347.

Bauer, M., Heinz, A., Whybrow, P. C. (2002). Thyroid hormones, serotonin, and mood: of synergy and significance in the adult brain. *Molecular Psychiatry, 7*, 140-156.

Beauchaine, T. P., Gartner, J., Hagen, B. (2000). Comorbid depression and heart rate variability as predictors of aggressive and hyperactive symptom responsiveness during inpatient treatment of conduct-disordered. ADHD boys. *Aggressive Behavior, 26*, 425–441.

Beaver, B. (1992). *Canine behavior, aguide for veterinarians, 1th edition*, W. B. Saunders Co, Philadelpia, X+355.

Beaver, B. V. (1983). Clinical classification of canine aggression. *Applied Animal Ethology, 10*, 35–43.

Beaver, B. V. (1999). *Canine social behavior. In: Beaver, B.V. (Ed.), Canine Behavior: A Guide for Veterinarians*. W.B. Saunders, Philadelphia, PA, USA, 151–175.

Beaver, B. V. & Haug, L. I. (2003). Canine behaviors associated with hypothyroidism. *Journal of the American Animal Hospital Association, 39*, 431–434.

Beitchman, J. H., Zai, C. C., Muir, K., Berall, L., Nowrouzi, B., Choi, E. (2012). Childhood aggression, callous-unemotional traits and oxytocin genes. *European Child & Adolescent Psychiatry, 21*, 125-132.

Berger, M., Gray, J. A., Roth, B. L. (2009). The expanded biology of serotonin. *Annual Review of Medicine, 60*, 355-366.

Bernal, J. (2005). Thyroid hormones and brain development. Vitamins and hormones, 71, 95–122.

Bernal, J. and Nunez, J. (1995). Thyroid hormones and brain development. *European Journal of Endocrinology*, 133 (4), 390–398.

Bielsky, I. F. and Young, L. J. (2004). Oxytocin, vasopressin, and social recognition in mammals. *Peptides, 25*, 1565–1574.

Bielsky, I. F., Hu, S. B., Ren, X., Terwilliger, E. F., Young, L. J. (2005). The V1a vasopressin receptor is necessary and sufficient for normal social recognition: A gene replacement study. *Neuron, 47*, 503–513.

Bielsky, I. F., Hu, S. B., Szegda, K. L., Westphal, H., Young, L. J. (2004). Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. *Neuropsychopharmacology, 29*, 483–493.

Blacksaw, J. K. (1991). An overwiew of types of agressive behaviour in dogs and methods of treatment. *Applied Animal Behaviour Science, 30*, 351-361.

Brent, G. A. (2012). Mechanisms of thyroid hormone action. *Journal of Clinical Investigation, 122*, 3035–3043.

Buisman-Pijlman, F. T., Sumracki, N. M., Gordon, J. J., Hull, P. R., Carter, C. S., Tops, M. (2014). Individual differences underlying susceptibility to addiction: Role for the endogenous oxytocin system. *Pharmacology Biochemistry and Behavior, 119*, 22-38.

Çakıroğlu, D., Meral, Y., Sancak, A., Çiftçi, G. (2007). Relationship between the serum concentrations of serotonin and lipids and aggression in dogs. *The Veterinary Record, 161*(2), 59-61.

Camps, T., Amat, M., Manteca, X. (2019). A review of medical conditions and behavioral problems in dogs and cats. *Animals, 9*(12), 1133.

Chapman, B. L. and Voith,V. L. (1990). Behavioral problems in old dogs 26 cases (1984-1987). *Journal of the American Veterinary Medical Association*.

Cheng, S. Y., Leonard, J. L., Davis, P. J. (2010). Molecular aspects of thyroid hormone actions. *Endocrine Reviews*, *31*, 139 –170.

Choleris, E., Gustafsson, J. A., Korach, K. S., Muglia, L. J., Pfaff, D. W., Ogawa, S. (2003). An estrogen-dependent four-gene micronet regulating social recognition: A study with oxytocin and estrogen receptor-alpha and -beta knockout mice. *Proceedings of the National Academy of Sciences , 100*, 6192–6197.

Churchland, P. S. and Winkielman, P. (2012). Modulating social behavior with oxytocin: how does it work? what does it mean? *Hormones and Behavior, 61*, 392-399.

Crawley, J. N., Chen, T., Puri, A., Washburn, R., Sullivan, T. L., Hill, J. M., Young, N. B., Nadler, J. J., Moy, S. S., Young, L. J., Caldwell, H. K., Young, WS. (2007). Social approach behaviors in oxytocin knockout mice: Comparison of two independent lines tested in different laboratory environments. *Neuropeptides, 41*, 145–163.

de Oliveira, D. C., Zuardi, A. W., Graeff, F. G., Queiroz, R. H., Crippa, J. A. (2012). Anxiolytic-like effect of oxytocin in the simulated public speaking test. *Journal of Psychopharmacology, 26*, 497–504.

Diederich, N. J., Moore, C. G., Leurgans, S. E., Chmura, T. A., Goetz, C. G. (2003). Parkinson disease with old-age onset: a comparative study with subjects with middle-age onset. *Archives of neurology, 60*, 529–533.

Dodman, H. D., Donnelly, R., Shuster, L., Mertens, P., Rand, W., Miczek, K. (1996a). Use of fluoxetine to treat dominance aggression in dogs. *Journal of America Veterinary Medicine Association, 209*, 1585-1587.

Dodman, N. H., Moon, R., Zelin, M. (1996c). Influence of owner personality type on expression and treatment outcome of dominance aggression in dogs. *Journal of America Veterinary Medicine Association, 209*, 1107-1109.

Dodman, N. H., Reisner, I., Shuster, L., Rand, W., Luescher, U. A., Robinson, I. & Houpt, K. A. (1996b). Effect of dietary protein content on behavior in dogs. *Journal of America Veterinary Medicine Association, 208*, 376-379.

Dodurka, H. T. (1999). *Köpek Psikolojisi, 1.* Baskı, Teknik Yayınları, İstanbul, XII+201.

Dodurka, H. T. (2001). Köpeklerde görülen davranış sorunları ve bunlara etki etmesi. *Yüksek lisans Tezi,* Sosyal Bilimler Estitüsü.

Dodurka, H. T. (2005). *Köpeklerde Davranış Sorunları.* 1. Baskı, Remzi Kitabevi, İstanbul.

Duffy, D. L., Hsu, Y., Serpell, J. A. (2008). Breed differences in canine aggression. *Applied Animal Behaviour Science, 114*, 441–460.

Engelmann, M., Landgraf, R., Wotjak, C. T. (2004). The hypothalamicneurohypophysial system regulates the hypothalamic-pituitaryadrenal axis under stress: an old concept revisited. Frontiers in Endocrinology, 25, 132-149.

Feddersen-Petersen, D. (1990). Behavior of dogs. *Dtsch Tierarztl Wochenschr, 97*(6), 231-236.

Fekete, C. and Lechan, R. M. (2014). Central Regulation of Hypothalamic-Pituitary-Thyroid Axis under Physiological and Pathophysiological Conditions. *Endocrine Reviews, 35*, 159–194.

Ferguson, J. N., Young, L. J., Hearn, E. F., Matzuk, M. M., Insel, T. R., Winslow, J. T. (2000). Social amnesia in mice lacking the oxytocin gene. *Nature Genetics, 25*, 284–288.

Fitzgerald, P. (1999). Long-acting antipsychotic medication, restraint and treatment in the management of acute psychosis. *Australian & New Zealand Journal of Psychiatry, 33*, 660–666.

Frasch, A., Zetzsche, T., Steiger, A., Jirikowski, G. F. (1995). Reduction of plasma oxytocin levels in patients suffering from major depression. *Advances in Experimental Medicine and Biology, 395*, 257-258.

Gary, K. A., Winokur, A., Douglas, S. D., Kapoor, S., Zaugg, L., Dinges, D. F. (1996). Total sleep deprivation and the thyroid axis: effects of sleep and waking activity. Aviation*, Space, and Environmental Medicine, 67*, 513–519.

Glazer, W. M. and Dickson, R. A. (1998). Clozapine reduces violence and persistent aggression in schizophrenia. *Journal of Clinical Psychiatry, 59*(Suppl 3), 8–14.

Gou, Z. H., Wang, X., Wang, W. (2012). Evolution of neurotransmitter gamma-aminobutyric acid, glutamate and their receptors. *Zoological Research, 33*, E75-E81.

Graham, P. A., Lundquist, R. B., Refsal, K. R., Nachreiner, R. F. (2004). *Reported clinical signs in 8317 cases of canine hypothyroidism and 2647 cases of subclinical thyroiditis*. In: 2004 Scientific Proceedings of the British Small Animal Veterinary Association Congress, Birmingham, UK, 529.

Gunter, L. M., Barber, R. T., Wynne, C. D. L. (2016). What's in a Name? Effect of Breed Perceptions & Labeling on Attractiveness, Adoptions & Length of Stay for Pit-Bull-Type Dogs, *PLoS One, 11*(3), e0146857.

Hall, J. E., Simon, T. R., Lee, R. D., Mercy, J. A. (2012). Implications of direct protective factors for public health research and prevention strategies to reduce youth violence. *American Journal of Preventive Medicine, 43*(2 Suppl 1), S76–S83.

Hansen, N. and Manahan-Vaughan, D. (2012). Dopamine D1/D5 receptors mediate informational saliency that promotes persistent hippocampal long-term plasticity. *Cerebral Cortex, 24,* 845-858.

Henley, W. N. and Koehnle, T. J. (1997). Thyroid hormones and the treatment of depression: an examination of basic hormonal actions in the mature mammalian brain. *Synapse, 27(*1), 36–44.

Henley, W. N. and Valdic, F. (1997). Hypothyroid-induced changes in autonomic control have a central serotonergic component. *American Journal of Physiology-Heart and Circulatory Physiology, 272*, 894–903.

Henley, W. N., Chen, S., Klettner, C., Bellush, L., Notestine, M. A. (1991). Hypothyroidism increases serotonin turnover and sympathetic activity in the adult rat. *Canadian Journal of Physiology and Pharmacology, 69*, 205–210.

Holt-Lunstad, J., Birmingham, W., Light, K. C. (2011). The influence of depressive symptomatology and perceived stress on plasma and salivary oxytocin before, during and after a support enhancement intervention. *Psychoneuroendocrinology, 36*, 1249-1256.

Horwitz, D. F. (2000). Differences and similarities between behavioral and internal medicine. *Journal of America Veterinary Medicine Association, 217*, 1372-1376

Houpt, K. A. and Reisner, I. R. (1995). *Behavioral disoders,* volume 1, 4th edition. Editors: Etine, S. J. and Feldman, E. C. Veterinary Internal Medicine. W. B. Saunders Co. Philadelphia, 179-187.

Houpt, K. A., Honig, S. U., Reisner, I. R. (1996). Breaking the human-Companion animal bond. *Journal of America Veterinary Medicine Association, 208*, 1653-1658.

Hsu, Y. and Serpell, J. A., (2003). Development and validation of a questionnaire for measuring behavior and temperament traits in pet dogs. Journal of America Veterinary Medicine Association, *223*, 1293–1300.

Indrieri, R. J., Whalen, L. R., Cardinet, G. H., Holliday, T. A. (1987). Neuromuscular abnormalities associated with hypothyroidism and lymphocytic thyroiditis in three dogs. *Journal of the American Veterinary Medical Association*, *190*(5), 544–548.

Insel, T. R. (2010). The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. *Neuron, 65*, 768-779.

Ishak, W. W., Kahloon, M., Fakhry, H. (2011). Oxytocin role in enhancing well-being: a literature review. *Journal of Affective Disorders, 130*, 1-9.

Ito, J. M., Valcana, T., Timiras, P. S. (1977). Effect of hypo- and hyperthyroidism on regional monoamine metabolism in the adult rat brain. *Neuroendocrinology, 24*(1), 55–64.

Jackson, I. M. D. (1982). Thyrotropin-releasing hormone. *The New England Journal of Medicine, 306*, 145–155.

Jagoe, J. A. (1994). *Behaviour problems in the domestic dog: a retrospective and prospective study to identify factors influencing their development* (Doctoral thesis). https://doi.org/10.17863/CAM.31066Phd thesis.

Juarbe-Diaz, S. V. (2002). *Behavioral imposters of medical disorders in small animals*, In: Proceedings of the Forum of the American College of Veterinary Internal Medicine.

Kennedy, J. S., Bymaster, F. P., Schuh, L., Calligaro, D. O., Nomikos, G., Felder, C. C., Bernauer, M., Kinon, B. J., Baker, R. W., Hay, D., Roth, H., Dossenbach, M., Kaiser, C., Beasley, C. M., Holcombe, J. H., Effron, M. B., Breier, A. (2001). A current review of olanzapine's safety in the geriatric patient: from pre-clinical pharmacology to clinical data. *International Journal of Geriatric Psychiatry*, *16*, 33–61.

Kırlı, S. (2000). *Depresyonun Biyolojik Oluşumu ve Farmakolojik Tedavisi*, F. Özcan Matbaacılık San. Ve Tic. Ltd. Şti., Bursa, 31-97.

Kogan, L. R., Schoenfeld-Tacher, R. M., Hellyer, P. W., Oxley, J. A., Rishniw, M. (2019). Small Animal Veterinarians' Perceptions, Experiences, and Views of Common Dog Breeds, Dog Aggression, and Breed-Specific Laws in the United States. *International Journal of Environmental Research and Public Health, 16*(21), 4081.

Kuhne, F. (2012). Castration of dogs from the standpoint of behaviour therapy. *Tierarztl Prax Ausg K Kleintiere Heimtiere, 40*(2), 140-145.

Kwan, J. Y. and Bain, M. J. (2013). Owner attachment and problem behaviors related to relinquishment and training techniques of dogs. *Journal of applied animal welfare science, 16*(2), 168-183.

Landsberg, G. M. (1990). Diagnosing dominance agresyon. *Canadian Veterinary Journal, 31*, 45-46.

Landsberg, G. M., Hunthausen, W. L., Ackerman, L. J. (1997). *Handbook of behavior problems of the dog and cat*. Saunders.

Lee, G. and Gammie, S. C. (2009). GABAA receptor signaling in the lateral septum regulates maternal aggression in mice. *Behavioral Neuroscience, 123*(6), 1169-1177.

Lee, R., Ferris, C., Van de Kar, L. D., Coccaro, E. F. (2009). Cerebrospinal fluid oxytocin, life history of aggression, and personality disorder. *Psychoneuroendocrinology, 34*, 1567-1573.

Lesch, K. L. and Merschdorf, U. (2000). Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. *Behavioral Science and Law*, *18*, 581-604.

Liinamo, A., van den Berg, L., Leegwater, P. A. J., Schilder, M.B.H., van Arendonk, J.A.M., van Oost, B.A., (2007). Genetic variation in aggression-related traits in golden retriever dogs. *Applied Animal Behaviour Science. 104*, 95 –106.

MacNeil-Allcock, A., Clarke, N. M., Ledger, R. A., Fraser, D. (2011). Aggression, behaviour, and animal care among pit bulls and other dogs adopted from an animal shelter. *Animal Welfare, 20*, 463-468.

Mano, T., Sakamoto, H., Fujita, K., Makino, M., Kakizawa, H., Nagata, M., Kotake, M., Hamada, M., Uchimura, K., Hayakawa, N., Hayashi, R., Nakai, A., Itoh, M., Kuzuya, H., Nagasaka, A. (1998). Effects of thyroid hormone on catecholamine and its metabolite concentrations in rat cardiac muscle and cerebral cortex. *Thyroid, 8*, 353–358.

Masi, G. (2004). Pharmacotherapy of pervasive developmental disorders in children and adolescents. CNS *Drugs, 18*, 1031–1052.

Mertens, P. and Dodman, N. (2003). Animal behavior case of the month. *Journal of the American Veterinary Medical Association, 223*, 1436-1442.

Miczek, K. A., de Almeida, R. M. M., Kravitz, E. A., Rissman, E. F., de Boer, S. F., Raine, A. (2007). Neurobiology of escalated aggression and violence. *Journal of Neuroscience, 27*, 11803–11806.

Miczek, K. A., Faccidomo, S., de Almeida, R. M., Bannai, M., Fish, E. W., de Bold, J. F. (2004). Escalated aggressive behavior: new pharmacotherapeutic approaches and opportunities. *Annals of the New York Academy of Sciences journal, 1036*, 336–355.

Miczek, K. A., Fish, E. W., de Bold, J. F. (2003). Neurosteroids, GABAA receptors, and escalated aggressive behavior. *Hormones and Behavior, 44*, 242-257.

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

Miller, K. A., Touroo, R., Spain, C. V., Jones, K., Reid, P., Lockwood, R. (2016). Relationship Between Scarring and Dog Aggression in Pit Bull-Type Dogs Involved in Organized Dogfighting. *Animals, 6*, 72.

Mokler, D. J., Dugal, J. R., Hoffman, J. M., Morgane, P. J. (2009). Functional interrelations between nucleus raphé dorsalis and nucleus raphé medianus: a dual probe microdialysis study of glutamate-stimulated serotonin release. *Brain Research Bulletin, 78*, 132-138.

Motomura, K. and Brent, G. A. (1998). Mechanisms of thyroid hormone action. Implications for the clinical manifestation of thyrotoxicosis. *Endocrinology & Metabolism Clinics of North America, 27*, 1–23.

Neumann, I. D. (2007). Stimuli and consequences of dendritic release of oxytocin within the brain. *Biochemical Society Transactions, 35*, 1252-1257.

Niyyat, M. R., Azizzadeh, M., Khoshnegah, J. (2018). Effect of Supplementation with Omega-3 Fatty Acids, Magnesium, and Zinc on Canine Behavioral Disorders: Results of a Pilot Study. *Topics in Companion Animal Medicine, 33*(4), 150-155.

Notari, L., Burman, O., Mills, D. (2015). Behavioural changes in dogs treated with corticosteroids. *Physiology & behavior, 151*, 609-616.

Noyan, A. (2007). *Yaşamda ve Hekimlikte Fizyoloji*, Palme Yayınları.

O'Farrell, V. (1992). *Manual of canine behviour 2th edition,* Cheltenhan Glos British Small Animal Veterinary Assoiation, XII+132.

Odendaal, J. S. J. (1997). A Diagnostic Classification of Problem Behavior in Dogs and Cats. Veterinary Clinics of *North America: Small Animal Practice, 27*, 427-442.

Odore, R., Rendini, D., Badino, P., Gardini, G., Cagnotti, G., Meucci, V., Intorre, L., Bellino, C., D'Angelo, A. (2020). Behavioral Therapy and Fluoxetine Treatment in Aggressive Dogs: A Case Study. *Animals (Basel), 10*(5), 832.

O-Klein, M., Battagello, D. S., Cardoso, A. R., Hauser, D. N., Bittencourt, J. C., Correa, R. G. (2019). Dopamine: Functions, Signaling, and Association with Neurological Diseases. *Cellular and Molecular Neurobiology, 39*(1), 31-59.

Overall, K. L. (1997). Pharmacologic treatments for behavior problems. *Veterinary Clinics of North America: Small Animal Practice, 27*, 637-665.

Ozsoy, S., Esel, E., Kula, M. (2009). Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. *Psychiatry Research, 169*, 249-252.

Pineda, S., Anzola, B., Olivares, A., Ibáñez, M. (2014). Fluoxetine combined with clorazepate dipotassium and behaviour modification for treatment of anxiety-related disorders in dogs. *The Veterinary Journal, 199*(3), 387-391.

Quadros, I. M., Miguel, T. T., de Bold, J. F., Miczek, K. A. (2009a). *Opposing action of CRF1 vs. CRF2 receptors in the dorsal raphé: modulation of alcohol-heightened aggression*. Neuroscience meeting planner. Society for neuroscience, Chicago, Program No. 445.5/T8.

Quadros, I. M., Takahashi, A., Miczek, K. A. (2009b). *Serotonin and aggression.* In: Müller CP, Jacobs BL (eds) Handbook of the behavioral neurobiology of serotonin. Academic Press, 687–714.

Rapport, M. M., Green, A. A., Page, I. H. (1948). Serum vasoconstrictor, serotonin; isolation and characterization. *Journal of Biological Chemistry, 176*, 243–251. Reisner, I. R., Erb, H. N., Houpt, K. A. (1994). Risk factors for behavior -related euthanasia among dominant-aggressive dogs: 110 cases (1989-1992). *Journal of America Veterinary Medicine Association, 205*, 855-863.

Reisner, I. R., Mann, J. J., Stanley, M., Huang, Y., Houpta, K. A. (1996). Comparison of cerebrospinal fluid monoamine metabolite levels in dominant-aggressive and non-aggressive dogs. *Brain Research, 714* (1-2), 57-64.

Resmi Gazete, 01.07.2004; https://www.resmigazete.gov.tr/eskiler/2004/07/20040701.htm

Resmi Gazete, 14.07.2021; https://www.resmigazete.gov.tr/eskiler/2021/07/20210714-9.htm

Rosell, D. R. and Siever, L. J. (2015). The neurobiology of aggression and violence. *CNS Spectrums, 20,* 254–279.

Roth, B. L., (2007). editor. The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics. Totowa, NJ: Humana.

Sanchez, C., Arnt, J., Hyttel, J., Moltzen, E. K. (1993). The role of serotonergic mechanisms in inhibition of isolation-induced aggression in male mice. *Psychopharmacology, 110*, 53–59.

Serpell, J. A. and Hsu, Y. A. (2005). Effects of breed, sex, and neuter status on trainability in dogs. *Anthrozoös, 18*(3), 196-207.

Siddiq, A. B. (2019). Tarih öncesi toplumlarda insan-hayvan ilişkisi ve Orta Anadolu çanak çömleksiz neolitik dönem faunası. 1. Baskı. Konya: Çizgi Kitabevi.

Stepherd, R. C. (2018). *Pit Bull:* Journal. Independently published, ISBN-10: 1720108668.

Strawn, J. R., Ekhator, N. N., D'Souza, B. B., Geracioti Jr, T. D. (2004). Pituitary-thyroid state correlates with central dopaminergic and serotonergic activity in healthy humans. *Neuropsychobiology, 49*, 84–87.

Sweidan, S., Edinger, H., Siegel, A. (1991). D2 dopamine receptor-mediated mechanisms in the medial preoptic-anterior hypothalamus regulate effective defense behavior in the cat. *Brain Research, 549*, 127–137.

Takahashi, A., Kwa, C., de Bold, J. F., Miczek, K. A. (2010a). GABAA receptors in the dorsal raphé nucleus of mice: escalation of aggression after alcohol consumption. *Psychopharmacology, 211*, 467-477.

Takahashi, A., Quadros, I. M., de Almeida, R. M., Miczek, K. A. (2011). Brain serotonin receptors and transporters: initiation vs. termination of escalated aggression. *Psychopharmacology, 213*, 183–212.

Takahashi, A., Quadros, I. M., de Almeida, R. M., Miczek, K. A. (2012). Behavioral and pharmacogenetics of aggressive behavior. *Current Topics in Behavioral Neurosciences, 12*, 73-138.

Takahashi, A., Shimamoto, A., Boyson, C. O., De Bold, J. F., Miczek, K. A. (2010b). GABAB receptor modulation of serotonin neurons in the dorsal raphé nucleus and escalation of aggression in mice. *Journal of Neuroscience, 30*(35), 11771-11780.

Takayanagi, Y., Yoshida, M., Bielsky, I. F., Ross, H. E., Kawamata, M., Onaka, T. (2005). Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. *Proceedings of the National Academy of Sciences of the United States of America* , *102*, 16096-16101.

Tidey, J. W. and Miczek, K. (1992a). Effects of SKF38393 and quinpirole on patterns of aggressive, motor and schedule-controlled behaviors in mice. *Behavioural Pharmacology,* Tidey, J. W. and Miczek, K. A. (1992b). Morphine withdrawal aggression: modification with D1 and D2 receptor agonists. *Psychopharmacology, 108*, 177–184.

Turan, T., Uysal, C., Asdemir, A., Kılıç, E. (2013). May oxytocin be a trait marker for bipolar disorder? *Psychoneuroendocrinology, 38*, 2890-2896.

Uchida, Y., Dodman, N., Denapoli, J., Aronson, L. (1997). Characterization and treatmant of 20 canine dominance aggression cases. *Journal of Veterinary Medical Science, 59*(5), 397-399.

van der Spek, A. H., Fliers, E., Boelen, A. (2017). The classic pathways of thyroid hormone metabolism. *Molecular and Cellular Endocrinology, 458*, 29-38.

Vara, H., Martinez, B., Santos, A., Colino, A. (2002). Thyroid hormone regulates neurotransmitter release in neonatal rat hippocampus. *Neuroscience, 110*(1), 19–28.

Wassef, A, Baker, H., Kochan, L. D. (2003). GABA and schizophrenia: a review of basic science and clinical studies. *Journal of Clinical Psychopharmacology, 23*(6), 601-640.

Weisman, O., Zagoory-Sharon, O., Schneiderman, I., Gordon, I., Feldman, R. (2013). Plasma oxytocin distributions in a large cohort of women and men and their gender-specific associations with anxiety, *Psychoneuroendocrinology, 38*, (5), 694-701.

Whybrow, P. C. and Prange, A. J. (1981). A hypothesis of thyroid-catecholaminereceptor interaction: its relevance to affective illness. *Archives of General Psychiatry, 38*(1), 106–113.

Wright, H. F., Mills, D. S., Pollux, P. M. J. (2012). Behavioural and physiological correlates of impulsivity in the domestic dog (Canis familiaris). *Physiology and Behaviour, 105*(3), 676-682.

Yeon, S. C., Erb, H. N., Houpt, K. A. (1999). A retrospective study of canine house soiling: *Diagnosis and treatment, 35*, 101-106.

Yoshida, M., Takayanagi, Y., Inoue, K., Kimura, T., Young, L. J., Onaka, T. (2009). Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. *Journal of Neuroscience, 29*, 2259-2271.

Yu, C. J., Zhang, S. W., Tai, F. D. (2016). Effects of nucleus accumbens oxytocin and its antagonist on social approach behavior. *Behavioral Pharmacology, 27*, 672–680.

Yu, Q., Teixeira, C. M., Mahadevia, D., Huang, Y., Balsam, D., Mann, J. J., Gingrich, J. A., Ansorge, M. S. (2014). Dopamine and serotonin signaling during two sensitive developmental periods differentially impact adult aggressive and affective behaviors in mice. *Molecular Psychiatry, 19*(6), 688-698.

Zapata, I., Serpell, J. A., Alvarez, C. E. (2016). Genetic mapping of canine fear and aggression. *BMC Genomics*, 17, 572.