THESIS

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Neurotransmitter changes in different neurological diseases in dogs

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1. Thesis Topic Declaration Form

Appendix 1. Thesis topic declaration form

University of Veterinary Medicine Student name: Jennifer Servos

THESIS TOPIC DECLARATION FORM

I hereby request approval from the Head of Department of the Department of/and.....
Physiology and Biochemistry
to prepare a thesis based on a topic announced and supervised by said Department as follows.

Date: Budapest, 23.03.2021 J. Servos
Student signature

Thesis topic:
Hepatoencephalopathy in dogs
the neural changes/neurotransmission alteration

Title of Thesis (English title as well):

Supervisor signature:

Approved by:

Head of Department signature

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2. Abstract

The first part of this thesis is about the neurotransmitters itself, about the physiology of neurotransmission and the different effects of those. There main purpose is to transmit signals either between two nerve cells or a nerve cell and another cell.

The neurotransmitters are in correlation with neurological diseases, which belong to the second part of this thesis. In neurological diseases, like epilepsy, narcolepsy, hepatic encephalopathy, and dementia, neurotransmission is disturbed due to an imbalance of the neurotransmitters, which results in misinformation in signal transmission. Not just one neurotransmitter is causing the disease it is the interaction between several neurotransmitter imbalances. Neurotransmitters are not only the cause of the disease, but they are also important to find an appropriate therapeutic approach for those disease, where the concurrent imbalance of the neurotransmitters is corrected.

The information about the neurotransmitters and their changes in neurological diseases are important to develop new diagnostic and therapeutic methods. This topic is scarcely researched, and more specific studies are needed to further clarify the different changes of neurotransmitters in neurological diseases in dogs.

3. Introduction Neurotransmitter

Neurotransmitters are heterogeneous biochemical substances, which give information from one nerve cell to another via the contact point of the nerve cells, the synapse. If action potentials enter the synapse, chemical messenger substances are released from their storage locations, the synaptic vesicles. This happens through an exocytotic mechanism. As a result of the fusion of the vesicle membrane with the membrane of the presynaptic nerve endings, the transmitter molecules reach the synaptic gap. Through the synaptic gap, they diffuse to the specific receptors of the postsynaptic neuron. After their release, the neurotransmitters are deactivated or broken down in various ways (1).

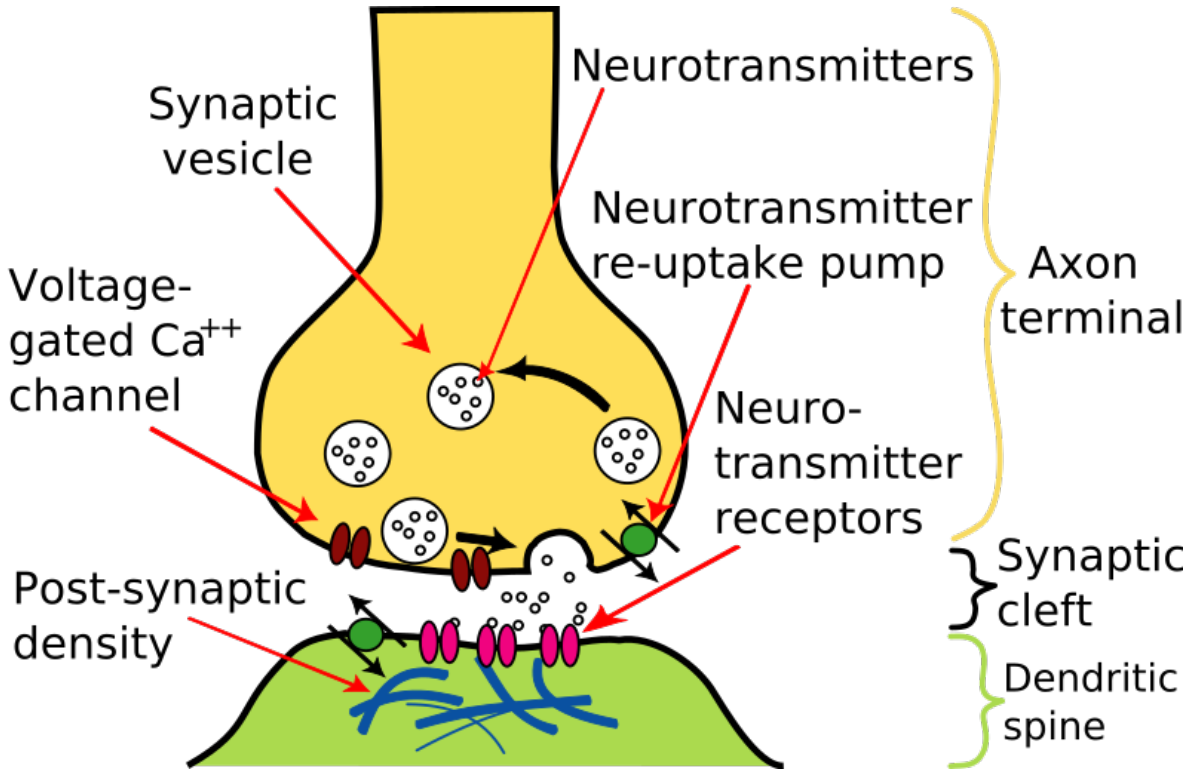

Figure 1: *Diagram showing the basic model of neurotransmission. This figure was redrawn by the author of this review. Original figure source: (Speller, 2018).*

3.1 Gamma-aminobutyric acid (GABA)

Gamma-aminobutyric acid (GABA) is an amino acid and a natural neurotransmitter that has central nervous system inhibitory activity. The function of gamma-aminobutyric acid is to reduce neuronal excitability by inhibiting nerve transmission.

This neurotransmitter is found in the neurons of the hippocampus, thalamus, basal ganglia, hypothalamus, and brainstem. It is synthesized by glutamate with help of the enzyme glutamate decarboxylase and vitamin B6 (2).

So, the most important excitatory become the most important inhibitory neurotransmitter. When gamma-aminobutyric acid has been synthesized, it is released into the postsynaptic terminals of neurons. There are two different types of these receptors GABAa and GABAb. GABAa is a ligand-gated ion channel and an inotropic receptor. They are located throughout the central nervous system. GABAb is a G-couple protein receptor, and they are located in the thalamic pathways and cerebral cortex.

The relation between inhibitory neuronal transmission via gamma-aminobutyric acid and excitatory neuronal transmission via glutamate is essential for proper cell membrane stability and neurologic function (3).

3.2 Glutamate

Glutamate is the most common free amino acid in the brain and the excitatory neurotransmitter in the central nervous system. The glutamate receptors are present on the surface of brain cells. Uptake system like glutamate transporters prevent excessive stimulation of these receptors by removing glutamate from the extracellular fluid in the brain to prevent excitotoxicity of nerve cells (4).

In the hippocampus, two types of glutamate receptors are present N-methyl-D-aspartate and non-N-methyl-D-aspartate, which are the basis for long-term neural stimulation. The excitation of the glutamate synapse causes the release of glutamate. A less intensive presynaptic stimulation results only in the opening of the non-N-methyl-D-aspartate. A receptor on the postsynaptic membrane. The N-methyl-D-aspartate receptors can only stimulate if there is strong depolarization from the postsynaptic membrane or a transfer of a large amount of glutamate (4).

Glutamate is the dominant excitatory neurotransmitter and neurotoxic in higher concentrations. It is the most important excitatory neurotransmitter, which is quantitatively most strongly represented in the central nervous system. This means that glutamate is also the direct antagonist of gamma-aminobutyric acid. The neurotransmitter influences motor functions (muscle work, senses, coordination), memory and learning ability, sensory perceptions, appetite and the secretion of pituitary hormones. Glutamate can be also used as energy source for brain cells if the glucose levels are low (5).

3.3 Dopamine

Dopamine is an organic chemical of the catecholamine and phenethylamine families and functions as a neurotransmitter in the brain (6). It has many functions in the brain including motor control, motivation, reward, cognitive function, maternal and reproductive behaviors (7).

Five different dopamine receptors, named D1, D2, D3, D4, and D5, are present in the central nervous system, specifically in the hippocampal dentate gyrus and subventricular zone, where they control motor function, emotional states and endocrine physiology (8). But Dopamine receptors are also expressed in the periphery, especially in kidney and vessels. All receptors have different functions, the D1 receptors regulate the memory, attention, impulse control, renal function and locomotion. D2 influence locomotion, attention, sleep memory and learning. Both D3 and D4 regulate cognition, impulse control, attention and sleep. D5 receptors influence decision making, cognition, attention and renin secretion. D1 and D5 receptors bind to G stimulatory sites and activate adenylyl cyclase. The activation of adenylyl cyclase leads to the production of the second messenger cAMP, which leading to the production of protein kinase A, leading to transcription in the nucleus. D2, D3, and D4 receptors bind to inhibitory sites, which inhibit adenylyl cyclase and activate potassium channels. The D1 receptors are the most common in the central nervous system and help to regulate the development of neurons when the dopamine binds to it.

Dopaminergic signaling pathways are essential to the maintenance of physiological processes and an unbalanced activity may lead to dysfunctions that are related to neurodegenerative diseases (9).

3.4 Serotonin

Serotonin (5-hydroxytryptamine) is a monoamine, inhibitory neurotransmitter which regulate a variety of physiological processes, including sleep, body temperature, and blood pressure, cognitive functions, emotional states, and behaviors (10).

The synthesis of serotonin consists of two steps during which tryptophan is hydroxylated to 5-hydroxytryptophan by the enzyme tryptophan-hydroxylase and subsequently decarboxylated to 5-hydroxytrptamine by the enzyme aromatic amino acid decarboxylase (11).

Serotonin is most found in the enteric nervous system located in the gastrointestinal tract and regulates intestinal function, but it is also produced in the central nervous system especially in the raphe nuclei located in the brainstem. Brain-derived serotonin acts as a neurotransmitter, while gut-derived serotonin works as a hormone.

There are 15 types of serotonin receptors with 6 families that are G-protein coupled receptors and one family that consists of ligand-gated ion channels (12).

One main function of brain-derived serotonin is the effect on modulating mood. Serotonin is a natural mood stabilizer, and it helps to be happy, calm and emotionally stable. Low serotonin levels within in the brain can lead to down in mood or feeling depressed, aggression or feelings of anxiety (13).

3.5 Acetylcholine

Acetylcholine is the neurotransmitter at neuromuscular junction, at synapses in the ganglia of the visceral motor system and within the central nervous system. In the central nervous system, it can function as a neurotransmitter and as a neuromodulator and plays a role in motivation, arousal, attention, learning, and memory (15).

It is synthesized from acetyl coenzyme A and choline and this reaction is catalyzed by choline acetyltransferase. Acetylcholine is transported in vesicles, which are released by the action potential. After the neurotransmitter is released into the synaptic cleft, where it binds to receptors or is rapidly degraded by the enzyme acetylcholinesterase.

There are two classes of cholinergic receptors called nicotinic and muscarinic. The nicotinic receptor is an ion channel and binds nicotine. The response is brief and fast. However, the receptor can also be blocked by curare. The nicotinic receptor is located at neuromuscular junctions, autonomic ganglia, and to a small extent in the central nervous system. Muscarine is bound by the muscarinic receptor, which is coupled to G-proteins. The response is slow and prolonged. The receptor is found on myocardial muscle, certain smooth muscle, and in discrete central nervous system regions. Atropine can block the muscarinic receptor (14).

Acetylcholine is clinically significant in many diseases like Alzheimer disease, Lambert-Eaton myasthenic syndrome and myasthenia gravis (16).

3.6 Histamine

Histamine is a low-molecular weight amine synthesized by the decarboxylation of histidine by the enzyme histidine decarboxylase. In the central nervous system, it functions as a neurotransmitter. There histamine affects cognition and memory, regulation of the sleep-wake cycle, energy, and endocrine homeostasis. Histaminergic neurons are located in the tuberomammillary nucleus of the posterior hypothalamus and project widely in the brain (18). The histamine content of the central nervous system is generally low, except for the posterior pituitary. In the peripheral nervous system, histamine is most common in the autonomic nerves.

The effects of the neurotransmitter are mediated via G-protein-coupled H1-H4 receptors. Histamine influence also the release of other neurotransmitters via presynaptic H3 receptors (19). It exerts regulatory influence on noradrenergic, serotonergic, cholinergic, dopaminergic and glutaminergic neurons (17).

3.7 Hypocretin (Orexin)

Hypocretin-1 and Hypocretin-2, also called Orexin A and B, are excitatory neuropeptides that are produced in the posterolateral hypothalamus. These neurotransmitters play a crucial role in the regulation of sleep and wakefulness and influence also food-intake and energy expenditure (20).

Hypocretins have an excitatory effect via G-protein coupled receptors. There are two known receptors to which they can bind: hypocretin receptor 1 (Hcrtr1) and hypocretin receptor 2 (Hcrtr2). Hcrtr1 is predominantly found in the ventrolateral hypothalamus, locus coeruleus, hippocampus and dorsal raphe nuclei, whereas Hcrtr2 is predominantly found in paraventricular, hypothalamic, subthalamic, thalamic and pretectal nuclei, but also in the medulla oblongata, tuberomammillary cells, nucleus accumbens and in the cortex. These core areas are all involved in regulating the sleep-wake cycle.

A mutation in the gene that encodes the hypocretin receptor is suspected to be the cause of narcolepsy. In addition to sleep-wake regulation, hypocretin is involved in the regulation of food intake by increasing food intake and decreasing energy consumption (21).

The following part of this thesis explains how the already mentioned neurotransmitters change in different neurological diseases like epilepsy, narcolepsy, hepatic encephalopathy, and dementia. Neurological diseases caused by an imbalance or disruption in neurotransmission.

4. Epilepsy

Epilepsy is a neurological disease in which brain activity becomes abnormal. It is defined as having two or more unprovoked seizures. There are two different forms of epilepsy. The condition can be inherited, genetically or idiopathic epilepsy, caused by structural problems in the brain and the second form is the epilepsy of unknown cause, which is used to describe a condition in which a structural cause is suspected but has not been identified.

Epilepsy is the most common neurological disease in dog and affects approximately 0.75% of the canine population (22).

4.1 Pathophysiology

Epileptic seizures are caused by an imbalance between excitatory and inhibitory activity in specific areas of the brain, leading to either excessive brain activity or activity that is unusually depressed (23). Abnormal excitatory processes may be caused by functional abnormalities in neurons, specifically mutations in the ion channels that are essential for electrical function of cells (24).

A seizure is a clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. The hypersynchronous discharges that occur during a seizure may begin in very discrete region of cortex and then spread to neighboring regions. Two concurrent events happen during the initiation of seizures: high- frequency bursts of action potential and hyper synchronization of neuronal population (22).

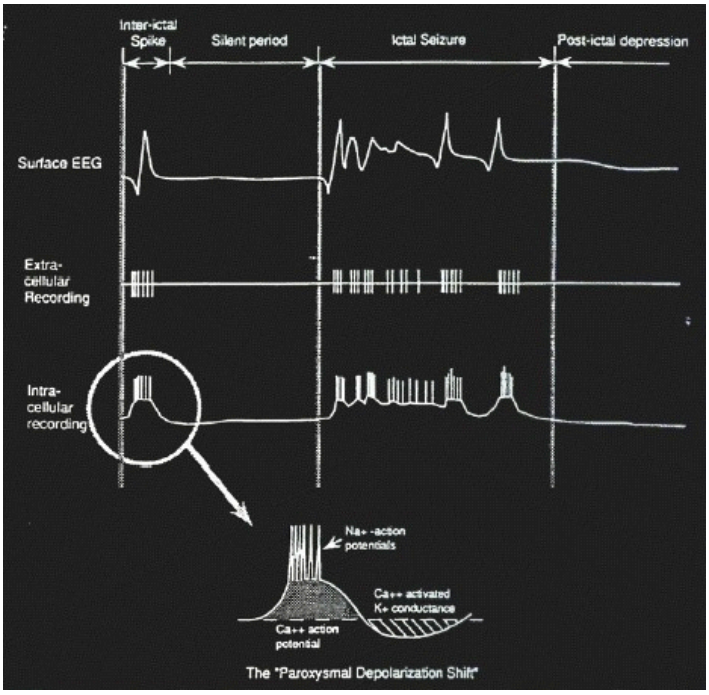

Figure 2: *Intracellular and extracellular events of the paroxysmal depolarizing shift underlying the interictal epileptiform spike detected by surface EEG. This figure was redrawn by the author of this review. Original figure source: (Bromfield, Cavazos and Sirven, 2015).*

4.2 Neurotransmitter changes

Glutamate and gamma-aminobutyric acid are the main neurotransmitters playing a crucial role in the pathophysiology of epilepsy. Irreversible neuronal damage may occur because of abnormal changes in these molecules (25). Increased excitation or decreased inhibition may lead to epileptiform activity in the brain (28). Glutamate is the main excitatory neurotransmitter and gamma-amino-butyric acid is the main inhibitory neurotransmitter in the central nervous system. Seizures caused by blocking gamma-aminobutyric acid inhibition (26). However, the concentration of excitatory glutamate is increased. Glutamate opens calcium channels and increases intracellular free calcium concentrations by activating N-methyl-D-aspartic acid receptors. The increase in intracellular free calcium concentration within neurons activates metabolic pathways that finally trigger cell death. This process is called excitotoxicosis (27).

Acetylcholine is the main stimulant of the autonomic nervous system and mediates signal transmission through cholinergic and nicotinic receptors. The dysfunction of nicotinic

acetylcholine receptors, which are found in hippocampal and cortical neurons, are involved in the formation of neuroinflammation in epilepsy due to loss of anti-inflammatory effects (25).

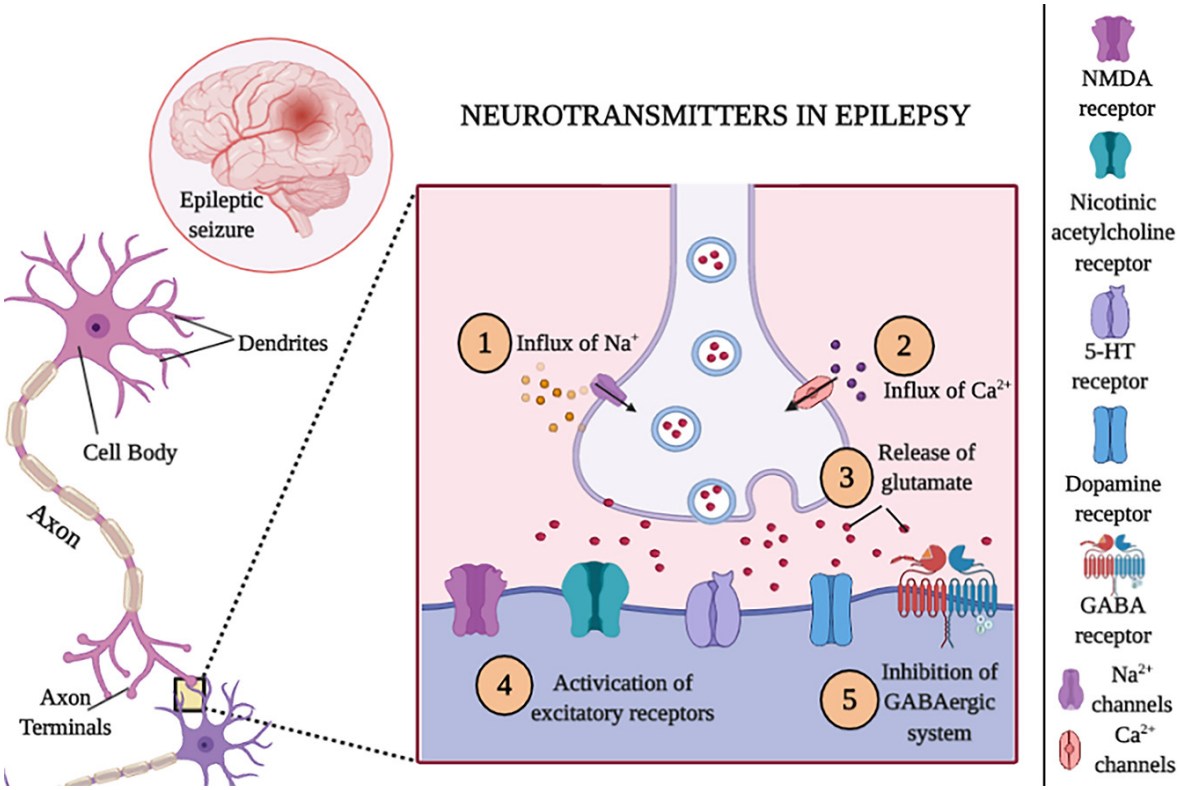

Figure 3: *Neurotransmitter in epilepsy. This figure was redrawn by the author of this review. Original figure source: (Akyuz et al., 2021).*

5. Narcolepsy

Narcolepsy is a sleep disorder, and cataplexy is the sudden loss of muscle tone in the body. Narcolepsy and cataplexy are common in our pets, especially dogs and horses. The animal appears to be dozing or simply falling asleep spontaneously. If the muscle tension that supports the entire body is lost, the animal collapses and falls helplessly to the ground. The episodes can often be triggered by a specific stimulation such as feeding or, in the case of the horse, grooming. On the other hand, narcolepsy rarely occurs during walks or horseback rides. In the horse, sleep suppression, for example due to stress in a herd where the horse does not dare to lie down to sleep, can also lead to narcoleptic symptoms. But this is not narcolepsy. Testing for narcolepsy involves ruling out other causes of collapse. For example, heart-related diseases, which can also cause such collapses, must be ruled out. Tumors that press on the brainstem (e.g., in horses with Cushing syndrome) can also trigger narcoleptic episodes. When in doubt, there are pharmacological tests to diagnose narcolepsy. The animal is given medications that either trigger or suppress the seizures. There is an inherited form, which shows up in young animals, and an acquired form, which an animal develops later in life. These forms of narcolepsy can be detected by the messenger substance hypocretin, which is present in reduced quantities in the cerebrospinal fluid of affected animals. In addition, there is a genetic variant in some dog breeds (Labrador, Doberman, Dachshund) as well as in humans. In this familial form of narcolepsy, a hereditary gene mutation in the hypocretin receptor gene 2 is the trigger. The hypocretin concentration is normal in these cases. The affected animals or humans only lack the receiver (receptor) for the messenger substance, so that it cannot work. There are different drug therapy approaches (29).

5.1 Pathophysiology

Narcolepsy is characterized by the diversity of its symptoms. The discovery of the neuropeptide orexin, which cannot be detected in the cerebrospinal fluid of narcolepsy patients, has provided new insights into the pathophysiology of the disease. The orexin influences various neurotransmitter systems involved in sleep regulation. The orexin deficiency can cause both reduced excitation of noradrenergic neurons and disinhibition of cholinergic tone. Some narcoleptic symptoms can be explained by this change in interaction.

Symptoms like narcolepsy can be produced in animal experiments by manipulating the orexin system. In narcolepsy the orexin-containing neurons are destroyed by an autoimmune process (30).

5.2 Neurotransmitter changes

A disruption of monoaminergic and cholinergic systems plays a crucial role in narcolepsy because these two systems interfere with the regulation of REM (rapid eye movement) sleep. So far, no abnormalities are visible under the light microscope in postmortem brain tissue samples from narcolepsy patients, but neurochemical investigations show abnormalities in these systems. There is an increased turnover of monoamines, an increase in dopamine receptors D1 and D2 in the striatum and possibly regional changes in alpha-adrenergic receptors (31, 35).

Similar findings were seen in the brain tissue of narcoleptic dogs. A reduced brain concentration of substance P, which promotes dopamine release, was also found in narcolepsy patients (31).

In summary, cataplexy arises from an increased sensitivity of the cholinergic systems. This is thought to be responsible for atony in REM sleep or caused by dysfunction of the noradrenergic neurons that modulate cholinergic activity (33, 34).

Canine narcolepsy is also associated with a deficit in hypocretin/orexin neurotransmission. An autosomal recessive mutation in the hypocretin receptor 2 gene is responsible for the inherited form of narcolepsy in dogs. This mutation results in a non-functional receptor that is not located in the plasma membrane as in healthy dogs and thus inhibits postsynaptic hypocretin neurotransmission (32,36). There is no difference in hypocretin levels in the cerebrospinal fluid from these dogs to healthy dogs. In contrast, the hypocretin levels in cerebrospinal fluid of dogs suffering from the sporadically acquired form of canine narcolepsy are lower and usually even below the detection limit. The sporadic cases have decreased hypocretin production, probably due to postnatal loss of hypocretin-producing neurons. (37).

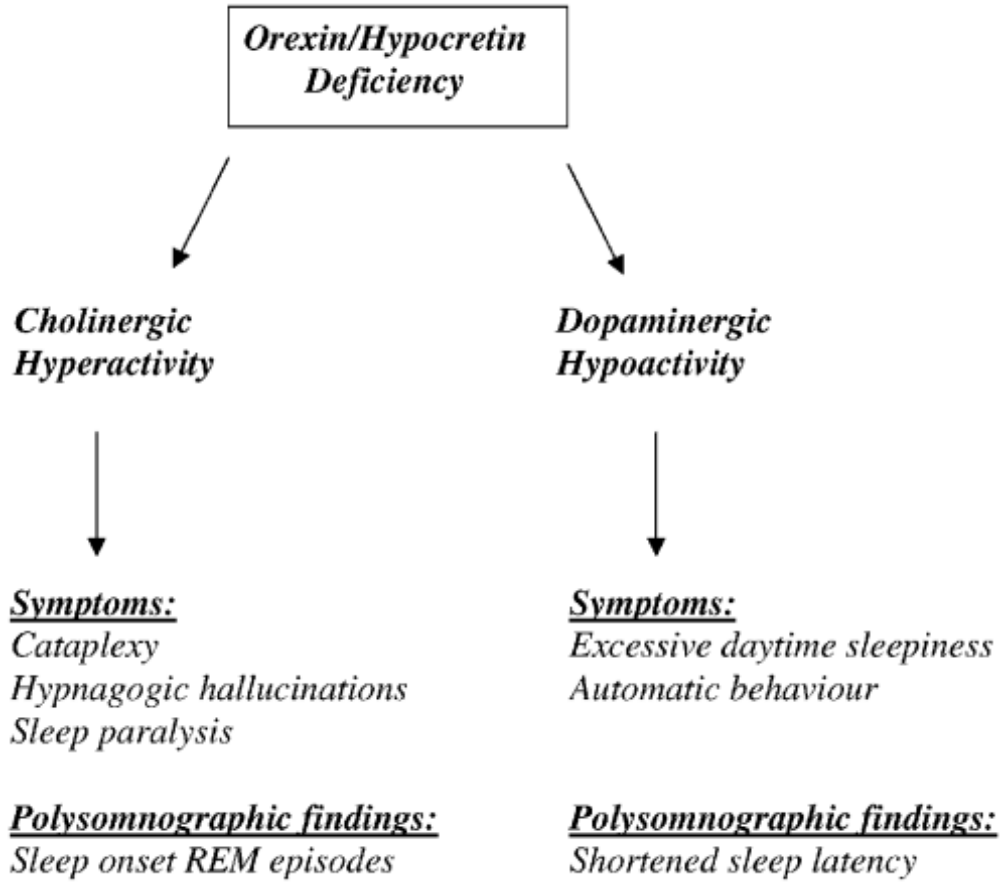

Figure 4: *The role of hypocretins in the pathophysiology of narcolepsy. This figure was redrawn by the author of this review. Original source: (Dalal et al., 2002).*

6. Hepatic Encephalopathy

In hepatic encephalopathy the brain function worsens because of toxic substances that are normally cleared by the liver and now rise in the blood and migrate to the brain (39). Hepatic encephalopathy describes a dysfunction of the central nervous system caused by acute or chronic liver disease. It is often based on a chronic liver disease such as liver cirrhosis. Liver disease leads to retention of neurotoxic substances in the blood, especially ammonia. The detoxification function of the liver is insufficient. The disease is also described in patients without cirrhosis with either spontaneous or surgically created portosystemic shunts (38). Neurological-psychiatric alterations are the result of these abnormalities (40).

6.1 Pathophysiology

As a result of a portosystemic shunt or acute/chronic liver disease, substances that are normally detoxified in the liver enter the systemic circulation and can cause toxic effects in the brain, for example a unfold in the cerebral cortex. The substances that have toxic effect on the brain are not exactly known.

Ammonia, a breakdown product of protein metabolism, plays an important role, but other factors like changes in cerebral benzodiazepine receptors and neurotransmitter such as gamma-aminobutyric acid also contribute to encephalopathy. The concentration of the aromatic amino acids in the serum is usually high, whereas of the branched-chain ones low. However, this constellation probably does not cause encephalopathy (38, 40).

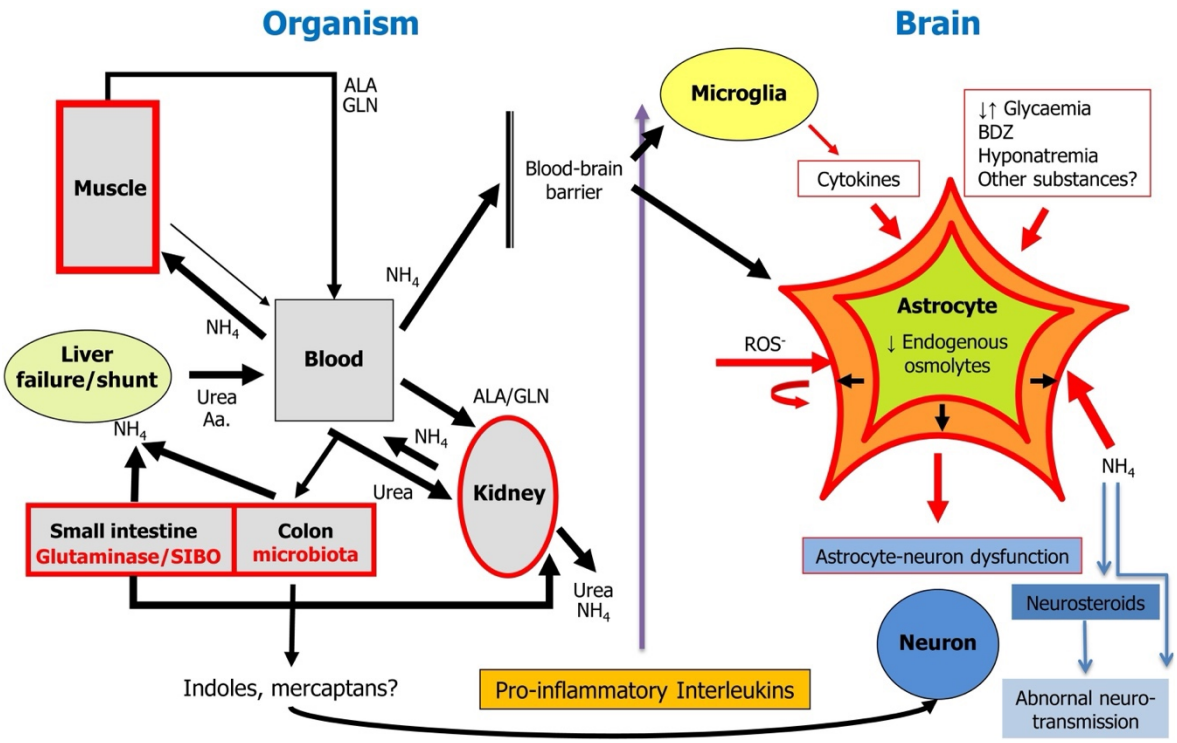

Figure 5: *The pathophysiology of hepatic encephalopathy. This figure was redrawn by the author of this review. Original figure source: (Montagnese et al., 2019).*

6.2 Neurotransmitter changes

In animals with acute or chronic hepatic encephalopathy the central nervous system glutamatergic neurotransmitter is altered. Astrocytes protect the brain from excessive neurotransmission by inactivating glutamate released from presynaptic nerve terminals. Hyperammonemia decreases glutamate uptake by astrocytes, which result in elevated extracellular glutamate levels. The high ammonia concentration also inactivates neuronal chloride extrusion pumps, suppress inhibitory postsynaptic potential formation, depolarize neurons, and therefore promote increased neuronal excitation and a preconvulsive state. Increased glutamate concentration at synapses causes overstimulation that can result in seizures in animals with hepatic encephalopathy (41, 44).

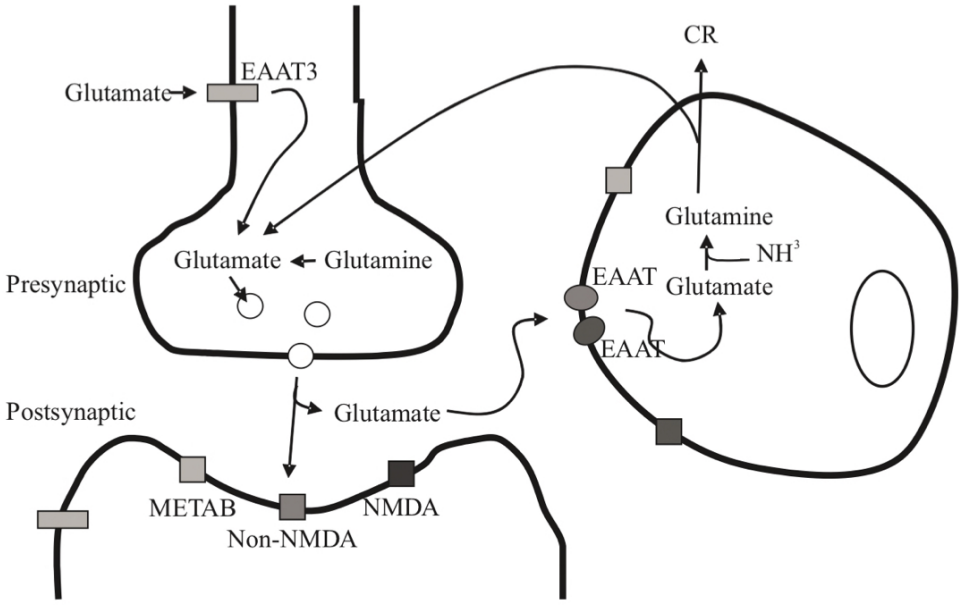

Figure 6: *The glutamate-glutamine cycle. Glutamate released upon stimulation from presynaptic terminals into the synaptic cleft and can activate glutamate receptors (METAB: metabotropic; NMDA: N-methyl-D-aspartate and non-NMDA) on post-synaptic neurons or astrocyte. The uptake of glutamate is mediated by the astrocytic glutamate transporters: EAA1 and EAA2. In astrocytes, glutamate is converted to glutamine via the glutamine synthetase pathway. The glutamine is released back to neurons, where glutamate is regenerated via the phosphate-dependent glutaminase, a mitochondrial enzyme. This figure was redrawn by the author of this review. Original figure source: (Lemberg and Fernandez, 2009).*

An excess of or an increased sensitivity to gamma-aminobutyric acid is also responsible for hepatic encephalopathy. Due to decreased hepatic extraction in animals with liver failure the plasma levels of gamma-aminobutyric acid increase. In acute liver failure or hepatic encephalopathy, the blood-brain barrier is more permeable and increased gamma-amino-butyric acid can enter the brain and activates gamma-aminobutyric acid receptor complexes,

inducing the opening of chloride channels. The neuronal membrane becomes hyperpolarized and inhibits neurotransmission. In dogs with portosystemic shunt or cirrhosis is no evidence of increased blood-brain barrier permeability (42, 43).

Abnormal changes in the serotonergic system were also found in dogs with hepatic encephalopathy. The levels of serotonin, serotonin receptors and monoamine oxidase in the central nervous system are increased in diseased patients, but the exact role of the inhibitory neurotransmitter serotonin is undefined. The level of tryptophan, an amino acid precursor of serotonin is increased in the plasma of animals with acute liver failure because of ammonia detoxification in astrocytes (41).

7. Dementia

Dementia caused by the slow death of nerve cells, especially those responsible for memory, orientation or consciousness. The condition is related to the aging of the brain. This results in an impairment of the behavior.

Dementia in dogs is known as canine cognitive dysfunction, which is a cognitive disorder in dogs associated with effects like those of Alzheimer in humans (45). The initial symptoms of dog dementia are often mild, but they gradually worsen over time. The most common symptoms are disorientation, anxiety, failing to remember routines, extreme irritability, decreased desire to play, aimless wandering, staring blankly at walls, lack of self-grooming, loss of appetite, and changes in sleep cycle (46).

7.1 Pathophysiology

The exact cause of dementia in dogs is still unknown. There are physical and chemical changes in the brain that cause dysfunction during the aging process. The two pathological hallmarks of dementia are extracellular beta-amyloid deposits and intracellular neurofibrils. The beta-amyloid deposits and neurofibrils lead to loss of synapses and neurons. This results in a gross atrophy of the affected areas of the brain, typically beginning in the mesial temporal lobes (47,48).

7.2 Neurotransmitter changes

The abnormal concentration of certain neurotransmitters like acetylcholine, dopamine and serotonin in the brain is characteristic for dementia.

The neurotransmitter acetylcholine has a central importance for memory and attention. This is also shown by the fact that in dementia, acetylcholine-producing nerve cells are affected particularly early and severely, and the result is lack of acetylcholine (49).

The levels of dopamine and the D2 dopamine receptors are also decreased in canine cognitive dysfunction syndrome. Both the catecholamines and the serotonergic system are affected. It has been observed that the brain levels of this neurotransmitter and its metabolites in the cerebrospinal fluid are low in neurodegenerative diseases. In old animals the

monoamine oxidase concentration is increased, which may influence the observed decrease of these neurotransmitters. Monoamine oxidase controls the catabolism of dopamine. The decreased action of neurotransmitters (serotonin, acetylcholine, and dopamine) and the increase of monoamine oxidase leads to membrane damage and cellular death due to the greater release of free radicals with an affinity for fatty acids present in the cellular membrane (50).

8. Conclusion

Neurotransmitters are biochemical substances that transmit, amplify or modulate stimuli from one nerve cell to another nerve cell or cell. Neurological diseases are caused by an imbalance or disruption in individual neurotransmitters.

Epilepsy can result from blocking the inhibitory activity of gamma-aminobutyric acid and an increase of excitatory glutamate. The dysfunction of nicotinic acetylcholine receptors may be significantly implicated in the pathogenesis of epilepsy. The elucidation of the role of the main mediators and receptors in epilepsy is important for developing new diagnostic and therapeutic approaches.

An abnormal alteration in monoaminergic and cholinergic systems plays a crucial role in narcolepsy because these two systems interfere with the regulation of REM sleep. Cataplexy arises from an increased sensitivity of the cholinergic systems. Canine narcolepsy is also associated with a deficit in hypocretin neurotransmission.

In animals with hepatic encephalopathy the central nervous system glutamatergic neurotransmitter is altered. Hyperammonemia decreases glutamate uptake by astrocytes, which result in elevated extracellular glutamate levels. Increased gamma-aminobutyric acid can enter the brain and inhibits neurotransmission.

The neurotransmitter acetylcholine has a central importance for memory and attention. This is also shown by the fact that in dementia, acetylcholine-producing nerve cells are affected particularly early and severely, and the result is lack of acetylcholine.

The outcomes of previous studies have provided information about the neurotransmitter alterations which are well researched, but it has to be mentioned that not all diseases are as well researched as others, for example in case of dementia in dogs there is still room for further research. Particularly the genetic differences of different breeds are very important for understanding the cause of the disease and especially for further treatment of those breed related diseases, like epilepsy in Labradors. Those genetic differences are related to neurotransmission, especially to differences in neurological diseases where different breeds are predisposed to. This can be the basis for early detection and improved treatment of the neurological disease for the improvement of the life quality of the patients. That is the reason why the Author of this thesis outlines the neurotransmitter changes in epilepsy, narcolepsy, hepatic encephalopathy, and dementia in dogs to provide a solid foundation for further research on this veterinary field, especially in pharmacology. This further research will not

only provide new treatment possibilities for neurological diseases, it also opens up further options for modulation of mental disorders and gives therefore a better quality of life not only for the patients but also for the owners.

So, all in all the author of the thesis believes that the information provided in the thesis are already well researched, but it should encourage further veterinarians to perform more studies in this field to enable dogs with neurological diseases a better quality of life and not only treat the symptoms but also the cause of the disease.

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10. Figure Bibliography

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Appendix 6. Electronic License Agreement and Copyright Declaration

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Thesis progress report for veterinary students

Name of student: Jennifer Servos

Neptun code of the student: HZ1QCS

Name and title of the supervisor: Dr. David Sandor Kiss

Department: Department of Physiology and Biochemistry

Thesis title: Neurotransmitter changes in different neurological diseases in dogs

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	02	09	Correction of structure, removing some sections and bring them in order	
2.	2022	02	29	Adding transitions for each section	
3.	2022	03	05	Improvements of figures	
4.	2022	04	15	Improvement of own created figure	
5.	2022	04	20	Adding abstract, conclusion, discussion	

Grade achieved at the end of the first semester: 5 (excellent)

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3.	2022	10	08	Correction of caption of figures	
4.	2022	10	19	Corrrection of list of references	

5.	2022	11	03	Correction of formating	

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The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

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Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in..... .....