The human as a model for Attention deficit hyperactivity disorder (ADHD) in domestic dogs (*Canis familiaris*)

Master thesis Behavioural Neuroscience

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Abstract

Attention deficit hyperactivity disorder (ADHD) has a high prevalence in human children. Many studies have investigated the ethiology, diagnostics and therapeutics of the disorder in humans. Domestic dogs (*Canis familiaris*) display a behavioural disorder that appears to be identical to ADHD in humans. Nevertheless, this disorder is not as thoroughly analysed as in humans. The studies that were conducted on ADHD in domestic dogs have demonstrated many similarities in behavioural characteristics, diagnostics and therapeutics compared to ADHD in humans. This suggests that the same underlying mechanisms are involved in the ethiology of the disorder. It seems that the human can serve as a suitable model for ADHD in domestic dogs to expand the knowledge on the ethiology of ADHD and to assist in developing alternative pharmacological interventions.

1. Introduction

1.1 ADHD in humans

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurobehavioural disorder that is characterized by persistent symptoms of inattention, hyperactivity and impulsivity that typically has an onset during childhood and can persist into adulthood (Davids et al. 2003, Pelsser et al. 2009, Wilens 2006)(Box 1). Inattention may refer to the lack of persistence in activities, frequent changes in activity and being easily distracted by task-irrelevant stimuli in the environment (Sandberg 2002). Hyperactivity includes excessive motor activity and can be observed as restlessness when being awake or in sleep (Sandberg 2002, Culpepper 2006). Impulsivity can be defined as acting or making decisions without appropriate forethought that can therefore enhance negative consequences (Sandberg 2002, Culpepper 2006).

ADHD is the one of the most prevalent behavioural disorders in children, since about 3 to 7 percent of school-aged children is affected (Antshel et al. 2011, Biederman 2006, Fone & Nutt 2005). ADHD is both diagnosed in boys and girls, but is more often recognized in boys since they display more overactive and disruptive behaviour (Davids et al. 2003). Many of these children remain influenced by symptoms of ADHD in adolescence and 20 to 50 percent of these children are still affected in adulthood (Buitelaar & Kooij 2000). Therefore, about 4 to 5 percent of adults are affected by the disorder (Antshel et al. 2011, Weiss et al. 2006). It has been demonstrated that the symptoms of hyperactivity and impulsivity decline with increasing age, whereas the symptoms of inattention remain at the same level with increasing age (Culpepper 2006, Lahey et al. 1994).

Humans with ADHD often have severe impaired social relationships, behavioural and educational functioning, together with increased substance abuse, aggressiveness, risk-taking behaviour and underemployment (Antshel et al. 2011, Lit et al. 2010, Spencer 2006). ADHD often co-occurs with other psychiatric and learning disorders, such as mood disorders, conduct disorder and anxiety disorders (Antshel et al. 2011, Spencer 2006).

Three subtypes of ADHD are distinguished, namely the primarily inattentive type (ADD), primarily hyperactive-impulsive type (ADDH) and the combined type (ADHD) (Lahey et al. 1994, Rader et al. 2009) (Box 1). The predominantly inattentive type is not very often diagnosed in children, since this type is more associated with depression, anxiety disorders and reduced school performance and less with behavioural problems (Culpepper 2006, Buitelaar & Kooij 2000). The combined type is most often diagnosed and is meant when we speak about ADHD (Buitelaar & Kooij 2000).

Box 1. DSM-IV[a] Criteria for attention deficit hyperactivity disorder diagnostics

I. Either A or B

A. **Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level:**

Inattention

1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
2. Often has trouble keeping attention on tasks or play activities.
3. Often does not seem to listen when spoken to directly.
4. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions).
5. Often has trouble organizing activities.
6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
7. Often loses things needed for tasks and activities (e.g. toys, school assignments, pencils, books, or tools).
8. Is often easily distracted.
9. Is often forgetful in daily activities.

B. Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:

Hyperactivity

1. Often fidgets with hands or feet or squirms in seat.
2. Often gets up from seat when remaining in seat is expected.
3. Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
4. Often has trouble playing or enjoying leisure activities quietly.
5. Is often "on the go" or often acts as if "driven by a motor".
6. Often talks excessively.

Impulsivity

1. Often blurts out answers before questions have been finished.
2. Often has trouble waiting one's turn.
3. Often interrupts or intrudes on others (e.g., butts into conversations or games).

II. Some symptoms that cause impairment were present before age 7 years.

III. Some impairment from the symptoms is present in two or more settings (e.g. at school/work and at home).

IV. There must be clear evidence of significant impairment in social, school, or work functioning.

V. The symptoms do not happen only during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder. The symptoms are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Based on these criteria, three types of ADHD are identified:

1. ADHD, *Combined Type*: if both criteria 1A and 1B are met for the past 6 months
2. ADHD, *Predominantly Inattentive Type*: if criterion 1A is met but criterion 1B is not met for the past six months
3. ADHD, *Predominantly Hyperactive-Impulsive Type*: if Criterion 1B is met but Criterion 1A is not met for the past six months.

[a]*Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition

1.2 Causes of ADHD in humans

Genetic factors play a dominant role in the ethiology of ADHD (Biederman 2006, Fone & Nutt 2005). Family studies have shown that first-degree relatives of children with ADHD have a 2- to 8-fold increase in risk for ADHD (Fone & Nutt 2005, Buitelaar & Kooij 2000). Twin and adoption studies have also shown that ADHD is highly heritable (Banaschewski et al. 2010). About 77% of the variance in inattention, hyperactivity and impulsivity between children can be explained by genetic factors (Buitelaar & Kooij 2000). However, studies have also shown inconsistent outcomes of gene variants associated with ADHD, which can be due to the influence of environmental factors that differ between study samples (Wermter et al. 2010).

The prevalence of ADHD varies in the literature, since risk factors include age, family dysfunction, medical conditions that affect brain development, low socioeconomic status, urban living, other behavioural disorders and several environmental factors (Rader et al. 2009, Lavigne et al. 1996). Environmental risk factors consist of low birth weight, foetal exposure to nicotine and alcohol, psychosocial adversity, and lead contamination and are associated with ADHD (Davids et al. 2003, Sandberg 2002, Buitelaar & Kooij 2000, Das Banerjee et al. 2007). In more detail, when the child's birth weight is lower than 2500 gram or when the pregnancy is shorter than 32 weeks, a heightened risk for ADHD is demonstrated (Buitelaar & Kooij 2000). Similarly, prenatal exposure to maternal alcohol use causes children to be hyperactive, disruptive and impulsive and they show an increased risk for multiple psychiatric disorders and psychosocial deficits (Das Banerjee et al. 2007). Prenatal exposure to maternal smoking has an influence on the pre- and postnatal growth, cognitive development and behaviour of children and adolescents and increases the risk of foetal mortality (Das Banerjee et al. 2007). Psychosocial adversity, such as maltreatment and emotional trauma can enhance the development of ADHD (Davids et al. 2003, Buitelaar & Kooij 2000, Das Banerjee et al. 2007).

In summary, the emergence of ADHD in humans seems to be caused by genes and the development of ADHD is affected by the interaction of genes with environmental

factors, whereby the most important external risk factors the ones are that occur during early development (Das Banerjee et al. 2007). The genetic and environmental interaction is probably the reason for the phenotypic complexity of ADHD (Das Banerjee et al. 2007).

1.3 ADHD in domestic dogs (Canus familiaris)

Apparently, ADHD-like behaviour pathologies seem to be present in animals such as domestic dogs (*Canis familiaris*), which display a disorder that appears to be similar to ADHD in humans (Corson & Corson 1988). Dogs of the ADHD-type are described to be unable to relax and show spontaneous activity even when no stimulation is present. They have an increased temperature, heart rate and respiration rate during rest, which remain at the same level when active (Bowen & Heath 2007). These dogs have a poor attention span, lack trainability and sometimes display aggressive behaviour (Landsberg et al. 2004). ADHD seems to be a rare and severe behavioural disorder that has a neurophysiologic origin (Bowen & Heath 2007, Landsberg et al. 2004). The symptoms of ADHD are associated with other medical conditions such as neurological, endocrine, liver disease and food allergy (Bowen & Heath 2007). However, the precise ethiology of ADHD in dogs remains unclear but it seems that genetic factors interact with environmental factors, which is similar to the ethiology of the human variant of ADHD (Corson & Corson 1988, Hejjas et al. 2007b).

1.4 Comparison between ADHD in humans and domestic dogs

Many studies have analysed ADHD in humans, concerning prevalence, causes, underlying mechanisms, diagnostics and therapy, whereas only a few studies have analysed ADHD in domestic dogs. Nevertheless, it is assumed that research and knowledge on humans may provide a better insight into genetic disorders such as ADHD (Hejjas et al. 2007b). Humans can thereby serve as a model for ADHD in domestic dogs.

The criterium that has to be met when the human is used as a model for ADHD in domestic dogs is that the model should resemble the disorder in as many details as possible in relation to ethiology, pathophysiology, treatment and biochemistry (Davids et al. 2003, Sagvolden et al. 2005). In other words, a model for ADHD must resemble the fundamental behavioural characteristics of ADHD (face validity), conform the theoretical rationale (construct validity) and predict unknown aspects of ADHD, such as genetics, novel therapeutics and neurobiology (predictive validity) (Davids et al. 2003, Lit et al. 2010, Sagvolden et al. 2005).

In the number of genes, humans and dogs are genetically quite similar and many of these genes have evolved from the same ancestral genes (Lit et al. 2010). Human

psychopharmacological agents for other behaviour disorders, such as obsessive-compulsive disorders and generalised anxiety disorders, have been successfully used in dogs with phenotypically similar behaviour (Lit et al. 2010). This demonstrates that the same biological underlying mechanisms might be involved in humans and dogs for these behavioural disorders. Since there are similarities between humans and dogs in behaviour, genes and the action of therapeutic agents, the same biological underlying mechanisms are also assumed to be involved in ADHD (Lit et al. 2010, Vas et al. 2007).

Since many criteria of an ideal model are met when the human is proposed as a model for ADHD in domestic dogs, it seems that the human may be suitable for this purpose. Moreover, knowledge on humans might be helpful in ADHD diagnostics and therapeutics in companion animals in the future, in this case domestic dogs.

In the following chapters, the underlying mechanisms, diagnostics and therapeutics for humans and domestic dogs are described. The similarities and dissimilarities between ADHD in humans and domestic dogs are revealed. This will finally demonstrate to what extent the human can serve as a model for ADHD in domestic dogs.

2. Underlying mechanisms of ADHD

2.1 The human prefrontal cortex

Many studies have demonstrated neurocognitive dysfunctions that are associated with ADHD in humans (Doyle 2006). Many brain regions and several neurotransmitters are associated with ADHD in humans, whereby the prefrontal cortex (PFC) is mostly affected in ADHD (Davids et al. 2003, Antshel et al. 2011, Arnsten 2006). The PFC uses information from the working memory to guide overt (movements) and covert responses (attention) to inhibit inappropriate behaviours and the processing of irrelevant stimuli (Arnsten et al. 2007).

The PFC can be divided in five subdivisions, namely the prefrontal (orbital, dorsolateral and mesial), premotor and motor regions. The orbital frontal (OF) and dorsolateral prefrontal cortex (DLPFC) appear to be mostly involved in ADHD (Seidman et al. 2005). Orbital frontal lesions are associated with social and impulse dyscontrol, whereas DLPFC lesions are associated with organizational, planning, working memory and attention dysfunctions (Davids et al. 2003, Seidman et al. 2005). Functional imaging studies have shown that patients with ADHD usually have a smaller PFC volume, especially in the right hemisphere (Arnsten et al. 2007, Castellanos et al. 1996). Other studies have shown that the blood flow or metabolism in the PFC is inefficient or reduced in ADHD patients (Buitelaar & Kooij 2000, Arnsten 2006). Related subcortical structures, such as the basal ganglia, cerebellum, corpus callosum, pallidum and the parallel

projections between the PFC and these structures are also reduced in volume in ADHD patients (Seidman et al. 2005, Castellanos et al. 1996).

The PFC is very sensitive for its neurochemical environment. The influence of PFC on behaviour and attention is determined by the levels of catecholamines that are released in the PFC, which include dopamine, epinephrine and norepinephrine, (Arnsten et al. 2007). Moderate levels of catecholamines are essential for PFC functioning, while very low or high levels, e.g. during stress, can impair PFC functioning (Arnsten 2006). Similarly, the basal ganglia are regulated by dopamine and the cerebellum is modulated by norepinephrine (Arnsten 2006).

2.2 The human dopaminergic system

The dopaminergic system is mostly studied in ADHD, since many brain circuits associated with ADHD are dependent on optimal dopaminergic neurotransmission (Banaschewski et al. 2010). Dopamine regulates behaviours such as risk taking and impulsivity (Rader et al. 2009) and acts at the D1 (D1,D5) and D2 (D2, D3, D4) families of dopamine receptors and thereby regulates PFC functioning (Arnsten 2006). The D4 receptor has also affinity for norepinephrine and is therefore actually a catecholamine receptor (Wilens 2006). The most frequently analysed genes of the dopaminergic system are the genes that encode for the D4 dopaminergic receptor (DRD4) and the dopamine transporter gene (DAT1/SLC6A3) (Banaschewski et al. 2010, Nieoullon 2002). ADHD is associated with a 48 base-pair (48 bp) tandem repeat polymorphism of exon III of the DRD4 gene, since the D4-receptor sensitivity is weakened by a certain variant of the exon (Arnsten 2006). The DRD4 gene encodes for a receptor that is mainly expressed in the prefrontal cortex (Banaschewski et al. 2010) and variations of the gene are related to the behavioural traits excitability and aggression (Hejjas et al. 2007b).

Polymorphism in a 40 base-pair (40 bp) variable tandem nucleotide repeat in the 3'-untranslated region of the human DAT1 gene is also associated with ADHD (Fone & Nutt 2005). This gene plays a role in the uptake of dopamine in dopaminergic neurotransmission (Hejjas et al. 2007a). Although a role for the genes of the dopaminergic system has been established in the ethiology of ADHD in humans, further research is necessary, since many genes that are involved in ADHD are still unidentified.

2.3 The human noradrenergic system

Another well-studied neurotransmitter system is the noradrenergic system, which is associated with the regulation of attention, alertness and vigilance (Arnsten 2006). The noradrenergic system seems to be more involved in the inattentive symptoms, rather than the hyperactivity and impulsivity symptoms of ADHD (Banaschewski et al. 2010).

Norephineprine acts at the α_1- and α_2-adrenergic receptors and the β_1-, β_2- and β_3-adrenergic receptors (Arnsten 2006). Postsynaptic actions at the α_{2A}-adrenergic receptor (ADRA2A) improve PFC functioning, whereas actions at the α_1- and β_1-adrenergic receptors impair PFC functioning (Arnsten 2006). The mostly investigated noradrenergic genes are the ones that encode for the noradrenergic transporter (NET1/SLC6A2), the α_{2A}-adrenergic receptor and the α_{2C}-adrenergic receptor (ADRA2C) (Banaschewski et al. 2010, Faraone & Khan 2006). There is evidence that these genes are associated with ADHD, but this is mainly based on studies with a small sample size whereby only single polymorphisms were investigated (Faraone & Khan 2006). Therefore, more research is necessary to establish the role of the noradrenergic system in the ethiology of ADHD in humans.

2.4 The human serotonergic system

The serotonergic neurotransmission system has also been related to the ethiology of ADHD in humans. Serotonin is associated with the impulsivity symptoms of ADHD (Banaschewski et al. 2010, Hawi et al. 2002, Winstanley et al. 2006). The genes of the serotonergic system that have been intensively studied are the ones that encode for the serotonin transporter (HTT/SLC6A4), the 1B (HTR1B) and 2A (HTR2A) serotonin receptors and the rate-limiting enzyme tryptophan hydroxylase (TPH2), that is involved in the catalyzation of serotonin (Banaschewski et al. 2010, Faraone et al. 2005, Mick & Faraone 2008). Polymorphisms in the TPH gene are associated with impulsivity and aggression (Faraone & Khan 2006, Mick & Faraone 2008). Although these genes are demonstrated to be associated with ADHD by many studies, contradictory findings have been shown as well (Faraone et al. 2005). It seems that the serotonin neurotransmitter system needs further analysis, because only small sample sizes have been used in previous studies (Banaschewski et al. 2010). The study samples, also varied in age, gender, ethnicity and comorbidity and these factors could have influenced the results (Banaschewski et al. 2010).

2.5 The canine dopaminergic system

The dopaminergic neurotransmitter system has been associated with ADHD in domestic dogs (Luescher 1993). The variable number of tandem repeats polymorphisms (VNTRs) in multiple genes of the dopaminergic system of the dog have been investigated (Hejjas et al. 2007a). The dopamine D4 receptor gene (DRD4) is the most intensively analysed candidate gene in association with ADHD in humans (Faraone et al. 2005). Polymorphisms in exon III of the DRD4 gene seem to be associated with ADHD in humans and also in multiple dog breeds (Hejjas et al. 2007b, Hejjas et al. 2007a, Ito et

al. 2004). However, this association between ADHD and the DRD4 gene in dogs was only demonstrated in a homologues police dog sample, since the dogs were from the same breed and had similar environmental conditions (Hejjas et al. 2007b). Therefore, it seems that a genetically and environmental homologues sample is necessary for the analysis of a phenotype-genotype association (Hejjas et al. 2007a).

VNTRs in other genes, such as the dopamine transporter (DAT), the dopamine β-hydroxylase (DBH) and the tyrosine hydroxylase (TH) gene, have also been studied in dogs (Hejjas et al. 2007a). Preliminary results with small sample size have shown that polymorphisms of the DAT and DBH genes are associated with ADHD in one dog breed (Hejjas et al. 2007a). Large genetic variation has also been demonstrated between dog breeds, which show that large sample sizes are needed for reliable measures (Hejjas et al. 2007a). More research is necessary to identify the role of certain genes in the ethiology of ADHD in dogs.

2.6 Summary

ADHD is a highly heritable behavioural disorder which is demonstrated by familial studies in humans. ADHD in humans and dogs has a very complex genetic background whereby many genes are involved in the ethiology of the disorder. Many human candidate genes are already identified but these genes have small and sometimes inconsistent effects, whereas in dogs only a few genes with similarly small and inconsistent effects have been identified (Faraone et al. 2005). Therefore, it is advised to identify more candidate genes in humans and dogs to provide enough statistical power for detecting small effects of genes (Mick & Faraone 2008). Polymorphisms in genes of the dopaminergic neurotransmitter systems are associated with ADHD in both humans and dogs (Hejjas et al. 2007b, Hejjas et al. 2007a, Ito et al. 2004), which shows that there are similarities in the genetic background of ADHD in humans and dogs.

3. Diagnostics for ADHD

3.1 Diagnostic methods for ADHD in humans

There is no specific psychological or biological diagnostic test available for the diagnosis of ADHD in children and adults (Davids et al. 2003, Buitelaar & Kooij 2000). The diagnosis of ADHD is made on the basis of clinical assessment of behaviour supplemented with psychological and neurocognitive evaluation (Davids et al. 2003). These last measures are obtained from questionnaires for parents, teachers, the child itself and clinical observation (Buitelaar & Kooij 2000). An ADHD diagnosis is valid when

the symptoms are reported in at least two settings, usually at home and at school/work (Sandberg 2002, Culpepper 2006).

The use of questionnaires is a widely accepted method in human behaviour disorder research (Vas et al. 2007). However, the outcomes of the questionnaires can be biased by multiple factors, such as cultural background (Barnard-Brak & To 2009). In conclusion, it seems that the diagnosis is clinically limited because it reflects only behavioural measures, with little consideration of cognitive dysfunctions (Davids et al. 2003).

3.2 Diagnostic methods for ADHD in domestic dogs

For the diagnosis of ADHD in domestic dogs, a questionnaire for dog owners has been developed as well, which is comparable to a parent questionnaire (Vas et al. 2007). It seems that this is an effective way of assessing specific behavioural measures, since the owner is assumed to be capable of judging the behaviour of his dog to common stimuli in the environment (Vas et al. 2007). The dog owner has the opportunity to describe the dog's activity and attention skills in multiple situations and over extended periods of time (Vas et al. 2007). However, the outcome of the dog-owner questionnaire can be biased by the dog owner: when a dog owner actively participates in training practices, it has been demonstrated that the owner is more willing to overestimate the attention skills of the dog (Vas et al. 2007).

Nevertheless, behavioural observations remain limited in obtaining a reliable measure for ADHD in domestic dogs. Activity and attention levels in domestic dogs can be influenced by multiple uncontrolled factors, such as the novelty of the environment, timing of testing, the amount of successful, previous training and the housing/living conditions of the dog (Neilson et al. 2001, Tobler & Sigg 1986). There is also considerable variation in the activity and attention skills between individual dogs and dog breeds. For example, small-sized dogs appear to display higher hyperactivity/impulsivity levels compared to large-sized dogs, whereas gender and training had no influence on these levels (Vas et al. 2007, Neilson et al. 2001). On the other hand, attention levels were influenced by age and training, namely young dogs had higher inattention levels compared to adult and old dogs and trained dogs had more self-control and therefore better attention skills, whereas gender did not have an influence (Vas et al. 2007).

In dogs, a simple diagnostic test can be performed to obtain a diagnosis for ADHD. When certain ADHD medication, namely d-amphetamine, is administered in a small dose, behavioural measures of activity levels and physiological measures of heart pulse, respiration and salivation are reduced within one hour in dogs with ADHD (Landsberg et al. 2004). In contrast, d-amphetamine increases these measures in overactive dogs that do not have ADHD (Luescher 1993). The hyperactivity of the latter

mentioned type of dogs can be found in alternative causes, such as high energy levels due to age (pups), stimulus poor environment and underexcisement (Bowen & Heath 2007, Landsberg et al. 2004).

3.3 Summary

Using a specific diagnostic test would be the best method to obtain a validated diagnosis for ADHD in humans, but according to our best information, such a test has not been developed yet. Instead, a parent questionnaire has been used for years and is demonstrated to be a valid clinical method for assessing ADHD in children. For dogs, a simple diagnostic test exists and behavioural observations are obtained to supplement this test. The use of a dog-owner questionnaire, based on a valid human questionnaire, appears to be a reliable and valid clinical method for assessing attention skills and activity in dogs as well. However, a study where the three diagnostic methods, namely the d-amphetamine test, behavioural observations and owner questionnaire are combined in dogs does not exist.

4. Therapeutics for ADHD

The treatment of ADHD in humans and dogs is based on two types of interventions, namely 1) the application of medication and 2) behavioural therapy (Antshel et al. 2011, Buitelaar & Kooij 2000). Pharmacological agents are the most commonly used treatment for ADHD. In humans, both stimulant and non-stimulant medication is applied, whereas in dogs, only stimulant medication is administered (Antshel et al. 2011). In the following sections both types of intervention method in humans and dogs will be described.

4.1 Medication: stimulating agents in humans

As previously mentioned, the ethiology of ADHD is associated with impaired dopaminergic, noradrenergic and serotonergic neurotransmitter functioning (Antshel et al. 2011). Stimulating agents are efficient in the treatment ADHD by altering neurotransmitter functioning, especially by targeting dopamine and/or norepinephrine receptors (Culpepper 2006). They block the re-uptake of these neurotransmitters into the presynaptic neuron and/or can also increase the neurotransmitter release (Wilens 2006). These psychostimulant actions are all mediated by the catecholamine receptor (Wilens 2006).

Stimulating agents are considered first choice treatment for ADHD in humans (Culpepper 2006, Antshel et al. 2011). The most commonly used stimulating agents are

methylphenidate (Ritalin®) and d-amphetamine (Dexedrine®) (Wilens 2006). There are several delivery mechanisms for administering these psychostimulants, such as liquid, sprinkle, tablet, capsule or patch. In this way, the stimulant duration of efficiency during the day can be varied and adjusted to the needs of the individual (Antshel et al. 2011). Psychostimulants are short-lasting agents with maximal plasma levels and therapeutic actions at 1 to 3 hours and plasma half-life of 4 to 8 hours. Therefore, a three times a day dosing is required for effective pharmacological treatment (Davids et al. 2003, Teo et al. 2003, Bakhtiar et al. 2004). The difficulty of psychostimulants is to administer the medication during school or during extracurricular activities, which can be solved by using a certain drug delivery mechanism (e.g. a patch) that administers the drug regularly during the day (Culpepper 2006).

U.S. Food and Drug Administration (FDA) has proven that long-acting formulations of the psychostimulants methylphenidate and d-amphetamine are safe and efficient (Culpepper 2006, Fone & Nutt 2005). In 70 to 80 percent of patients an obvious improvement is observed, whereby the symptoms of inattention, hyperactivity and impulsivity are decreased (Buitelaar & Kooij 2000, Kooij et al. 1999). In addition, a decrease in physical and verbal aggression and an improved school attitude are also demonstrated (Buitelaar & Kooij 2000).

However, not all patients can tolerate psychostimulants since the side-effects of stimulants consist of weight loss, stomach-aches, headaches, insomnia and some rare but serious cardiovascular side-effects (Culpepper 2006, Antshel et al. 2011). Another concern was raised about the repeated use of psychostimulants, which might have a substance abuse potential (Biederman 2006). A low dose of methylphenidate via the oral route of administration is more desirable, compared to the intravenous, since it has a decreased abuse potential due to the increased metabolism and lower bioavailability (Fone & Nutt 2005). However, the use of psychostimulants for ADHD patients with conduct disorder or comorbid substance abuse is not recommended (Fone & Nutt 2005).

4.2 Non-stimulating agents in humans

Based on the side-effects, substance abuse potential, short lasting effects of psychostimulants and since about 30 to 50 percent of all children and adults do not respond to psychostimulants, the development of alternative pharmacological treatments is required (Biederman 2006, Fone & Nutt 2005). Multiple non-stimulating agents, such as modafinil, atomoxetine and α-agonists are now used as pharmacological treatment for ADHD as well (Wilens 2006, Antshel et al. 2011). Atomoxetine is a second choice treatment which is demonstrated to be efficient in placebo-controlled trials, whereas α-agonists and modafinil have less extensive evidence to support their use (Rader et al. 2009).

4.2.1 Modafinil

Modafinil is a novel non-stimulating agent that reduces ADHD symptoms to a similar magnitude as d-amphetamine. Furthermore, it improves short-term memory span, visual memory and response inhibition tasks by reducing impulsivity symptoms of ADHD (Fone & Nutt 2005). The precise pharmacological mechanism of modafinil remains unclear, but it seems that modafinil is a selective norepinephrine re-uptake inhibitor that acts at the α_1- adrenergic receptor function (Fone & Nutt 2005). No abuse potential and less side-effects, compared to psychostimulants, of modafinil have been demonstrated in patients with ADHD (Culpepper 2006).

4.2.2 Atomoxetine (Strattera®)

Atomoxetine is the only non-stimulating agent that has been approved by the U.S. Food and Drug Administration for the treatment of ADHD in humans (Antshel et al. 2011). Atomoxetine blocks the presynaptic norepinephrine transporter of the noradrenergic neurotransmitter system and is therefore associated with decreased ADHD symptoms (Culpepper 2006). However, a black box warning has been added to the atomoxetine label, since a rare association has been suggested between atomoxetine and suicidal thought processes in children (Rader et al. 2009).

4.2.3 α-agonists

Two α-agonists, namely clonidine (Catapres®) and guanfacine (Tenex®), have also been developed as alternative medication for psychostimulants. Clonidine is efficient in reducing symptoms of hyperactivity, impulsivity and aggression in 50 to 60 percent of children, but is less effective in decreasing symptoms of inattention (Kooij et al. 1999). Similarly, guanfacine is effective in treating the classical ADHD symptoms of inattention, hyperactivity and impulsivity, although some contradictory results have also been demonstrated (Biederman 2006).

Clonidine blocks the release of norepinephrine at the α_1- and α_2-adrenergic receptors in the PFC, while guanfacine activates the α_{2A}-adrenergic receptor which improves PFC functioning and blood flow (Wilens 2006). Both α-agonists share certain characteristics and improve the adrenergic neurotransmitter system, which in turn improves the symptoms of ADHD (Wilens 2006). Common side-effects of clonidine and guanfacine are drowsiness, dizziness, a dry mouth and orthostatic hypotension (Antshel et al. 2011, Rader et al. 2009).

4.3 Canine stimulating agents

Psychostimulants, such as methylphenidate and amphetamine, have been used for the treatment of ADHD in dogs as well (Teo et al. 2003, Bakhtiar et al. 2004, Arnold 2000, Arnold et al. 1973). Some studies have analysed the effects of psychostimulants on physiological and behavioural measures in dogs. Normalizing effects on the symptoms of hyperactivity, impulsivity and inattention were obtained when dogs with ADHD were treated with psychostimulants (Corson & Corson 1988, Arnold et al. 1973). Side effects of psychostimulants in dogs were loss of appetite and weight loss, which are also demonstrated in humans (Teo et al. 2003, Bakhtiar et al. 2004). In conclusion, future research on pharmacological treatment in dogs with ADHD is necessary since only a few studies with a small sample size and contradictory findings are conducted and only a few agents are in use.

4.4 Cognitive-behavioural therapy (CBT) for humans

Multiple well-supported behavioural interventions have been developed for children and adults with ADHD. Most cognitive behavioural therapies for children focus on skills training for parents and teachers by providing techniques and tools for managing the child's behaviour (Antshel et al. 2011, Buitelaar & Kooij 2000). Such a technique is operant conditioning, whereby appropriate behaviour is reinforced by rewards (e.g. praises, privileges or tokens), whereas inappropriate behaviour is reinforced by punishment (e.g. loss of positive attention, privileges or tokens) (Antshel et al. 2011, Rader et al. 2009). The symptoms of ADHD are reduced by CBT, but the effect is smaller compared to pharmacological treatment (Buitelaar & Kooij 2000). In addition, CBT for adults can teach patients to cope with impaired functioning, by assisting in developing effective compensatory strategies, e.g. structuring the patient's environment (Safren 2006). Nevertheless, limited empirical evidence is available to show that CBT is efficient when applied as the sole treatment of ADHD (Antshel et al. 2011).

4.5 Combined therapy for humans

A combined treatment for ADHD-patients consists of pharmacotherapy together with CBT and appears to be more efficient than medication or CBT solely (Antshel et al. 2011, Rader et al. 2009). Medication is effective in reducing the symptoms of ADHD but still can only resolve about 50 percent of the symptoms of ADHD (Safren 2006). This outcome can be improved when medication is combined with CBT, since strategies and skills are essential for coping with impaired functioning (Safren 2006). The dose of medication can also be reduced by 20 percent when combined with CBT (Buitelaar & Kooij 2000).

4.6 Behavioural therapy for domestic dogs

Once pharmacological treatment is effective in dogs with ADHD, the owner can proceed with behavioural therapy, which consists of basic obedience training, increasing the amount of daily exercise and play time and attention-seeking behaviour should be ignored (Bowen & Heath 2007, Landsberg et al. 2004). Behavioural therapy can only be combined with pharmacological treatment, since ADHD-dogs without medication lack trainability (Landsberg et al. 2004). Pharmacological therapy can also not operate as the sole treatment, because after drug withdrawal the ADHD symptoms will reappear when medication is not combined with behavioural therapy (Corson & Corson 1988).

4.7 Summary

The two intervention methods for both humans and dogs consist of pharmacological treatment and behavioural therapy, with the first being the most effective one. Psychostimulants are the most often used pharmacological agents in humans and the only one used in dogs, whereas in humans, research is also done on identifying non-stimulating agents as alternative treatment for ADHD. Behavioural therapy on itself is not very efficient in treating ADHD in both humans and dogs, but when combined with pharmacological treatment it appears to be the most effective method for treating ADHD in both humans and dogs.

5. The human as a model for ADHD in domestic dogs

ADHD is a common behavioural disorder in humans that has been extensively analysed, whereas in domestic dogs, ADHD is rarely investigated. Nevertheless, it appears that the same disorder is involved in both species. Parallels in the fundamental behavioural characteristics (inattention, hyperactivity and impulsivity) of ADHD across humans and dogs were demonstrated and it seems that similar underlying mechanisms contribute to these homologues behaviours (Lit et al. 2010). The similarities and dissimilarities in the underlying mechanisms, diagnostics and therapeutics of ADHD in humans and domestic dogs will be summarized.

In humans, the dopaminergic, adrenergic and serotonergic system were often investigated and multiple polymorphisms in genes of these neurotransmitter systems have been associated with ADHD. However, only a few studies have investigated the dopaminergic neurotransmitter system in domestic dogs and have thereby identified some candidate genes. Moreover, these genes were similar to the ones identified in humans with ADHD. These preliminary findings suggest that homologues underlying mechanisms are involved in ADHD in both humans and domestic dogs.

In humans, it has been shown that the disorder is mainly caused by genes, but that the interaction of certain genetic and environmental risk factors is involved in the development and maintenance of the disorder. Many environmental risk factors have been identified in humans, whereas studies that have analysed environmental risk factors of ADHD in domestic dogs are unavailable.

The diagnostic methods for ADHD in humans consist of a valid questionnaire and behavioural observations and these methods have been adjusted for the use in domestic dogs as well. These methods seem to be effective in diagnosing ADHD in both humans and dogs. However, in dogs a diagnostic test with d-amphetamine exists as well to support the findings of the other diagnostic, though not yet validated methods, whereas in humans, such a test is unavailable.

The therapeutic methods applied in humans and domestic dogs consist of pharmacological and behavioural therapy. Pharmacological therapy includes the administration of psychostimulants, such as methylphenidate and d-amphetamine, whereas behavioural therapy consists mainly of operant conditioning. In both humans and dogs, the most effective treatment is the one that combines the administration of psychostimulants and behavioural therapy. In addition, non-stimulating agents with less side-effects and abuse potential have been developed and effectively used in humans, whereas in dogs the effects of these agents have not been studied at all.

6. Conclusion

The previously described similarities in behavioural characteristics, ethiology and therapeutic methods of ADHD between humans and dogs confirm the suitability of the human as a model for ADHD in dogs. For many years, research on ADHD in humans has been supplemented with animal models (rats and mice) (Davids et al. 2003). Therefore, it seems even more evident that the human can serve as a model to enlarge the knowledge on the 1) ethiology, 2) therapeutic methods and 3) underlying mechanisms of ADHD in companion animals, such as the domestic dog. In this way, the genes that were already identified as candidate genes of ADHD in humans can also be studied in domestic dogs to determine whether they are associated with ADHD. Similarly, environmental risk factors for ADHD in humans can also be studied in domestic dogs to demonstrate whether the same factors are involved in the development and maintenance of ADHD in dogs. Moreover, the non-stimulating agents that were effectively used in humans can be studied in dogs to demonstrate whether they are also efficient in the treatment of ADHD in dogs.

In summary, the human model seems suitable to assist in getting better insight in the genetic and environmental risk factors that are involved in ADHD and in the development of alternative pharmacological therapy for ADHD in domestic dogs.

7. Literature

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