Large animals as potential models of human mental and behavioral disorders

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Summary

Many animal models in different species have been developed for mental and behavioral disorders. This review presents large animals (dog, ovine, swine, horse) as potential models of this disorders. The article was based on the researches that were published in the peer-reviewed journals. A literature research was carried out using the PubMed database. The above issues were discussed in the several problem groups in accordance with the WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), in particular regarding: organic, including symptomatic, disorders; mental disorders (Alzheimer's disease and Huntington's disease, pernicious anemia and hepatic encephalopathy, epilepsy, Parkinson's disease, Creutzfeldt-Jakob disease); behavioral disorders due to psychoactive substance use (alcoholic intoxication, abuse of morphine); schizophrenia and other schizotypal disorders (puerperal psychosis); mood (affective) disorders (depressive episode); neurotic, stress-related and somatoform disorders (posttraumatic stress disorder, obsessive-compulsive disorder); behavioral syndromes associated with physiological disturbances and physical factors (anxiety disorders, anorexia nervosa, narcolepsy); mental retardation (Cohen syndrome, Down syndrome, Hunter syndrome); behavioral and emotional disorders (attention deficit hyperactivity disorder). This data indicates many large animal disorders which can be models to examine the above human mental and behavioral disorders.

Key words: mental disorders, behavioral disorders, large animal models

Introduction

Despite the growing knowledge on mental disorders and behavior important in the wider issues of mental health, there is still a need deepen it, hence these disorders are also the subject of many studies conducted on animal model, including laboratory animals – rodents (usually genetically modified). Mention may be made here for

the latest research on organic mental disorders, among which are neurodegenerative diseases causing dementia or with dementia – Alzheimer's disease [1, 2], Creutzfeldt-Jakob disease [3], Huntington's disease [4], and Parkinson's disease [5], or other specific diseases, such as epilepsy [6], multiple sclerosis [7], vascular dementia [8], and hepatic encephalopathy [9]. Mental disorders and behavioral problems due to psychoactive substance use were another category subject to animal testing [10, 11]. Many studies have also focused on mental disorders – schizophrenia [12–14], affective disorders – depression, including postpartum depression [15–19], and mania [20]. Many studies on neurotic disorders, including anxiety [21–24], obsessive-compulsive disorders [25], stereotypic disorders [26], and posttraumatic stress disorder [27], were performed in rodents. Another study involved behavioral syndromes associated with physiological disturbances and physical factors, such as anorexia nervosa [28], bulimia nervosa [29], insomnia [30], and sexual dysfunction [31]. Specific cases are studies on genetic diseases that severely impair intellectual function and human psychosocial development: Down syndrome [32], Hunter syndrome [33], autism [34, 35], and Rett syndrome [36], as well as on behavioral-emotional disorder, e.g., attention deficit hyperactivity disorder (ADHD) [37].

The attempts to adapt natural models of laboratory animals to mental disorders and human behavior are very difficult and involve major problems in their interpretation. Large animal models, due to some genetic, phenotypic, anatomical, and physiological similarities contributed much to the understanding of many problems of human health and the approach to new therapeutic methods [38]. It should be pointed that their use as models for studying multifactorial human diseases could be equally useful.

Aim

The aim of this study was to discuss – on the basis of the literature found in PubMed resources – studies of selected mental disorders and behavioral disorders performed on the so-called large animal model – dogs, sheep, pigs, and horses. In these animals, most often in natural way, occur medical conditions that may be potential models of many human disorders. These issues are described in the ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th) categories/subcategories, as shown in Tables 1–5.

Psychiatric disorders with dementia

Table 1. **Studies of Alzheimer's disease, Huntington's disease and pernicious anemia, hepatic encephalopathy/catatonia, on large experimental animals**

Species	Model of studies	References
	Alzheimer's disease (AD)	
Dog	Model of AD generated by overexpression of a mutated human APP gene, using SCNT technology.	[39] [40–44] [45]
	Natural, pre-clinical model of AD/ccSDAT, with cognitive impairment, increased levels of Aβ and oxidative stress. The analysis of cognitive impairment with the use of OFT and CT in dogs and analysis of end-products of lipid peroxidation: lipofuscin (LFP), protein carbonyls and vitamin E. Also the assessment of effect of atorvastatin on BVR-A levels and determining the correlation between BVR-A upregulation and post-translational modifications with BACE1 levels in the brain of aged beagles.	
	In the model of AD, effect of GSIs and GSMs on the level of Aβ(37), Aβ(38), Aβ(40), and Aβ(42) in CSF has also been studied.	
	Model of CDS in aged subjects and evaluation of cognitive impairment and level of Aβ1-42 i Aβ1-40 in the blood plasma. Determining the Aβ42/40 ratio – as a marker of development of AD and vDNMP – as an early marker of cognitive decline in a model of human aging and dementia. Also determining the level of APP and Aβ profiles in brain tissue in beagles.	[46–48]
	Huntington's disease (HD)	
Sheep	GABAα1 receptor and leu-enkephalin immunoreactivity as well as molecular characteristic of neutrophile aggregates in the cortex of OVT73 transgenic sheep model of HD/JHD	[49]
	Addison-Biermer anemia (vitamin B12 deficiency anemia) (Pernicious Anemia – PA)	
Dog	Genetic basis of IGS in beagles and border collie – a potential model of human PA.	[50]
	Hepatic Encephalopathy – HE/Catatonic-Like Symptoms – CLS	
Dog	SCPS as a natural model of HE and behavioral changes assessed using EEGs and VEPs in beagles with Eck's fistula (Portacaval shunt – PCS) inducing HE.	[51–53]

APP – Amyloid Precursor Protein; BACE1 – Beta (β)-secretase 1; BVR-A – Biliverdin Reductase-A; ccSDAT – canine counterpart of Senile Dementia of the Alzheimer Type; CDS – Cognitive Dysfunction Syndrome; CSF – Cerebrospinal Fluid; CT – Curiosity Test; EEGs – Electroencephalograms; GSIs – Gamma-secretase inhibitors; GSMs – Gamma-secretase modulators; IGS – Imerslund-Gräsbeck syndrome; JHD – Juvenile Huntington's disease; LFP – Lipofuscin-like Pigments; OFT – Open-Field Test; SCNT – Somatic Cell Nuclear Transfer; SCPS – Spontaneous Congenital Portosystemic Shunt; vDNMP – visuospatial Delayed Non-Matching to Position; VEPs – Visually Evoked Potentials

Table 2. **Studies of epilepsy, Parkinson's disease and Creutzfeldt-Jakob disease on large experimental animals**

Species	Model of studies	References
	Epilepsy – EPI	
Dog	Behavioral changes (fear/anxiety, defensive aggression, and abnormal perception) in dogs associated with the development of drug-resistant idiopathic EPI. Also the assessment of risk factors for spontaneous EPI.	[54,55]
	A natural model of posttraumatic EPI (head injury) in dogs and anti-epileptic treatments.	[56]
	Mining continuous iEEG in focal EPI (in comparison to dynamics between epileptiform discharges) and also long-term prediction of epileptic seizures using iEEG.	[57, 58]
Sheep	An adult sheep model for the study of focal EPI (triggered by injection of penicillin into the right prefrontal cortex) with the use of iEEG and fMRI.	[59]
Pig	A characteristic of time sequence of epileptic seizures in EEG during focal EPI triggered by dynamic penicillin injection into the somatosensory cortex during deep isoflurane anesthesia.	[60]
Horse	Potential similarity between the JIE/BFNC and idiopathic EPI in human newborns, with regard to KCNQ2 gene.	[61]
	Parkinson's disease – PD	
Dog	Model of PD in beagles after the administration of MPTP (isoquinoline) and symptoms of depression and progressive dementia. Also PD model after MPTP intoxication and the assessment of metabolic changes in the brain (striatum) with the use of ¹H-MRS.	[62, 63]
Pig	Model of PD after MPTP injection in miniature pig. The changes in behavioral patterns were evaluated using a new motor scoring system based on the UPDRS in human PD patients, while the pathological brain changes were examined using PET-CT and IHC.	[64]
Horse	NPE ("Chewing Disease") as a model of toxic PD (TPD), with clinical picture directly attributable to lesions in globus pallidus, and substantia nigra and dopaminergic neurons	[65]
	Creutzfeldt-Jakob disease – CJD	
Sheep	Model of scrapie and evaluation of quinacrine action, with potential respect to CJD	[66]

fMRI – functional Magnetic Resonance Imaging; ¹H-MRS – Single voxel ¹H water suppressed magnetic resonance spectroscopy (¹H-MRS at 3 T); IHC – Invasive Immunohistochemistry; iEEG – intracranial Electroencephalography; JIE – Juvenile Idiopathic Epilepsy/BFNC – Benign-Familial Neonatal Convulsion; MPTP – 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; NPE – Nigropallidal Encephalomalacia; PET-CT – Positron Emission Tomography-Computed Tomography; TEP – Toxic Equine Parcinsonism; UPDRS – Unified Parkinson's Disease Rating Scale

According to data contained in tables 1–2, individual domestic animals were recognized as models of many psychiatric disorders occurring with dementia in hu-

mans. Alzheimer's disease, which is accompanied by neurodegenerative changes in the brain, including the formation of neurofibrillary tangles (NFT) and senile plaques (SP) is described as first. The genetic basis of familial form of late-onset AD is associated with a mutation in the APP gene (Amyloid Precursor Protein) located on chromosome 21, which encodes a of amyloid-β (Aβ) precursor protein. In dogs, the model of Alzheimer's disease (by the overexpression of the human APP gene containing well-characterized familial AD mutations) with characteristic symptoms (AD-like symptoms) and pathological changes similar to those that have been observed in AD in humans (enlarged ventricles, atrophied hippocampus and β-amyloid plaques in the brain), was generated [39]. In turn, the natural model of ccSDAT/CDS in beagle dogs demonstrated numerous cognitive problems, excessive accumulation of Aβ and oxidative stress. The assessment of the end-products of lipid peroxidation: lipofuscin (LFP), protein carbonyls and vitamin E, related to oxidative damage of the brains of dogs with dementia, was also performed. In dogs of this breed (depending on age), there was also an increase in biliverdin reductase-A activity (BVR-A) in the parietal cortex after the administration of atorvastatin and the correlation between BVR-A upregulation, post-translational modifications and β-secretase 1 (BACE1) in the brain. Other studies have identified Aβ brain profiles and Aβ1-42 and Aβ1-40 levels in the blood plasma, as well as the effect of GSIs (γ-secretase inhibitors) and GSMs (γ-secretase modulators) on the level of Aβ(37), Aβ(38), Aβ(40), and Aβ(42) in the cerebrospinal fluid of the dogs. The Aβ42/40 ratio has been identified as a marker of the development of AD and vDNMP as an early marker of cognitive decline for model of human aging and dementia [40–48].

Huntington's disease (HD) is a genetic neurodegenerative disease of the CNS (HD mutation in the gene encoding the huntingtin protein, located on chromosome 4) with involuntary, uncontrolled movements (chorea), psychiatric disorders and dementia. In the juvenile form of HD (children and some teenagers), rigidity of muscles most often occurs instead of chorea. Also, in contrast to adult people with HD, epilepsy can occur more commonly in patients with JHD.

The model of transgenic (OVT73) sheep indicated a decrease in GABA α1 receptor in the striatum and immunoreactivity of the neurotransmitter leu-enkephalin in the globus pallidus. In this animals progressive age-related neurodegenerative changes occurring in HD: aggregates of neutrophils (NAs) in the cerebral cortex and neuronal intranuclear inclusions (NIIs) in the piriform cortex [49], were identified.

Addison-Biermer anemia (Pernicious Anemia – PA) is an autoimmune disease. A deficiency of vitamin B_{12} in addition to megaloblastic anemia may cause irreversible changes in the central nervous system manifested by neurological and psychiatric disorders, including, from mild cognitive impairment (MCI) to dementia, confusion, delusional disorders and depression. In dogs, beagle and border collie, tested for genetic IGS (Imerslund-Gräsbeck syndrome) – a potential model of PA in humans. In these studies an association between the phenotype of dogs with IGS and CUBN:c.786delC gene variant [50] was found.

Portal venous fistula, Eck's fistula (portacaval shunt – PCS) leads to the development of hepatic encephalopathy (HE), this is why dogs (wolfhounds) affected with SCPS (in dogs intrahepatic and extrahepatic shunt is possible) can be a study model of this disease in humans. Affected beagle dogs had signs of apathy, drowsiness and symptoms similar to those described in catatonia (catatonic-like symptoms) and increased levels of C-reactive protein [51–53].

Epilepsy (specific neurological disorder with seizures as a result of excessive activity of nerve cells of the cerebral cortex) has been described by several authors using the animal model – dogs, sheep, pigs, and horses. In the first ones, studies on spontaneous epilepsy (EPI) were carried out. The risk factors and behavioral disorders (fear/anxiety, defensive aggression and abnormal perception) in dogs suffering from EPI were discussed, and a continuous iEEG in focal EPI (in comparison to dynamics between epileptiform discharges) as well as long-term prediction of epileptic seizures using iEEG were presented [54–58]. Cases of epilepsy in dogs induced by head injury (posttraumatic epilepsy – PET), which can be models of EPI caused by traumatic brain injury (TBI) in humans, were also described [58].

Focal epilepsy was also caused by injection of penicillin into the right prefrontal cortex (adult sheep), and a dynamic injection of this antibiotic to the somatosensory cortex (pigs). In these models, diagnostic testing was conducted using iEEG and/or fMRI [59, 60]. In turn, there is a potential overlap between JIE/BFNC in horses and benign familial infantile epilepsy (BFIE) in human children in connection with the existence of KCNQ2 gene. In a veterinary literature, there are indications that humans can also be a research model of JIE in foals of Arabian horses [61].

Parkinson's disease is a neurodegenerative disease of the extrapyramidal system with degeneration of dopaminergic nerve cells and impairment of neurotransmitter release – dopamine in the substantia nigra and striatum. In humans, it leads to bradykinesia/akinesia, resting tremor, muscle rigidity and postural instability, numerous vegetative disorders as well as slowing of mental processes and memory. Domestic animals were also models of Parkinson's disease (PD). In beagle dogs, PD was induced by MPTP, Isoquinoline – a chemical compound responsible for the damage to the nervous system. Those animals, in addition to symptoms of depression, demonstrated increasing dementia. The PD model after MPTP intoxication was also used also to evaluate metabolic changes in the brain (striatum), using ^{1}H-MRS [62, 63]. The model of PD after MPTP injection in the miniature pig was also described. These animals showed many abnormal behaviors and pathological brain lesions (destruction of dopaminergic neurons in PET-CT imaging and INC tests) [64]. In horses, a natural model of toxic (poisoning caused by the ingestion of plants from Asteraceae family, *Centaurea solstitialis*) parkinsonism is NPE ("Chewing Disease"). Studies showed degenerative changes in the substantia nigra and globus pallidus of the brain [65].

Prion diseases, transmissible spongiform encephalopathies (TSE) are a group of specific diseases of the nervous system of humans and animals caused by abnormal protein PrP^{sc}. It seems, that studies of Creutzfeldt-Jakob disease (CJD), also the evalu-

ation of substances that inhibit the process of accumulation of pathological proteins in nerve cells, can be carried out using the scrapie model in sheep. The presented in vivo studies did not confirm the therapeutic effect of quinacrine [66].

Mental and behavioral disorders due to psychoactive substance use and affective and psychotic disorders

Table 3. **Studies of alcoholic intoxication, abuse of morphine, manic and depressive episode, schizophrenia and postpartum psychosis on large experimental animals**

Species	Model of studies	References
Alcoholic Intoxication (AI)		
Sheep	A model of AI (alcohol administered intravenously) in Suffolk pregnant ewes, with neurodevelopmental damage in fetuses.	[67]
Abuse of morphine (AM)		
Dog	A model of AM in beagle dogs and assessment of canine cerebral 5-HT2A receptor measured with (123)I-R91150 SPECT.	[68]
Pig	A model of AM (and actions of opiate-like compounds) after acute and chronic morphine, intravenous administration in swine.	[69]
Manic Episode (ME)		
Pig	This model represents induction (after central administration of pCRF) of psychomotor hyperactivity and stereotyped behaviors – as a new model for the study of ME and central injection of astressin (CRH antagonist – Corticotropin-Releasing Hormone Antagonist).	[70]
Depressive Episode (DE)		
Horses	An ethological model of spontaneous expression of "behavioral despair" in domestic horses (68% – French Saddlebred, 32% – mixed breed), with respect to human DE. FSM was used here for observation of postures of horses placed in boxes, in response to environmental stimuli – tactile stimulations and sudden human approach. The perception/level of anxiety (using tests to assess emotionality – AT, NOT, HT) was also evaluated, and the concentration of cortisol in blood plasma – as exponent of stress – was determined.	[71]
Schizophrenia		
Sheep	Intrauterine endotoxemia (intravenous administration of high dose of LPS) in pregnant animals and assessment of changes in the cytoarchitecture, ACC and in GABA-ergic interneurons in the fetal brains.	[72]
Postpartum Psychosis (PP)		
Pig	Natural model of PP and identification of QTL genetic basis of porcine maternal infanticide (PMI) – abnormal behavior in PP.	[73]

ACC – Anterior Cingulate Cortex; AT – Arena Test; FSM – Focal Samplic Method; HT – Handling Test; LPS – Lipopolysaccharide/ENDO – Endotoxin; NOT – "Novel Object" Test; PMI – Porcine Maternal Infanticide; QTL – Quantitative Trait Loci; SPECT – Single-Photon Emission Computed Tomography

Studies in this thematic group (Table 3) were carried out in many species of domestic animals. The problem of intoxication during pregnancy and the risk of the development of Fetal Alcohol Spectrum Disorders (FASDs) are still valid. In sheep, the model of intoxication was described (alcohol was administered intravenously to pregnant Suffolk sheep), with changes in neuronal development in fetuses, additionally intensified by cortisol [67].

Mental and behavior disorders were also observed in people under the influence of narcotic substances. In dogs, model of repeated administration of opiate (AM) and its effect on the level of brain receptor 5-HT2A (decrease) was described, also showing the relationship between opiates and serotonin system [68]. In pigs, state of acute and chronic drug intoxication was induced after intravenous administration of morphine (action of opiate-like compounds were also tested here also) [69].

Mania and depression are mental disorders that belong to the group of affective disorders. In bipolar disorder, depressive and manic phases (extreme elation) occur with periods of normal mood in between episodes. Many patients with this disorder may have memory problems.

In pigs, hyperactivity disorder and stereotypical behavior – as a new model for studies of ME – was described (after central administration of pCRF). The central injection of astressin (CRH antagonist) prevents some pCRF-induced behaviors in these animals [70]. In turn, the model of "behavioral despair" in domestic horses may be potentially related to DE in humans and, to some extent, explain a complex etiology of the problem. In these studies, a higher percentage of horses demonstrated an upward trend in experiencing emotions/anxiety and lower levels of cortisol in "withdrawn" individuals, compared to "non-withdrawn" horses [71].

Schizophrenia is a serious mental disorder which involves psychosis, with a broad spectrum of disorders of social behavior and experiencing surrounding reality. The causes of schizophrenia are genetic and environmental factors.

In sheep, intrauterine endotoxemia (induced by a high doses of LPS) in pregnant animals induces many changes in the cytoarchitecture of the ACC and in GABA-ergic interneurons in fetal brains, similar to those observed in schizophrenia in humans [72].

Postpartum psychosis is a severe mental disorder and particularly extreme woman's reaction to having a baby. Genetic research in aggressive sows (attacking and killing their own newborn offspring within 24 hours after giving a birth) has identified 4 QTL (on chromosome 2 (SSC2), 10 (SSC10) and X (SSCX)), related to the quantitative traits of PMI. There are several potential candidate genes in humans in these regions to link them to this abnormal behavior [73].

Neurotic disorders and anxiety related to stress and behavioral syndromes associated with physiological disturbances and physical factors

Table 4. **Studies of posttraumatic stress disorder, obsessive-compulsive disorder, panic disorder, anorexia nervosa and narcolepsy on large experimental animals**

Species	Model of studies	References
Posttraumatic Stress Disorder (PTSD)		
Pig	Pharmacological model in Sus Scrofa swine (in critical condition after TCAs – amitriptyline overdose) with reference to the use of ILE and SB, and assessment of hypotension and ECG.	[74]
Obsessive-Compulsive disorder (OCD)		
Dog	CTC in Standard (BT) and Miniature (MBT) Staffordshire Bull Terriers (SBT), and German Shepherds (GS) – as classical compulsive disorder, which may be a potential model for OCD in humans. Natural model of CTC (identification of genes and functional noncoding variants of genomic loci associated with CCD) in Doberman and Pinscher.	[75, 76]
	Model of CCD and assessment of structural changes in the brain using RM 3Tesla, similar to those recorded in humans in obsessive-compulsive disorder.	[77]
	Natural model of CCD in the assessment of the level of serotonin receptor (5-HT 2A), DAT and SERT using SPECT with (123) I-R91150 and (123) I-FP-CIT, and in combination with (99m) Tc-ECD in the frontal and temporal cortex.	[78]
Pig	Central administration of different doses of corticotropin-releasing factor (pCRF) – model of hyperactivity and stereotyped behaviors in swine in studies on OCD.	[70]
Horse	Stereotyped disorder (weaver) in horses as a potential model of human CSB.	[79]
	Analysis of stereotyped behavior in working horses (French Saddlebred) – a potential model of adverse effects of working conditions on the occurrence of certain behavioral disorders in humans	[80]
Panic Disorder (PD)		
Dog	ANPD is as a model for studies of anxiety disorder in Pointer dogs, including PD. The results of this animal model have been discussed in the context of noradrenergic-hypothalamic-GH dysfunction (response to the administration of clonidine) and in reference to selected anxiety disorders in humans.	[79, 81]
Sheep	Pharmacological model of high and low levels of anxiety in the Merino sheep in relation to mCPP and diazepam. In sheep, tests assessing their general movement and vocalizations, performance in moving down a raceway for a food reward, response to sound stimuli (98 dB), and behavior in isolation (RT/RST, FMT, IBT) (General Movement Test, Runway Task, Runway Startle Task and Isolation Box Test or Feed Motivation Test) were used.	[82]
Anorexia Nervosa (AN), Atypical Anorexia Nervosa (AAN)		
Dog	Neuroendocrine control of somatostatinergic function in beagle dogs with restriction of calories (glucose or TRH) and patients with AN/AAN (arginine), after administration of somatoliberin and pirenzepine.	[83]

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Narcolepsy		
Dog	Evaluation of the level of hypocretin-2 in the brain and CSF of Doberman (Hcrtr – 2 mutation), in relation to the sporadic and familial cases of canine narcolepsy and evaluation of the expression of MHC class II (age-dependent) in the CNS (in microglia).	[84, 85]

ANPD – Adult Nervous Pointer Dog, CCD – Canine Compulsive Disorder; CNS – Central Nervous System; CTC – Compulsive Tail Chasing; CSF – Cerebrospinal Fluid; CSB – Compulsive Spectrum Behaviors; ECG – Electrocardiogram; FMT – Feed Motivation Test; GH – Growth Hormone; GMT –General Movement Test; ILE – Intravenous Lipid Emulsion; IBT – Isolation Box Test; mCPP – 1-(m-chlorophenyl)piperazine; MHC class II – Major histocompatibility class II molecules; RT/RST – Runway Task/RST Runway Startle Task; SB – Sodium Bicarbonate; TCAs –Tricyclic Antidepressants; TRH – Thyrotropin-releasing Hormone

Table 4 shows large animal models of a range of issues related to neurotic and anxiety disorders as well as sleep and nutrition disorders in humans.

Posttraumatic Stress Disorder (PTSD) is a psychiatric disorder (a specific form of reaction) in response to trauma/experience of an extreme situation, with complex diagnostic criteria, complex clinical picture and therapeutic program, including the use of antidepressants. Among the TCAs (tricyclic antidepressants), amitriptyline has the strongest anticholinergic and cardiotoxic effect. In the domestic pig, high dose of amitriptyline (critical state model) and intravenous lipid emulsion and sodium bicarbonate therapy were used as a medication to counteract toxic effect of this TCA [74].

Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts (obsessions) and/or actions (compulsions), which are hard to resist. CTC (Compulsive Tail Chasing) can be a harmless expression of excitement, but in certain dog breeds, especially in some dog breeds (terriers and German shepherds), it has a darker side and can be indicative of a neurological disorder or CCD/autism. CTC/CCD is therefore a classical compulsive disorder, which may be a potential model of OCD in humans. Genes, functional variants and regulatory pathways underlying complex psychiatric disorders are mechanistically similar in dogs and humans. Also the structural changes in the brain (as shown with the use of MRI 3Tesla) are similar to those found in humans in obsessive-compulsive disorder. Conversely, the assessment of the serotonin receptor (5-HT) 2A), dopamine transporter (DAT) and serotonin transporter (SERT) with the use of SPECT with (123) I-R91150 and (123) I-FP-CIT, and in combination with (99m) Tc-ECD in the frontal and temporal cortex displayed a significantly lower subcortical perfusion and (hypo)thalamic SERT availability in compulsive dogs [75–78]. Central administration of different doses of corticotropin-releasing factor (pCRF) induces a state of hyperactivity and stereotyped behavior in pigs [70]. In turn, the observation of stereotyped disorder in horses (especially their utility to work) allows to assess the impact of adverse working conditions on the occurrence of certain behavioral disorders, which may have its reference to humans [79, 80].

Anxiety disorders (panic attacks) are in a group of common neurotic disorders typically disrupting normal functioning of human. ANPD is a model of anxiety disorders,

e.g., in Pointer dogs. The results obtained in this animal model have been discussed in the context of noradrenergic-hypothalamic-GH in response to administration of clonidine (α_2-adrenergic agonist) and with reference to certain types of anxiety disorders in humans [81]. In Merino sheep, pharmacological model of high and low levels of anxiety associated with the administration of psychoactive substance – mCPP (1-(3-chlorophenyl)piperazine) (increase in experiencing fear and distress during isolation) and benzodiazepine – diazepine, was described [82].

Anorexia nervosa (AN) is a very strong feeling of aversion to food and excessive weight loss (people are often hungry but refuse food anyway). There is a suggestion that the cause of this disorder can be a combination of certain personality traits, emotions, and thinking patterns, as well as biological and environmental factors.

Studies in beagle dogs (animal model of anorexia) undergoing a progressive reduction of calories intake and in adolescent women with anorexia nervosa (AN) in acute and recovery phase, and in patients with AN, do not support the view that somatostatinergic function is impaired in the described states of food deprivation [83].

Narcolepsy is a complex disorder covering excessive daytime sleepiness, sleep attacks, sleep paralysis as well as hypnagogic and hypnopompic hallucinations. Hypocretin – protein associated with backup standby (its reduced synthesis contributes to the development of this disorder) – plays an important role in the pathogenesis of narcolepsy. In models of narcolepsy in Doberman dogs, the level of hypocretin 2 (Hcrtr – 2 mutation) in the brain and CSF, in the familial and sporadic form of the disorder, and the expression of MHC class II (age-related) in the CNS (the microglia) of the animals, were assessed [84, 85].

Mental retardation, behavioral and emotional disorders

Table 5. **Studies of Cohen syndrome, Down syndrome, Hunter syndrome and ADHD on large experimental animals**

Species	Model of studies	References
Cohen syndrome (CS, COH1)		
Dog	TNS – a potential model of CS, COH1 in humans, in relations to transcript of VPS13B in the brain of border collie dogs.	[86]
Down syndrome (DS)		
Dog	CMA – in relation to DS and AD in humans; in immunomolecular studies of d7C16 Aβ (Amyloid-β) progression in DS and brains of aged dogs (it is present in all senile plaque subtypes).	[87]
Hunter syndrome (HS)		
Dog	Clinical and morphological features of MPS II in Labrador retriever as a natural model of human HS. Genetic, clinical and morphological tests.	[88]

Attention Deficit Hyperactivity Disorder (ADHD)		
Dog	Assessment of behavior of dogs of various breeds using the modified dog-ADHD Rating Scale and subscales: IAS, HA-IM	[89]

AD – Alzheimer's disease; CMA – Canine Model of Aging; TNS – Trapped Neutrophil Syndrome, VPS13B – Vacuolar Protein Sorting 13 Homolog B; IAS – Inattention Scale; HA-IM – Hyperactivity-Impulsivity Scale

Table 5 presents studies conducted in dogs in reference to selected neurodevelopmental disorders. Autosomal recessive Cohen syndrome is caused by mutation in the COH1 gene, also known as VPS13B (Vacuolar Protein Sorting 13B). In border collie dogs occur Trapped Neutrophil Syndrome (TNS), recessive neutropenia, which may be a potential model of Cohen syndrome in humans (in 99% of cases dogs present mental retardation). Examination of sequences of 63 exons (coding regions) of VPS13B in dogs showed that the mutation is associated with 4 bp deletion in the axon 19 [86].

In turn, the CMA in dogs can be a model of DS (also AD) in humans. In people with Down syndrome, deepening of mental retardation with age is often observed. People with DS have an extra chromosome 21 (trisomy 21) where the gene (APP) of amyloid precursor protein b is located. Progression of d7C16 Aβ (Amyloid-β) was found in all subtypes of senile plaques in individual cases of DS in humans and in brain of old dogs [87].

Hunter syndrome (mucopolysaccharidosis type II) is a genetic disease (the gene of this disease is located on a sex chromosome X), which belongs to the lysosomal storage diseases caused by a deficient (or absent) iduronate 2-sulfatase (IDS). One study [88] described a clinical (with neurological disorders) and morphological picture of MPS II in Labrador retriever dogs as a natural model of SH in humans. These animals showed a reduced activity of the lysosomal IDS in skin fibroblasts compared to healthy dogs. Genetic analysis of the hair roots also showed that a mother was a carrier of the defective chromosome X.

The disorder coexisting with ASDs (Autism Spectrum Disorders) is ADHD, where 3 subtypes are distinguished: predominantly inattentive type (ADHD-PI), predominantly hyperactive-impulsive type (ADHD-HI) and combined type (ADHD-C). In people affected by of ADHD spectrum disorders, attention deficit, hyperactivity, physical hyperactivity or impulsivity are observed.

The modified human ADHD Rating Scale for dogs was used in Europe in studies on dogs of different breeds [89]. The credibility of these analyzes was confirmed using the subscales: inattention (IA) and hyperactivity-impulsivity (HA-IM). The information obtained from these analyzes can be the basis for assessments of genetic and environmental determinants of ADHD in dogs, in a potential relation to humans.

Recapitulation

In the above-mentioned animal species, the discussed disturbances in most cases occurred in a natural way, becoming potential models of degenerative diseases of the brain that may occur with dementia, anxiety and obsessive-compulsive disorder, narcolepsy, mental retardation and ADHD (dogs), transmissible spongiform encephalopathy (sheep), postpartum psychosis with a murder of offspring (pigs), as well as Parkinson's disease, depressive episodes and behavioral disorders, including stereotyped disorder (horses). Some mental and behavioral disorders were induced by administration of psychoactive substances (sheep – alcohol; dogs – morfine), intraventricular injection of penicillin (sheep, pigs – model of epilepsy), LPS (sheep – model of schizophrenia), central corticotropin-releasing factor, CRF (pigs – model of mania and obsessive-compulsive disorder), MPTP – isoquinoline (dogs and pig – model of Parkinson's disease), as well as by poor nutrition (dogs – model of anorexia nervosa) and head injury (dogs – model of posttraumatic epilepsy). There were also exceptional cases of animals with specific genetic mutations, e.g., mutation of APP gene in dogs (Alzheimer's disease), transgenic sheep model, OVT73 (Huntington's disease) and Hcrtr – 2 mutation in dogs (narcolepsy).

The data included in this work show that large animals (dogs, sheep, pigs, and horses) can be successfully used (after further validating in some cases) as the study model of selected human mental and behavioral disorders. Despite the undeniable ethical objections, these animals can be an interesting alternative to studies conducted on small laboratory animals, which much more different from humans, comparing to large animal models (dogs, sheep, pigs, and horses).

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