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Karolína Mainerová

Role of glutamate in obsessive-compulsive disorder: clinical and experimental findings

Role glutamátu v obsedantně kompulzivní poruše: klinické a experimentální nálezy

Bachelor ‘s thesis

Supervisor: prof. RNDr. Aleš Stuchlík, Ph.D., DSc.

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze,

Podpis

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Abstract

Obsessive - compulsive disorder is a common and chronic illness that decreases quality of life and leads to serious limitations. Its treatment is currently only successful in some patients and many of them remain with their problems without proper help and medication. The exact cause of the disease is not yet known, but the role of the glutamatergic system in the pathophysiology of obsessive-compulsive disorder is apparently very important and its modulation can potentially lead to increase in treatment success. Animal models of genetic, behavioural, pharmacological and optogenetic origins are very useful in gaining new insights into the principles and underlying causes of the disease. Clinical studies indicate the efficacy of glutamatergic modulators for disease manifestations and could serve as new avenues for the development of new drugs.

Key words: obsessive-compulsive disorder (OCD); glutamate, animal model, clinical findings

Abstrakt

Obsedantně kompulzivní porucha je časté a chronické onemocnění, které významně snižuje kvalitu života pacientů a vede k výrazným omezením v jejich fungování. Jeho léčba je v současnosti úspěšná jen u některých pacientů a spousta z nich zůstává se svými problémy bez vhodné pomoci a medikace. Přesná příčina onemocnění doposud není známa, ale zapojení glutamátergního systému do patofyziologie obsedantně kompulzivní poruchy se zdá velmi zásadní, a možnost jeho modulace může vést ke zvýšení úspěšnosti léčby. Genetické, behaviorální, farmakologické a optogenetické zvířecí modely jsou velmi užitečné při získávání nových poznatků o principech a příčinách nemoci. Klinické studie naznačují účinnost glutamátergních modulátorů na projevy nemoci a mohly by sloužit jako východisko pro vývoj nových léčiv.

Klíčová slova: obsedantně kompulzivní porucha (OCD); glutamát, animální model, klinické nálezy

List of abbreviations

The list of abbreviations does not contain abbreviations for genes and proteins.

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ARPs	AMPA receptor potentiators
cAMP	Cyclic adenosine monophosphate
CBT	Cognitive behavioural therapy
CNF	Cerebrospinal fluid
CNS	Central nervous system
CSTC	Cortico – striatal – thalamic – cortical
DBS	Deep brain stimulation
DSM	Diagnostic and Statistical Manual of Mental Disorders
DCS	D-cycloserin
EX/RP	Exposure and ritual prevention
GABA	γ-aminobutyric acid
GABHS	Group A beta-hemolytic streptococcal infections
GAD	Generalized anxiety disorder
GPe	Globus pallidus external
GPi	Globus pallidus internal
HIV	Human Immunodeficiency Virus
ITs	Intrusive thoughts
KO	Knock – out
IPSP	Inhibitory postsynaptic potential
ITs	Intrusive thoughts
LSD	Lysergic acid diethylamide
LTD	Long-term depression
LTP	Long-term potentiation

mCPP	Meta-Chlorophenylpiperazine
MDD	Major depressive disorder
MSNs	Medium spiny neurons
NAc	Nucleus accumbens
NAC	N-acetylcysteine
NMDA	N-methyl D-aspartate
OCD	Obsessive – compulsive disorder
OFC	Orbito – frontal cortex
PANDAS	Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
PCP	Phencyclidine
PET	Positron Emission Tomography
PFC	Prefrontal cortex
PSD	Postsynaptic densities
ROS	Reactive oxygen species
SNr	Substantia nigra
SRIs	Serotonin reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
STN	Subthalamic nuclei
YBOCS	Yale-Brown Obsessive-Compulsive Scale

Contents

1. Introduction

Obsessions and compulsions are in a focus of study for almost a century now. Obsessive–compulsive disorder is a common (1-3 % worldwide) debilitating neuropsychiatric condition, that can significantly affect life of afflicted patients. Obsessions are repeated intrusive and inadequate thoughts. Patients usually find them disturbing. Those thoughts create anxiety, that is often partly relieved by repeated compulsions. Compulsions can be mental or physical. Compulsive behaviour is characterized by repetitive and often senseless actions. Obsession and compulsions can be addressed at many different things or feelings, such as fear of contamination, but they can be also aggressive or sexual. Compulsions usually occur more frequently in more the severe cases and sometimes they fill the whole day or a significant part of it. Although OCD patients are mainly aware of no sense of their actions, they cannot resist the urge to make them. Therefore, they search for medication and therapy to help them control their life again. However, in many cases there is no sufficient treatment and some patients are left with their overwhelming symptoms. Therefore, studying this disease and its neurological basis is very significant, especially for the development of new treatment options.

Results from many studies in animal models and clinical trials as well as genetic studies have supported the theoretical basis of involvement of the cortico-striato-thalamic-cortical (CSTC) circuit and glutamate upregulation within it in the pathophysiology of OCD. Impairments in glutamate neurotransmission and homeostasis are contributing to OCD, hence using glutamate-modulating agents in treatment of refractory OCD seems to have a promising potential in treating patients, that respond weakly or not at all to current medication. Pharmacologic agents that target glutamate neurotransmission in the CNS are being widely studied on animal models as well as in clinical trials.

In this thesis, I will review knowledge of glutamate dysfunction in OCD from animal models, neuroimaging, and candidate genes, developing new treatments targeting the glutamatergic system, and highlight the use of some glutamate modulating agents in possible treatment of OCD.

2. Obsessive-compulsive disorder: an overview

Obsessive-compulsive disorder (OCD) is a psychiatric disease in obsessive-compulsive spectrum within the DSM-V by American Psychiatric Association along with body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), and excoriation (skin-picking) disorder (American Psychiatric Association, 2013). More illnesses have the same base in obsessive and compulsive actions, even though they belong to a different diagnostic category, such as autism, pathological gambling, and some eating disorders. According to a study done in Germany, up to 70% of OCD cases are not recognized as OCD by their consultant psychiatrists (Wahl et al., 2010). Prevalence of obsessive-compulsive disorder is 1 – 3 % worldwide with men making the majority of onsets before age of 10 and women, on the other hand, have much more often onsets after reaching the age of 10 and mostly in adolescence (Ruscio, Stein, Chiu, & Kessler, 2010). Generally, women are more likely to suffer from OCD than man and prevalence decreases with age within both genders. More than half of people with OCD suffer only with obsessions, around 11 % are purely compulsive and 34% have both obsessions and compulsions (Torres et al., 2006). Many people not diagnosed with the illness claim that they have some, but not all OCD symptoms, mostly hoarding, checking and ordering. And nearly 30% of population experience obsessions or compulsions at some point during their lives (Ruscio et al., 2010).

Symptoms of OCD are characterized by obsessions; uncontrolled repetitive thoughts creating anxiety and compulsions; the need to make repetitive, ritualistic and time – consuming actions (or mental acts), triggered by the feeling of necessity and pressure or a disaster in the case of not making those actions (Aouizerate et al., 2004). Even though OCD is being massively studied nowadays, it is still not clear to make appropriate diagnosis and research models, considering heterogeneous symptoms of the disease (McElroy, Phillips, & Keck, 1994). Symptoms of OCD are being evaluated and their severity is being scored by different systems. The factor analysing Yale-Brown Obsessive-Compulsive Scale, includes many different types of obsessions and compulsion (Goodman et al., 1989), however the need for a more homogenous system created a four-factor structure of OCD. Those factors are: a) obsessions on symmetry, ordering (the need for everything to have a special order and system and constantly pursuing this system) and counting compulsions b) aggression, sexual and religious obsessions c) obsessions with cleaning and fear of contamination and d) hoarding (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008). It was proposed, that different types of obsessions may have the basis in different circuits and therefore, this should be taken into

account in genetic and neurobiological studies and treatment results (Leckman et al., 2010). Obsessions are non-wanted thoughts or images creating anxiety, whereas compulsions are actions that relieve this anxiety (Figure 1) (M. T. Williams, Mugno, Franklin, & Faber, 2013). Obsessions can be differentiated into two subtypes, autogenous obsessions, and reactive obsessions. Autogenous obsessions are coming to one's mind without any identifiable stimuli and are of a sexual and aggressive type. When describing reactive obsessions, people usually do not have a hard time recognizing the stimuli. Those stimuli are realistic and external, such as thoughts and fear of contamination, accident, asymmetry etc. Also, these stimuli are perceived as rational, sufficient for creating actions to suppress them (Lee & Kwon, 2003). Obsessions can be anticipated by intrusive thoughts (ITs). Those thoughts sometimes occur without compulsions, and they are followed by depressions and anxiety, but can appear independently. ITs and obsessions are related with the difference that only a minor amount of many individuals experiencing ITs will develop obsessions, which are more severe and anxiety initiating (Rachman, 1971).

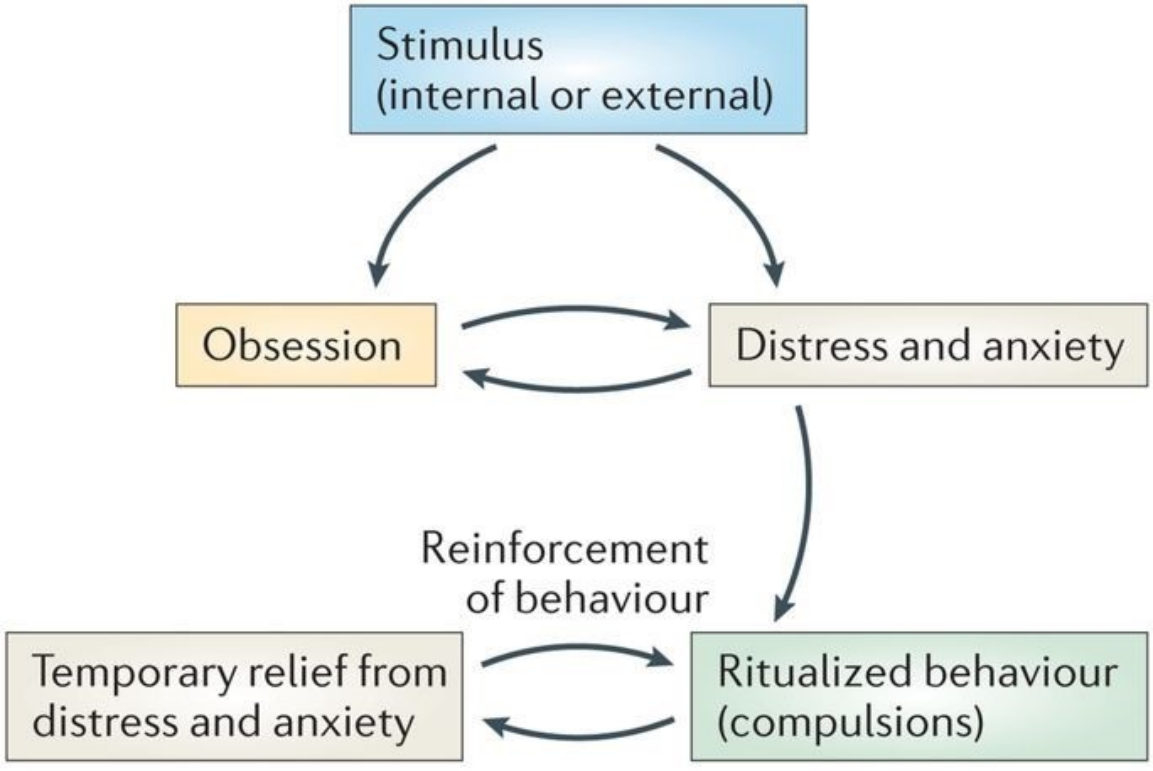

Figure 1: A theoretical diagram of obsessive and compulsive behaviour (D. Pauls, Abramovitch, Rauch, & Geller, 2014)

One of the most common and severe obsession is fear of contamination, which affects women more than men. The earlier the onset of OCD, the more sexual/aggressive and symmetry

obsessions occur. (Prabhu et al., 2013). Psychiatric diagnosis of other disorders is usually done by detection of presence of certain symptoms, where at least few of them must be present in patient to fulfil the diagnosis, however, OCD patients can have only one indication out of many possible manifestations. The discrepancy of OCD symptoms may lead to a conclusion, that OCD is not a single disorder but a collection of many, or single disorder with many manifestations. However, stability of symptoms in OCD patients is usually consistent in time. In cases when symptoms do change, they lead to the same division of OCD subtypes - autogenous or reactive spectrum (M. T. Williams et al., 2013).

More than 60 % of patients with OCD have some psychiatric comorbidity. Most frequent comorbidities, that occur without variance in gender are MDD (major depression disorder), GAD (generalized anxiety disorder), social and/or specific phobias. Addiction to alcohol, methamphetamine, ecstasy, cocaine, marihuana, and smoking is significantly higher in OCD patients than in non-neurotic controls and in other neurotic patients. Drug abuse (except tranquilisers which are abused more by women) is almost four times higher for men than for women (Torres et al., 2006). OCD commonly develops on pre-existing mental disorder, and according to "The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication" made by Ruscio et al., almost 90 % of OCD patients have their illness accompanied with another mental disorder in the DSM criteria and 80 % of those have onset of OCD later than the onset of comorbid anxiety disorders. Separation anxiety disorder (fear of leaving home or family) and posttraumatic stress disorder are exceptions where development is later than OCD onset or concurrent with it (Ruscio et al., 2010).

OCD onsets in preadolescent children or in adulthood. Gender representation in adult patients is equal, on the contrary patients with preadolescent onset are more likely to be males with less projecting anxiety and other comorbidities although tend to be less responsive to SSRIs (specific serotonin reuptake inhibitors) (Geller, 2006). Probabilities of having different comorbidities are distinctive during various life stages. Tic, anxiety, somatoform, eating and impulse-control disorders are more common at lower age. In different, there are comorbidities that do not correlate with age of onset, for example, major depression (De Mathis et al., 2008).

The exact cause of OCD is not yet fully understood but it is partly a genetic disease, which is indicated by increased chance of an OCD diagnosis in first degree relatives of OCD patients (Grabe et al., 1986; Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995), alongside that an earlier onset cases tends to be more familial. That would mean early-onset

OCD is somehow etiologically different than the one with later onset (Pauls, Abramovitch, Rauch, & Geller, 2014).

2.1. Genes associated with human OCD

Recently, potential genes responsible for OCD has been proposed, such as GRIN2B, a gene for NMDA receptor subunit that may be connected to vulnerability to OCD (Arnold et al., 2004) and a gene SLC1A1 for the glutamate transporter EAAT3, whose variabilities have an association with OCD diagnosis. Late onset of OCD may genetically differ from early onset, which is perhaps influenced by SLC1A1 alteration (Arnold, Sicard, Burroughs, Richter, & Kennedy, 2006). The SLC1A1 gene encodes glutamate transporter EAAT1/EAAT3 (excitatory amino acid transporters 1/3). EAAT1/EAAT3 is a primary neuronal transporter expressed on the postsynaptic membrane at 30-40 % synapses in the human brain (Nieoullon et al., 2006) and it is abundantly expressed in the cerebral cortex, striatum and thalamus, hence supporting the importance of glutamate transporters in the CSTC circuit (Kanai & Hediger, 2004). EAAT2 transporter in glial cells is responsible from removal of 90% glutamate from the synapse (Rothstein et al., 1996). However since EAAT3 is located mainly at the postsynaptic membrane its role in modulating glutamatergic transmission may be by modulating production of glutathione, therefore protecting neurons from oxidative stress (Nieoullon et al., 2006).

2.2. PANDAS

Pre-adolescent and childhood onset of OCD is sometimes associated with paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). The clinical picture of those children typically includes a relapsing-remitting symptom pattern with a presence of many psychiatric comorbidities, tics and motion hyperactivity. Behavioural and neurological abnormalities can be mediated by antineuronal antibodies, which emerge after abnormally acute immune response to streptococcal (group A β-hemolytic streptococcal (GABHS)) infection. These antineuronal antibodies react with cells in the central nervous system (CNS), neurons of the caudate, putamen, and globus pallidus and interfere with signal transduction (Snider & Swedo, 2004; E. Swedo et al., 1989; S. E. Swedo, Leonard, & Kiessling, 1994).

2.3. Neural circuits involved in the pathology of OCD

Over the last 30 years great steps in the field of non-invasive brain imaging were made, which enabled looking at the neural structures that might be implicated in the pathophysiology of OCD. Neuroimaging studies have demonstrated abnormalities in the cortico-striato-thalamo-

cortical circuit (CSTC loop) as a crucial factor in the disease as well as in many other diseases, like Parkinson's and Huntington's disease or ADHD (Utter & Basso, 2008). By using different analysing criteria, neuroimaging studies of OCD can be divided into four basic design categories; a) comparing of OCD patients and healthy controls at rest; b) comparing brain activity before and after treatment for cerebral activity measurement c) scanning brain activity of an OCD patient during symptom provocation; 4) studies of brain activity while performing cognitive or other mental tasks by OCD patients and healthy controls (Saxena & Rauch, 2000). Brain areas in OCD patients from the CSTC loop found to be hyperactive, are the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC) and the head of caudate nucleus. If treated with medication or cognitive-behavioural therapy this hyperactivity decreases. Contrarily, activation of OFC increases with symptom provocation (Saxena, Bota, & Brody, 2001). A misbalance of direct and indirect pathway in this system can be the cause of obsessions and compulsive thoughts and behaviours (Utter & Basso, 2008). In healthy individuals, glutamatergic projections from the frontal cortex (mainly OFC and ACC) excite the striatum. The striatum activates inhibitory GABA projections onto the internal globus pallidus (GPi) and substantia nigra (SNr) and therefore decreases their inhibitory projection on thalamus. This direct pathway creates a positive feedback loop and leads to excitatory glutamatergic projection from thalamus to OFC and ACC. The indirect pathway is a negative feedback loop system formed by inhibiting the globus pallidus externa (GPe) by striatum. GPe inhibits the subthalamic nucleus (STN), therefore when GPe is inhibited, STN can excite GPi and SNr and consequently inhibit the thalamus and its excitatory projection to the cortex (Pauls et al., 2014). Direct and indirect pathway counterbalance each other (Saxena et al., 2001) and in healthy individuals the indirect pathway modulates the direct. Overactivation of CSTC loop is caused by dominance of the direct pathway, leading to overly active OFC and can be responsible for creating persistent obsessions and compulsion in patient with OCD (Figure 2) (Rosenberg, 1967). Projections in these circuits are predominantly processed by glutamate and GABA (Graybiel & Rauch, 2000), but besides these, a major role has been attributed to dopamine and serotonin. Expression of genes that are responsible for systems of glutamate, serotonin, and dopamine can be modified by some environmental factors and events, such as psychological or neurological traumas. Those changes of expression thus change in action of neurotransmitters release can lead to obsessive and compulsive behaviours (Pauls et al., 2014).

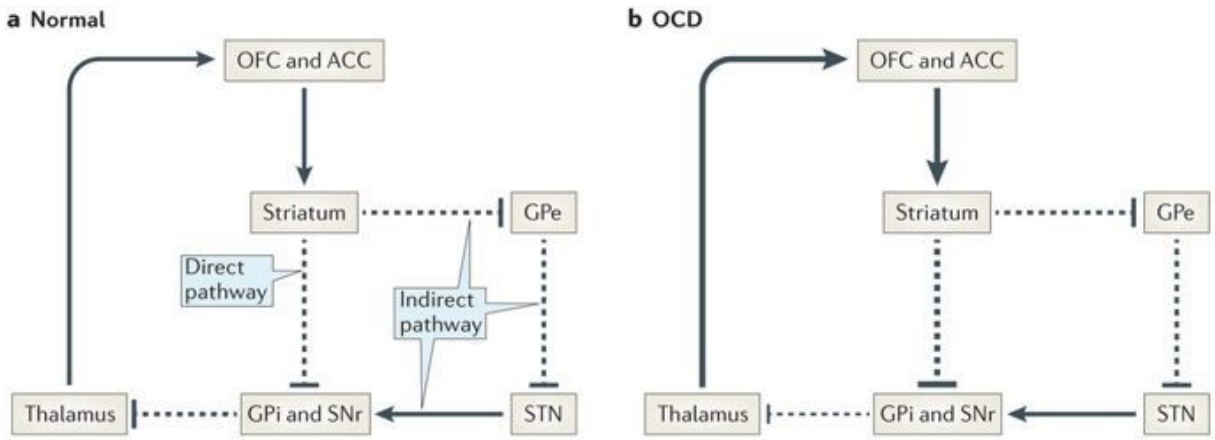

Figure 2: The CSTC loop shown in a normal condition and in OCD (Pauls et al., 2014).

Since glutamate and GABA are the principal neurotransmitters in the adult brain as well as during development, possible dysregulation in the developmental signalling can cause distortion in later CTST circuit functions. It is important to have a rich distribution of glutamate and GABA during sensitive periods of foetal and postnatal brain development because it modulates proliferation, neural growth, and maturation (Luján, Shigemoto, & López-Bendito, 2005). Dizocilpine (MK-801), phencyclidine or ethanol have been used to block NMDA receptors in prenatal period brain growth, resulting in apoptosis of specific neurons (Ikonomidou et al., 1999). This perturbation may cause hyperactivity in glutamate neurons and therefore contribute to or cause the emergence of the disease (M. L. Carlsson, 2000).

Increased concentration of glutamate in some areas of the brain were observed (Rolls, 2012) namely orbitofrontal cortex (Whiteside, Port, Deacon, & Abramowitz, 2006) and striatum (D. R. Rosenberg et al., 2000), however not in the anterior cingulate cortex (Rotge et al., 2010) and even decreased glutamate levels were found in the nucleus accumbens (NAc) (Figee et al., 2011)(Abarca, Gysling, Roth, & Bustos, 1995; Figee et al., 2011). Glutamate hyperactivity in the entire prefrontal area could enlighten the obsessions repetitiveness and compulsions initiating from stimulating positive CTST feedback loop, as well as chronical activation of inhibitory negative feedback loop causing overcautious behaviour in OCD patients (M. L. Carlsson, 2000).

It should be taken into consideration, that also other brain circuits and regions may be impaired in OCD and connected to CSTC loop, such as temporal lobe. Superior temporal lobe structures are connected to OFC, putamen and nucleus caudate (Yeterian & Pandya, 1998). Volume of grey matter in the right middle temporal gyrus was elevated in males with severe OCD symptoms, women with severe OCD symptoms had reduced volume of the same structure

(Den Braber, De Geus, Boomsma, & Van 't Ent, 2013). Amygdala, which is a structure in the temporal lobe, showed decrease of volume and function in OCD patients in distinct ways than in other anxiety disorders (Cannistraro et al., 2004). Anxiety component is a significant burden for OCD patients, that forces the behaviour and it is strongly connected to the OFC as well (Zhang et al., 2012). The severity of OCD and intensity of obsessive thought and actions correlates to volume of the left hippocampus (Atmaca, 2011), that could explain the impairments in procedural memory in OCD patients as well. Neural connections from PFC to the temporal lobe structures are supplied by glutamate (as well as with other neurotransmitters). Therefore, alleviating glutamate levels in those circuits may be effective in treating OCD symptoms as well.

2.4. Treatment of OCD

Successful treatment was first described in the late 1960s by Fernandez and Lopez-Ibor (1967) and Reynghe de Voxrie (1968) (reviewed in Fineberg & Gale, 2005) with clomipramine. Clomipramine is a tricyclic antidepressant with serotonin reuptake inhibition (SRIs) activity. Later, control studies with clomipramine and placebo OCD patients confirmed its effectiveness (Jenike et al., 1989; Marks, Mawson, Stern, Cobb, & McDonald, 1980). In the last two decades, many studies on selective serotonin reuptake inhibitors (SSRIs) have been made, such as fluvoxamine, fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. Because of lower incidence of side-effects of SSRIs, they are being prescribed more often than clomipramine (Jenike, 2004).

Successful treatment is not yet generalized and unfortunately, still, approximately 40 % of OCD patients are treatment-resistant (Skoog & Skoog, 1999). Different approaches have been evaluated for supporting the action of treatment. Monotherapy with other pharmacological agents or adding a drug from a different category (Pittenger, Krystal, & Coric, 2006). Some patients respond already to a small dose of SSRIs but often higher doses of antidepressants are needed (Ninan et al., 2006). Adding antipsychotics to treatment such as haloperidol (McDougle et al., 1994), or risperidone (Hollander, Rossi, Sood, & Pallanti, 2003) can be helpful. More invasive treatment methods are used sometimes, including ablative psychosurgery (Guarnieri et al., 2005), deep brain stimulation (DBS) (J. L. Abelson et al., 2005), electroconvulsive therapy, and repetitive transcranial magnetic stimulation (B. D. Greenberg et al., 1997). However, some patients report no reaction to existing treatment at all, which indicates an involvement of another neurotransmitter system than just serotonin and more complicated mechanism behind the disease. New therapies are considering drugs that normalize

glutamatergic neurotransmission. That could bring help to people that don't react to existing treatment (Pittenger et al., 2006). Glutamatergic system is excessively active in OCD patients, therefore drugs that decrease glutamate release may be useful in OCD treatment (Bhattacharyya & Chakraborty, 2007; Pittenger, Kelmendi, Wasylink, Bloch, & Coric, 2008).

The best results of currently available treatment come from a combination of pharmacotherapy and cognitive-behavioural psychotherapy (CBT). CBT for OCD patients has its own form. It is based on exposure and ritual prevention (EX/RP model). A patient is exposed to dreaded and anxiety-provoking situations and tries to block ritualized behaviour with the help of a psychotherapist (Franklin, Abramowitz, Kozak, Levitt, & Foa, 2000; Meyer, 1966). EX/RP model is problematic for some patients (for example patients with primary obsessions – pure mental obsessions or with compulsions that are hard to prevent). In those cases, classic CBT, without the use of EX/RP strategy, is used with nearly the same result success, however, it tends to be more efficient when delivered individually, on the contrary, CBT with EX/RP is better in group therapies (Whittal, Thordarson, & Mclean, 2005).

Patients suffering from OCD are often without treatment for a long time, due to hiding their symptoms or wrong diagnosis. Early diagnosis and treatment with SSRIs and CBT are the first choice that can relieve the symptoms and make the life for patients less demanding; they also prevent relapse if captured early (Jenike, 2004). Hopefully, we can uncover more of the illness heterogeneity and help with making more effective treatment options in the future. Animal models therefore seem to be of a big help in this effort because we can observe animal analogy to human OCD symptoms.

3. Animal models of obsessive-compulsive disorder

Animal models of psychiatric diseases are a big challenge, due to the nature of some symptoms which are not accessible in animals (for example feelings of guilt, suicidal thoughts). Consequently, animal models of OCD are models of compulsive behaviour, giving us insights into brain structures involved in the unconcealed, behavioural factors of the illness. There are specific criteria for valuing animal models of psychiatric diseases. Face validity describes phenomenological analogy between the behaviour in animals and in human patients. Construct validity is ideally achieved by exposing the animal to etiological factors, that cause disease pathology in humans. Due to nature of psychiatric diseases mentioned before, the fact that in most of the psychiatric diseases no etiological or environmental factor were clearly established and most of those illnesses seem to originate from many factors, it is significantly difficult to achieve construct validity (Nestler & Hyman, 2010). In practice, a construct validity is for example similarity in treatment effect (Ellenbroek & Cools, 1990). Predictive validity refers to the effectiveness of treatment and molecular targets of medications. It predicts, that the animal responds to treatment in the same way as a human would (Nestler & Hyman, 2010). Due to those criteria and levels of validity in animal models, it must be considered whether those models will be efficient for given study (Ellenbroek & Cools, 1990). Different models give us a different view and perspective of key factors and possible treatments of illnesses, due to different approaches. For modelling OCD there are many different approaches and many ways to model symptoms of the illness are used. Limitations of genetic animal models of such disease are substantial, but they can reveal new ways and possibilities result in development of more meaningful models that can clarify the way of how glutamate can affect the pathogenesis of OCD. They will be summarized below.

3.1. Genetic mouse models

Genetic modification in a mouse or sometimes even rats is a way to create a specific change in phenotype and symptoms like those in humans with OCD. With increasing knowledge about the neurobiology of this disease, this group of genetically modified animals is growing rapidly. Also, an understanding of genotype bases behind phenotype manifestations is getting easier with new techniques. In this chapter, I will introduce several genetic models of OCD. Simplified diagram of OCD candidate genes, some of which I reviewed in chapter 2.1., are shown in figure 3.

3.1.1. Sapap3 mice

An example of a genetic mouse model is a deletion of Sapap3. Sapap3 is a SAP90/PSD95-associated protein 3. It is a protein that is highly expressed in the *striatum* at the postsynaptic sides of excitatory synapses. More precisely, it is a protein embedded in postsynaptic densities (PSD) where it regulates and targets neurotransmitters receptors into the membrane. In the SAPAP3 mouse model increased anxiety and compulsive grooming occurs and leads up to hair loss and facial lesions. Those symptoms are successfully alleviated by a selective serotonin reuptake inhibitor (Welch, 2007). This reflects face validity as well as predicted validity for this model. Sapap3 mutant mice also reveal a structural and biochemical defect in corticostriatal synapses, which is expected to be very important in OCD (Welch, 2007).

3.1.2. Hoxb8 mice

Mice with a knock-out in HOXB8 gene express high levels of self-harming grooming. HOXB8 gene is important in brain development and when deleted, care of self is affected during adult life. Mice with Hoxb8 gene knock-out tend to overly groom themselves as well as their normal not genetically altered cagemates (Greer & Capecchi, 2002).

5.1.3. D1CT - 7

Transgenic mice D1CT – 7 express potentiating cholera toxin, that chronically activates G proteins and therefore elevates levels of cAMP in glutamatergic neurons and enhances excitability of those neurons (Burton, Hasel, Bloom, & Sutcliffe, 1991). Synthesis of cholera toxin subunits A1 was made to be driven by D1 dopaminergic receptors. Mice displayed stereotypic behaviours like compulsive biting, increased speed and locomotion when D1CT transgene was expressed in a corticolimbic section of the mouse brain. Simultaneously increased activity of the piriform cortex layer II, layers II-III of somatosensory cortical areas, and the intercalated nucleus of the amygdala was observed (K.M. Campbell et al., 1999) Alleviated tolerance for seizures proposed shifted balance between excitation and inhibition in the cortex (Keith M Campbell, Veldman, McGrath, & Burton, 2000). Treatment of D1CT transgenic mice with a non-competitive antagonist MK-801 has exacerbated the obsessive-compulsive symptoms (McGrath, Campbell, Parks, & Burton, 2000).

5.1.4. Sltrk5 knock-out mice

A study, suggesting a connection between the human Sltrk1 gene and Tourette's syndrome, (J. F. Abelson et al., 2005) has led to creating mice with a knock-outed gene Sltrk5. This gene is mainly expressed the cortex and striatum and these KO mice show augmented

activity in the OFC, reduced volume of the striatum and some glutamate receptor subunits (NR2A, NR2B, GluR1, and GluR2) alterations. This results in impairments of CSTC circuit hypothesised to be present in OCD patients. Sltrk5 KO mice show behavioural similarities with Sapap3 KO mice like excessive hair- loss and skin lesions. However, the functional and structural effects of these genes are not the same and they for example both affect subunit composition of glutamate receptors differently and therefore differentially affect the glutamate transmission (Shmelkov et al., 2010).

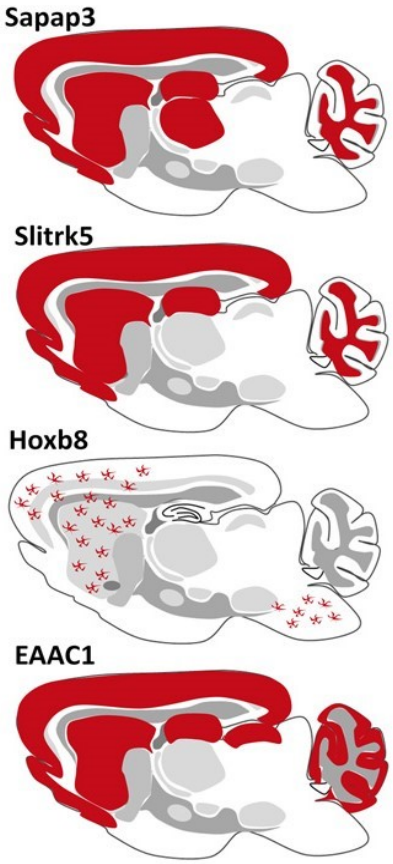

Figure 3: Diagram of simplified OCD candidate genes location (Ting & Feng, 2011).

3.2. Behavioural models

Behavioural models are characterized by spontaneous and naturally occurring compulsive-like behaviours in model animals. These activities must not be artificially induced by genetic or pharmacological interventions but can be behaviourally manipulated (e.g. food-restriction). Spontaneous ritualistic or stereotypic behaviour in animals can be tail chasing, grooming, cleaning etc. These actions relate to human compulsions, such as checking, washing, face picking, hair pulling etc. Models include the deer mouse (*Peromyscus maniculatus*) model of spontaneous stereotypy, marble burying model, extensive grooming – barbering or cleaning

model food-restriction-induced hyperactivity or polydipsia or signal attenuation model. Nowadays most of the behavioural models that are being used for modelling OCD are barbering, marble burying, signal attenuation, and deer mouse model.

3.2.1. Barbering

Barbering develops spontaneously in laboratory mice, but because it does not occur widely in all animals, it is studied as an abnormal behaviour. It was used to be considered a dominant behaviour because individuals pluck hair from their cage mates to such a scale they are left with big bold patterns on their bodies. Nonetheless, they sometimes barber them-selves. On the contrary human trichotillomania is usually oriented on individual's self-hair, but in some cases also hair of other people. Similarities between trichotillomania and barbering in mice are very persuading. Barbers pick predominantly hair around the eyes and scalp, it is female biased and it onsets during puberty. It has a good face validity and an advantage of a spontaneous and probably genetically conditioned onset. Unfortunately, at the moment it lacks predictive and construct validity (Garner, Weisker, Dufour, & Mench, 2004).

3.2.2. Marble burying

A model with a good predictive validity is marble burying. In the beginning, this model was used to model anxiety levels, according to the thought that burying of dangerous but also harmless objects by rodents is a behaviour induced by fear. However, in later studies of a wide spectrum of drugs that affect this behaviour SSRIs were established to be effective. Furthermore, animals were not avoiding new objects and rather were attracted by them, and alongside exploring, burying them (Londei, Valentini, & G. Leone, 1998; Thomas et al., 2009). That proposes a resemblance with compulsive behaviour, though the predictive validity of this model is undermined with the effectiveness of anxiolytic drugs such as diazepam and clomipramine. Those work as sedatives and are not very effective in reducing OCD symptoms (Broekkamp, Rijk, Joly-Gelouin, & Lloyd, 1986). Supporting the glutamate theory of OCD (see below), memantine and amantadine inhibit marble burying with no effect on locomotor activity. They act as NMDA antagonists and therefore they decrease the action of glutamate in the brain (Egashira et al., 2008). Marble burying was inhibited using various metabotropic glutamate receptors antagonists. Relieving of OCD symptoms might provide blockade of presynaptic inhibition of glutamate as tested with marble burying rodents. For instance a group II mGlu receptor antagonist MGS0039 was found to be effective, even though the mechanism of its anxiolytic and calming effects is not yet known (Shimazaki, Iijima, & Chaki, 2004). A potential

anxiolytic activity of mGlu5 receptor antagonists may likewise present new ways of anxiety treatment (Spooren et al., 2000).

3.2.3. Signal attenuation

The effect of signal attenuation is based on imitation of a psychological mechanism of compulsions. In the theory, compulsions are the results of insufficient respond feedback from an action (Szechtman & Woody, 2004). If, for example, the normal behaviour is to press a lever and get stimuli as food, the attenuation of the signal causes the animal to push the lever more intensively even though there is no food present after some time. Unlike from compulsions in OCD patients, who are experiencing the symptoms for a long time, this lever-pressing is exhibited only for a short duration. SSRIs and other drugs reduce this compulsive behaviour (Joel, 2006).

In the signal attenuation model, administration of NMDA receptor antagonist MK-801 highly exacerbated the level pressing and D-cycloserin (DCS), an NMDA receptor partial agonist, decreased level pressing (Albelda, Bar-On, & Joel, 2010). DCS is a partial ligand at glycine binding site of NMDA receptors. It exhibits 40–86% of glycine efficacy (Hood, Compton, & Monahan, 1989). Therefore, NMDA receptor activation may be a way to relieve compulsive behaviour in OCD patients. However, MK-801 showed inhibition of marble burying in marble burying model of OCD as well as another NMDA receptor antagonists memantine and amantadine, with amantadine not affecting prepulse inhibition nor locomotive activity, therefore, has shown good potential to become a possible OCD medication (Egashira et al., 2008).

3.2.4. Deer mouse model

An animal that exhibits a spontaneous stereotypy and therefore creates a perfect animal model of obsessive-compulsive behaviour is a deer mouse (*Peromyscus maniculatus bairdii*). In this species varying intensity of repetitive behaviour is presented, including jumping, backwards somersaulting, and patterned running. The intensity of these patterns is dependent on the enrichment of the environment. In a rich environment (bigger cages with more stimuli), fewer rodents have a large scale of repetitive behaviour and on the contrary animals in small cages tend to over-ritualize (Powell, Newman, Pendergast, & Lewis, 1999). Mice ritualization can be attenuated with SSRIs, e.g. fluoxetine (Korff, J. Stein, & H. Harvey, 2008). Therefore, deer mice create a good model with face, construct and predictive validity with no need for the experimenter to interfere.

3.3. Pharmacologic models

A pharmacologic model is created by inducing neurochemical misbalances and behavioural changes that resemble disease conditions with a pharmacological agent. The validity of pharmacologic models is significant in all three criteria when drugs used are carefully selected. Unfortunately, they tend to oversimplify heterogeneity of OCD (Korff & Harvey, 2006).

3.3.1. Quinpirole

After chronic treatment with quinpirole, a dopamine agonist binding to D2/D3 receptors, animals exhibit stereotypic ritual-like behaviours and path stereotypy with a face validity to motor compulsions of OCD patients. They return frequently and quickly to an object of interest and other structures of behaviour/objects are avoided. Treatment with clomipramine after chronic treatment with quinpirole shows attenuated checking behaviour, probably because clomipramine has also a dopamine-blocking activity. This unique model of compulsive checking behaviour supports the hypothesis of dopamine role in OCD (Szechtman, Sulis, & Eilam, 1998). Quinpirole has shown to increase extracellular levels of glutamate in SNr and lower extracellular concentrations of glutamate in nucleus accumbens (NAc) (Abarca, Gysling, Roth, & Bustos, 1995), which corresponds to findings on extracellular glutamate in humans (Figee et al., 2011). It has also showed reduced metabolism in the caudate putamen and the hippocampus (Stijn Servaes et al., 2016). In a trial of chronic quinpirole treatment, increasing expression of metabotropic glutamate receptors mGlu5 in regions of the CSTC loop was observed. This probably occurred because of D2 – mediated inhibition of glutamate release was inhibited by quinpirole (S. Servaes, Glorie, Verhaeghe, Stroobants, & Staelens, 2017). Hence, glutamatergic agents memantine and riluzole (see below) were tested on this model. However, memantine and riluzole showed no effect on alleviating the deficit created by quinpirole. On the contrary, memantine potentiated this deficit. This may be because quinpirole reduces glutamate activity in the nucleus accumbens, and administration of other glutamate-lowering agents can aggravate these symptoms (Janikova, Brozka, Radostová, Svoboda & Stuchlik, 2018).

3.3.2. mCPP

In contrast with dopamine antagonist quinpirole, mCPP (meta-Chlorophenylpiperazine) is a serotonin system activator with a minimal effect on the dopamine system. After mCPP administration to patients with OCD, an acute symptoms exacerbation, as well as an anxiety attack, has been shown (Pigott et al., 1991). To evaluate the mCPP model of OCD a persistent

index was used. Animals were treated with mCPP and then released to a T-maze. In the maze animals treated with the drug shown increased persistent behaviour. Fluoxetine works as a protection against mCPP effects. If animals were chronically treated with fluoxetine before mCPP administration, they showed no increase in persistent behaviour after mCPP (Tsaltas et al., 2005). This model shows good predictive validity although it is greatly time-consuming.

3.3.3. 8-OH-DPAT

The selective 5-HT1A and 5-HT7 agonist 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide) is used mainly in a spontaneous alternation model. This model is being tested in a T-maze, maze with two identical branches. Unaffected rats choose the opposite branch in each round. But when injected with 8-OH-DPAT, they show an increased tendency to choose always the same branch, therefore present a preservative behaviour. Fluoxetine demonstrated protection from the effect of 8-OH-DPAT (Yadin, Friedman, & Bridger, 1991). A similarity between 8-OH-DPAT and quinpirole in compulsive checking was shown despite their different neural mechanism. Quinpirole indicates compulsive checking by driving dopaminergic receptor uninterruptedly and hence suppress any feedback action for behaviour discontinuation. On the contrary, 8-OH-DPAT creates compulsive checking by inhibiting the activation of negative serotonergic feedback that usually deactivates motivation state driven by dopamine (Alkhatib, Dvorkin-Gheva, & Szechtman, 2013).

3.4. A neurodevelopmental model

A recent multifactorial model was made by exposing mice in early postnatal period to a tricyclic antidepressant clomipramine and therefore manipulating with neurotransmitter levels during growth. Later in adulthood, it causes symptoms, which are biochemically very similar to the ones in a patient with OCD, because it modifies the CSTC loop. By monitoring the receptors of this model animals, higher levels of expression in 5-HT2C in OFC and in D2 receptors in animals were demonstrated. The advantage of this model is, that adult animals present many behavioural changes like strengthen anxiety, worsen memory, hoarding or repetitive behaviour (Andersen, Greene-Colozzi, & Sonntag, 2010).

4. Mechanisms of action of drugs affecting glutamate system

Glutamate is an amino-acid with only a minor role in neurotransmission in a mammalian body, nonetheless its concentration in the central nervous system and cerebrospinal fluid (CNF) is exceptionally high (8–10 mmol/kg and even higher). With the amount of involvement in 90% of the synaptic connection in the human brain, it makes the principal excitatory neurotransmitter (Snyder & Ferris, 2000). It is involved in virtually all circuits in the brain. Glutamate binds to three ionotropic receptors, AMPA, NMDA and kainite receptors. Those receptors are cation channels and open when they bind to glutamate. Open channel allows sodium, potassium or calcium to move freely across the plasma membrane. As a result, they excite the postsynaptic cell. Metabotropic glutamate receptors, mGluRs, are coupled to several intracellular signalling cascades of second messenger systems. AMPA and NMDA receptors are evenly distributed throughout the whole brain, mGluRs are of three types, I and II are mostly found in forebrain/midbrain and type III in cerebellum, retina and spinal cord. A density of AMPA and NMDA receptors are responsible for postsynaptic response to glutamate and through the action of long-term potentiation (LTP) and long-term depression (LTD) they have an immense role in a neuronal plasticity, which is a foundation for learning and memory (Grados, Specht, Sung, & Fortune, 2013).

In past two decades, interest in glutamate modulators (antagonists and agonists) has been consistently growing, due to rising evidence of glutamate being the primary mediator of neuropsychiatric pathology (Grados et al., 2013). Glutamatergic agents are proposed to stabilise a deficit in glutamatergic synaptic function (glycineB receptor agonists, glycine transporter antagonists, AMPAkines, and mGluR5 agonists), or they could decrease the effect of glutamatergic hyperactivity (J. H. Krystal et al., 2003).

Metabotropic glutamate receptors (mGluR) are G-protein-coupled receptors that function through the second messenger pathways. Recently, EAATs transporters that remove glutamate from the synapse and converse it to glutamine are being investigated as a new possible way to manipulate with glutamate levels (Hashimoto, Malchow, Falkai, & Schmitt, 2013).

Role of NMDA (N-methyl-D-aspartate) receptor is very prominent in several disorders, it is an ion channel that regulates the influx of calcium and monovalent cations. NMDA receptors are located throughout the entire brain and take a great part in synaptic plasticity and memory function (Stephenson, Cousins, & Kenny, 2008). They are agonised with glutamate and glycine as a coagonist that means, that the receptor is not fully working without glycine

being bound. NMDA receptor is a heterotetramer connected from to dimers, one NR1 subunit and two NR2 subunits. NR1 bind glycine and NR2 bind glutamate (VanDongen, 2009). NMDA receptor antagonists can be pharmacologically divided whether they bound to NMDA (agonist) or glycine (co-agonist) site, the channel pore or several other modulatory sites (e.g. Zn^{2+} site, polyamine side…) (Wong & Kemp, 1991). NMDA agonists and therefore influx of Ca^{2+} in the cell depends on the amount of the agonist and by what modulatory side does it binds to (Lipton et al., 2002). A model of NMDA receptors binding sites is shown in figure 4. NMDA receptors are also involved in excitotoxic neuronal cell death. This condition happens when an excessive influx of Ca^{2+} ions is driven by overactivation of NMDA receptors, which can lead to increase in levels of free radicals and eventually in irreversibly destroying the cell (Lipton, 2006). This mechanism is included in many neuronal diseases such as Huntington's and Parkinson's disease or in cerebral ischemia after stroke (Kemp & McKernan, 2002).

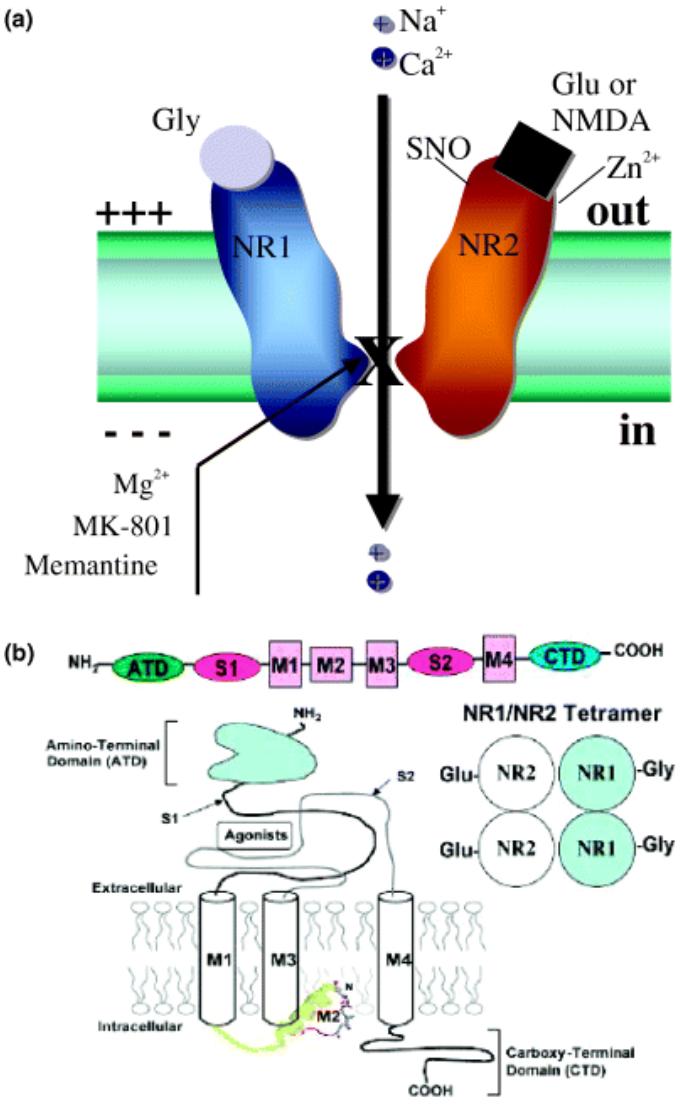

Figure 4: A model of NMDA receptor binding sites (Chen & Lipton, 2006)

Non-selective NMDA receptor antagonists, PCP and ketamine, were originally developed as an anaesthetic drug. In lower doses they create hallucinations, lower blood pressure and create psychosis-like symptoms. Because of those many side effects, there has been an approach to create only a partial antagonist. That is possible trough blocking the glycine site of the receptor, therefore even with high glycine levels, the receptor is not fully in function. (Kemp & McKernan, 2002). The agents that alter glycine levels (e.g. glycineB receptor agonists, GlyT-1 antagonist, AMPAkines) are a first treatment choice for the NMDA model of psychosis (J. H. Krystal et al., 2003).

Ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors are responsible for most of the excitatory neurotransmission in the CNS and contribute to synaptic plasticity through LTP and LTD and the formation of neural networks during development. AMPA receptors can be modulated by AMPA receptor potentiators (ARPs). They allosterically bind to them and slow down the frequency of receptor desensitization in the presence of glutamate. It has been demonstrated that ARPs LY 392098 was effective in decreasing immobility and depressive behaviour (Li, Witkin, Need, & Skolnick, 2003).

The CSTC circuit is primarily excited by glutamate and inhibited by GABA. Glutamate projections from the cortical areas, thalamus and hippocampus descend to act on the striatum, on the medium spiny neurons (MSNs). Pathological activation of the anterior-cingulate cortex (ACC) and the orbito-frontal cortex (OFC) collaterally activates glutamate release in both ACC and OFC and therefore increase glutamate release also in the striatum (Wu, Hanna, Rosenberg, & Arnold, 2012). However, MSNs do not express any glutamate and they are primarily inhibiting (GABA) neurons (Kreitzer, 2009). Consequently, all glutamate in this area is from metabolic pools. That means the glutamate in cells that work as a precursor of GABA synthesis, or glutamate rising from the afferent tracts. Many interneurons associated with MSNs together with glutamatergic affective synapses can highly regulate the output of the striatum (Monteiro & Feng, 2016). MSNs in ventral striatum can augment repetitive motor behaviour when disinhibited and it is not aligned with cerebellum and dorsal striatum, even though dorsal striatum is in general more important in motor coordination (Pauls et al., 2014). The repetitive behaviour of OCD may be a consequence of bursts of neuronal activity, respectively glutamatergic activity in specific brain areas (Monteiro & Feng, 2016). That can suggest that the dysfunction on this circuit, found in OCD patients, is a consequence of glutamate dysregulation. Extracellular glutamate level depends on its reuptake and if that would be

perturbed, hyperactive firing could take place in particular brain areas (Pittenger, Bloch, & Williams, 2011).

Edmund Rolls proposed a hypothesis, in which elevated glutamate neurotransmission, may be the reason of overly stable attractor network of cortical and related areas, hence creating strengthen firing rate and rigidity in behavioural actions. Depending on where those effects are considered, different symptoms may occur (Rolls, Loh, & Deco, 2008). In higher motor areas, increased firing rates of glutamate and therefore increased the stability of this network could create persistence in one motor pattern, because the lower motor areas cannot easily escape their actions such as it would repeat movement sequences. Transferring between actions or behavioural plans can be altered when attractor networks are profoundly stable in the cingulate cortex and dorsal medial prefrontal cortex (Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007).

4.1. Glutamate/Serotonin interaction

Positron emission tomography (PET) made after SSRIs/clomipramine treatment (S Saxena, Brody, Schwartz, & Baxter, 1998) and magnetic resonance spectroscopy after paroxetine treatment (Moore, MacMaster, Stewart, & Rosenberg, 1998), showed a decrease in metabolism and glutamate levels in prefrontal cortex and caudate. Therefore, the mechanism of SSRIs action could be attenuation of glutamate release in the cortex and the striatum and weakening the direct and the indirect pathway. This action would make it easier to switch from one behaviour to another and reduce repetitive thoughts and activities. The grounds for this mechanism could be reciprocal impact between serotonin 5-HT2A receptor and glutamate receptors. When glutamate receptors are antagonised, 5-HT2A receptor transmission is boosted, while stimulation of 5-HT2A receptor initiate reduction of glutamatergic transmission (M. L. Carlsson, 2000). LSD, psilocin, psilocybin and mescaline are 5-HT2A receptor agonist, therefore activates this receptor and its pathway. These psychedelic drugs have been demonstrated as helpful for OCD patients as well (Leonard & Rapoport, 1987). Clozapine, 5-HT2A/C receptor antagonist may produce or intensify OCD or epileptic symptoms (Baker et al., 1992). Blockade of 5-HT2A receptor by its antagonists (such as M 100907) was shown to accelerate NMDA receptor neurotransmission in PFC (Arvanov & Wang, 1998).

4.2. Glutamate/Dopamine interaction

Glutamatergic neurons running from cerebral cortex control dopamine neurotransmission as well as other monoaminergic transmission originating in the brain stem. They accelerate dopamine neurons directly by glutamate or by acting as a brake through

GABAergic interneurons (figure 5). This system is in balance in a healthy brain, with a minor dominance of the brake, and when disturbed by hypo/hyperglutemia the accelerate/break system goes of the balance accordingly to which one of those outweighs (A. Carlsson, Waters, Waters, & Carlsson, 2000). Glutamate NMDA receptors are spread through brain areas regulating dopamine release (Javitt, 2010). Glutamate antagonists, e.g. MK-801 (NMDA antagonist), can enhance dopamine release (Miller & Abercrombie, 1996). When dopamine levels are rapidly increased, by e.g. amphetamine, which is a monoaminergic modulator, negative feedback loop of glutamate/dopamine system is outweighed by the break part. If amphetamine is being pre-treated with NMDA antagonist (MK-801 or ketamine), this brake seems to not be activated as much and dopamine release is exceptionally high. This implies, that lower glutamate levels, could be the reason for an inadequate break system and amphetamine-induced enhancement of dopamine release in patients with schizophrenia (A. Carlsson et al., 2000) and maybe the dopaminergic discrepancy in schizophrenia is a secondary condition owing to dysfunction of the glutamatergic system (Javitt, 2010).

In context of OCD, dopaminergic D1 receptors are abundantly located on GABA neurons of the direct pathway and versus D2 receptors, D1s are proconvulsive (Starr, 1996). Their activation by D1 agonist SKF 38393 has revealed OCD resembling symptom of grooming/washing in laboratory mice and increased extracellular levels of GABA as well as of glutamate (Abekawa, Ohmori, Ito, & Koyama, 2000).

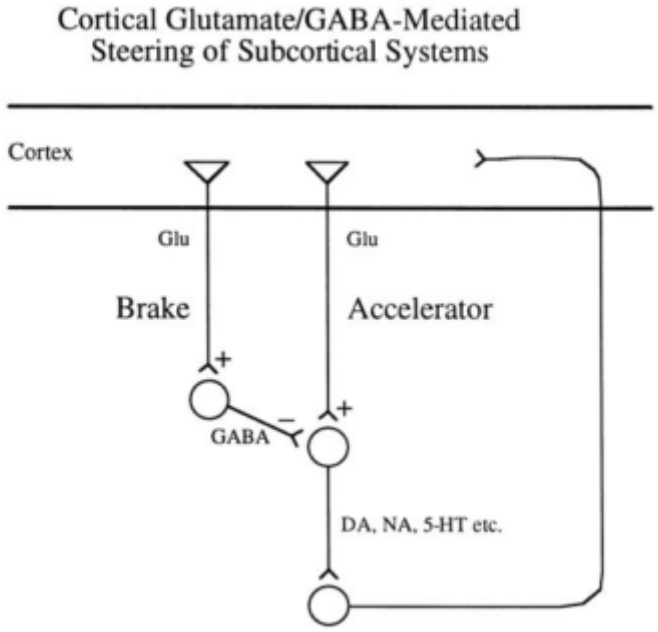

Figure 5: Interactions between glutamate and dopamine (A. Carlsson et al., 2000).

5. Effect of glutamatergic drugs on OCD – clinical findings

According to the evidence reviewed above, anti-glutamatergic agents can alleviate increased brain glutamate levels in OCD patients. This could be effective in diminishing the over-activity of direct pathway in the CSTC loop, powered by glutamate, for action and motor functions, hence stopping the forced and unstoppable repetition of actions, as well as help with switching from one type of behaviour to another. The stability of the attractor network is probably related to negative reward predictor cells and rule cells in the OFC and ACC (Rolls & Grabenhorst, 2008). Negative reward predictor cells fire when the expected reward is not received (Thorpe, Rolls, & Maddison, 1983), so when they are too stable they together with the rule cells, which are responsible for flexibly switching between behaviours, stay constricted in repetitive actions.

The effect of glutamatergic agents could be in diminishing the hyperactivity of glutamate e.g. by blocking the NMDA receptor. It is possible, that simultaneous treating with GABA activating drugs could increase its inhibitory effects and help with alleviating the stability (Rolls, 2012).

Despite SSRIs are to some extent successful in the treatment of OCD symptoms, the nonnegligible number of patients are left with little or no benefits with currently available treatment options. Alongside the evidence for glutamatergic function and dysfunction in OCD, the basis for finding glutamate modulating agents that could help with attenuating those symptoms arose. In clinical practice, SSRIs with CBT are still the first choice in treatment, however recent findings of anti-glutamatergic agents may be beneficial in creating another successful treatment (Wu et al., 2012).

The efficiency is usually measured by the YBOCS scale of OCD symptoms reviewed in chapter 2.

5.1. Riluzole

Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a neuroprotective compound with anti-compulsive properties, currently used for treating amyotrophic lateral sclerosis (ALS), with which it prolongs patients time before the need for using a respirator to a few months (Lacomblez, Bensimon, Leigh, Guillet, & Meininger, 1996). Its neuroprotective properties consist in reducing glutamatergic neurotransmission at the presynaptic level, by blocking voltage-gated Na^{2+} channels (Urbani & Belluzzi, 2000), inhibiting glutamate release by blocking vesicle fusion in the presynaptic terminal (Wang, Wang, & Wang, 2004). It also

enhances glutamate clearance from synaptic cleft by modulating astrocytes to uptake glutamate (Frizzo, Dall'Onder, Dalcin, & Souza, 2004).

Riluzole is generally very well tolerated and it is considered a safe drug (Zarate & Manji, 2008). Trials with children as well as with adults showed very good efficiency in riluzole treatment of OCD. In an early clinical trial with 13 patients who had been treatment-resistant before, 7 of them (54%) reported improvement of their symptoms after riluzole administration additionally to their on-going medication. (Coric et al., 2005). Many of other clinical trials reported very similar results with riluzole being effective in more than 50 % of treatment – resistant patients (P. Grant, Lougee, Hirschtritt, & Swedo, 2007; Pittenger et al., 2008). Riluzole also showed an improvement in a depression within OCD patients suffering from this comorbidity. Results of these trials may suggest that riluzole could be used in a monotherapy for OCD patients that had no response to SSRIs, however these trials still have some limitations as they administered psychotherapy or other medication in the process of testing (Pittenger et al., 2008). However, in a later double blind placebo controlled study with 60 patients, that were treatment – resistant as well as with many other comorbidities, riluzole did not show itself more effective than placebo (P. J. Grant et al., 2014). In a trial with 50 OCD inpatient and outpatients with MDD (major depressive disorder) comorbidity, riluzole showed no significant results in the whole group, but with a slight effect on the outpatient (Pittenger et al., 2015).

Riluzole has a big advantage of very few side-effects; however, its efficiency on OCD is not clear. It may have a potential for treating less severe OCD patients, but further trials and development is still needed.

5.2. NAC (N-acetylcysteine)

NAC, a cysteine derivate, is a very potent antioxidant, refiling endogenous glutathione and scavenging of reactive oxygen species (ROS), therefore its use has been for many years in helping the body to get rid of ROS in conditions such as treatment of HIV, chronic obstructive pulmonary disease and contrast-induced nephropathy (Dodd, Dean, Copolov, Malhi, & Berk, 2008). Modulation of glutamatergic neurotransmission is done through glutamate/cystine antiporter located on glial cells, which takes up cystine and exchange it for glutamate and results in increased glutamate in the synapse, which negatively feedbacks to presynaptic cells by mGluR2/3 receptors and reduces glutamate release (Moran, 2005).

In a study evaluating total levels of ROS and antioxidant in the serum high levels of oxidative stress was presented in children with OCD (Kandemir, Abuhandan, Aksoy, Savik, & Kaya, 2013) as well as in adults, in whom also lower levels of antioxidants were found (Ersan, Bakir, Erdal Ersan, & Dogan, 2006). In a one case study, NAC was effective in alleviating OCD symptoms alongside with fluoxetine treatment (Lafleur et al., 2006).

5.3. Memantine

Memantine (3,5-dimethyladamantan-1-amine) is a non-competitive NMDA receptor antagonist from a group of two aminoadamantanes that are today in clinical use. They both bind to the phencyclidine (PCP) binding of the NMDA receptor (Kornhuber, Weller, Schoppmeyer, & Riederer, 1994). It is a low – affinity channel blocker with rapid off-rate from the channel, that makes it a good NMDA channel blocker without disrupting normal and physiological synaptic activity (Chen & Lipton, 2006). Memantine is very potent in protecting neurons from excitoxic neuron cell death from glutamate and NMDA (Erdö & Schäfer, 1991). This fact substantiates the use of memantine in treating Parkinson's disease (Emre et al., 2010) Huntington's disease (Cankurtaran, Ozalp, Soygur, & Cakir, 2006) and Alzheimer's disease (Tariot et al., 2004); the latter, is currently the only disease where memantine is approved for use in treatment.

In OCD, its efficiency has been suggested by several studies and trials (Pasquini & Biondi, 2006; Poyurovsky, Weizman, Weizman, & Koran, 2005). In a case study with a 15-year old female, memantine successfully alleviated obsessions and rituals (added to treatment with citalopram) after 9 months of unsuccessful treatment (Hezel, Beattie, & Stewart, 2009). In an open-label trial made by Feusner et al., 2009, 70% of patients reported improvement in OCD symptoms, however, it has not shown to be effective in treating simultaneously occurrent GAD (generalized anxiety disorder). In a single blind Intensive Residential Treatment (IRT) trial, memantine was effective in improvement severity of OCD for at least 25 % (Stewart et al., 2010).

Similarly as with the riluzole, in memantine treatment the subtypes of OCD and comorbidities should be taken into consideration in further development (Pasquini & Biondi, 2006). Nevertheless, memantine is showing good results in modulating severe obsessions and compulsions. In recent studies, memantine showed a great efficiency and safety in supporting SSRIs treatment. Therefore, adding on memantine to current antidepressant treatment in OCD patient should bring better results (Kishi, Matsuda, & Iwata, 2018).

5.4. Amantadine

Amantadine (1-adamantanamine hydrochloride) was initially developed as an antiviral agent against influenza A (Galvao, Augusta, Crispino, & Jl, 2012). Amantadine is both a dopamine agonist and antagonist and it works as a weak non-competitive NMDA receptor antagonist as well. Currently it's used after traumatic brain-injuries, to prevent drowsiness and apathy (S. E. Williams, 2007). Thought amantadine works as a neuroprotectant, due to its anti-glutamatergic activity, it also has some serious side effects, such as hallucinations, delusions and other psychotic effects (Neagoe, 2013). In marble-burying model, amantadine turned out to be effective in alleviating compulsive symptoms, in contradiction to memantine or riluzole (Egashira et al., 2008). Amantadine showed its effectiveness added to clomipramine in one case study (Pasquini, Berardelli, & Biondi, 2010), correspondingly in an open-label trial adding amantadine to SSRIs treatment has showed to reduce the obsessions and compulsions (Stryjer et al., 2014).

5.5. Glycine

Glycine is a nonessential amino acid biosynthesised from serine and in CNS it works as a neurotransmitter. Elevated levels of glycine were observed in OCD patients compared to healthy controls (Bhattacharyya et al., 2009). In spinal cord, brain stem and retina, it plays major role in inhibitory postsynaptic potential and inhibitory interneurons, though in cerebellum and brain it is excitatory, due to its co-agonism for NMDA glutamate receptor (Clements & Westbrook, 1991). For this property, it has been widely studied as a pharmacological agent targeting neurological diseases. Activation of NMDA receptor glycine site or inhibition of glycine transport, has shown efficacy in models and trials for schizophrenia (Labrie & Roder, 2010). Double – blind clinical trial showed decrease of the YBOCS OCD severity scores after glycine administration 60 g/day, yet the taste of the compound caused several dropouts (Greenberg et al., 2009) and according to a small sample size, the results are not persuading.

5.6. D-cycloserine (DCS)

DCS is partial agonist of NMDA receptor at the glycine binding side. Its facilitation of conditioned fear extinction has been demonstrated (Norberg, Krystal, & Tolin, 2008; Walker, Ressler, Lu, & Davis, 2002), hence its contribution to anxiety release in contribution with exposure therapy OCD patients was proposed. Administration of DCS two hours before EX/RP therapy accelerated the therapy in contrary to placebo controls. Patients that were administered

with DCS did need less session to overcome their anxiety (Kushner et al., 2007; Wilhelm et al., 2008).

5.7. Ketamine

Non-competitive, high affinity NMDA receptor antagonist ketamine (2- [2-chlorophenyl] -2- [methylamino] cyclohexanone) is a dissociative anaesthetic and was first used this way. Later it was revealed that its sub-anaesthetic doses, beyond psychedelic effects, have prompt antidepressant properties (Berman et al., 2000; Caddy, Giaroli, White, Shergill, & Tracy, 2014). It also weakly binds to opiate receptor, monoamine transporter sites, and acetylcholinesterase receptor and it has psychotropic and psychotomimetic attributes. Administration of ketamine (NMDA receptor antagonist) to healthy subjects creates expression of several symptoms resembling psychosis, such as effects on working memory, attention deficit, hallucinations, paranoia and thought disorder (Krystal et al., 1994)

A single case report examined, if ketamine can alleviate symptoms of OCD. Patient with severe, refractory OCD stated 50 % reduction of obsessions, that lasted for three days after ketamine administration (Rodriguez, Kegeles, Flood, & Simpson, 2011). Open ketamine trial with OCD patients showed improvement in symptoms after ketamine administration up to three days, though subjects in this study were also using other medication (Bloch et al., 2012). Randomized controlled crossover trial of ketamine made by Rodriguez et al., 2013, on patients that had no history with medication and were currently medication free, revealed very good outcomes and rapid anti-obsessional action of ketamine. This rapid function is in contrast with memantine, which is also NMDA antagonist, hence its effects are 8-12 weeks delayed after administration. In a trial made with both ketamine and memantine, patients who did not got results after ketamine dose did not got results after memantine either. However, in patients that responded well on a ketamine dose, later memantine did restore ketamine effects in one patient and in two patients it helped the ketamine effect to persevere. Ketamine affects everyone in its very unique way, which is not clear yet and needs to be explored deeper (Rodriguez, Levinson, Zwerling, Vermes, & Simpson, 2016).

5.8. Rapastinel

Tolerability and effects of the new NMDA receptor glycine-site partial agonist of NMDA receptor Rapastinel (formerly GLYX-13) were tested and showed very similar effects as ketamine, however without ketamine diverse side effects. It showed very good antidepressant

properties and acute anti-compulsive effects, though these effects diminished after one week of treatment (Rodriguez, Zwerling, et al., 2016).

5.9. Other glutamatergic agents

There are some other glutamatergic agents that may provide some results, such as lamotrigine, anticonvulsant currently used for treating epileptic seizures and bipolar disorder. It limits neurotransmitter release in the synapse (Lingamaneni & Hemmings, 1999) and showed alleviation of OCD symptoms in several case reports (Kumar & Khanna, 2000; Uzun, 2010). Topiramate, also used as antiepileptic drug with glutamate modulation properties, alleviated OCD symptoms in some reports as well (Hollander & Dell'Osso, 2006; Vinkers & van der Wee, 2008). It also has unpleasant side-effects and therefore seems not to be ideal for treatment of OCD (Berlin et al., 2011).

6. Optogenetic studies in OCD

Optogenetics is a technique combining genetic and optical methods. Its power is in its capability of triggering (or inhibiting) specific well-defined cell populations or even individual cells. By transducing an opsin coding plasmid into the cells of need, depolarization and hyperpolarization can be achieved by photosensitization of those specific cells. Primarily used opsins are bacteriorhodopsin, halorhodopsin and channelrhodopsin. (Deisseroth, 2011). The genes are integrated into the cell with a virus vector into Cre recombinase expressing cells. Thus, generating transgenic lines carrying light-activatable molecules. Virus expands in the defined brain area in animals carrying Cre recombinase, hence creating specific tool for light manipulation. Channelrhodopsin is used for depolarisation by blue light (470 nm) and halorhodopsin for hyperpolarization by orange light (597 – 622 nm) (Zeng & Madisen, 2012).

Cre inducible adenovirus vector with channelrhodopsin was injected into OFC of Cre transgenic mice. Then it was stimulated by 473 nm light trough optic fibres and after two weeks enhanced yellow fluorescent protein staining from OFC cell bodies and axons to ventromedial striatum (VMS) was observed. Acute stimulation of this pathway led to immediate response in increased locomotion, however it diminished quickly after stimulation. Chronic stimulation for 5 minutes each day throughout 2 weeks, led to OCD–like behaviour, especially grooming. Later, fluoxetine was used to successfully alleviate the grooming symptoms, which occurred after chronic stimulation. Because this model seems to involve grooming solely, it could be useful to understand the circuit mechanism in OCD patients with obsession on fear of contamination. Due to the fact, that only 5 minutes of stimulation per day led to noteworthy behavioural effects, an idea was proposed, that pathological changes in OCD patients may result from small bursts of neuronal hyperactivity that results in circuit damage (Ahmari et al., 2013). Also, this could be a good explanation of DBS effectivity (reviewed in chapter 2.4.), because it is thought to work through short inhibition of OFC hyperactivity (de Koning, Figee, van den Munckhof, Schuurman, & Denys, 2011) (B. D. Greenberg et al., 2010), hence the opposite of what was done in the optogenetic study by Ahmari et al,.

Optogenetics could be a very efficient tool to discover the neural circuit basis in the disease with a purpose of revealing new drug targets for potential medication.

7. Conclusion

Obsessive-compulsive disorder is a severe illness that affects many individuals world-widely. It is a heterogenous disease with different manifestations; therefore, the pathogenesis of this disorder is complicated to uncover. The CSTC circuit forming direct excitatory and indirect inhibitory pathway from the striatum to thalamus, and from thalamus to OFC may be impaired in OCD patients and hence cause the obsessive and compulsive behaviour. Glutamate´s role in neural circuits is intensively studied, and not just in OCD but also in ADHD, Tourette's syndrome or schizophrenia. The dysregulation of glutamate in obsessive-compulsive disorder is not fully clear yet, but data from many methods and papers published in last 20 years, reviewed in this thesis, are together getting closer every day.

In CNS, inhibition and activation regulated by GABA and glutamate together with other neurotransmitters is the main process of maintaining homeostasis and therefore mental functions. Glutamate hyperactivity dysregulates this homeostasis by creating hyperactivity of the CSTC loop through hyperactivation of the direct pathway from striatum to thalamus and hypostimulation of the indirect pathway from striatum to thalamus, hence overactivating the OFC. Impairments of glutamate transmission in the temporal lobe and its connection to the prefrontal cortex are taken into consideration as well. This imbalanced homeostasis of glutamate could lead to obsessions, anxiety and compulsions.

Although creating an animal model or investigating the genetic bases of such a heterogeneous and complex disorder is not easy, developing novel therapeutic strategies that takes to account glutamate is surprisingly rapid and with neuroimaging, genetic, pharmacologic and optogenetic studies together, the possibility of understanding the pathogenesis of the illness, and therefore finding more effective treatment than what is currently available, is growing and should be supported. In the case of glutamate hypothesis, getting theoretical data and knowledge from animal models and genetic studies to clinical practice is evolving quickly. It requires very good coordination between different study groups creating animal models, genetic studies, optogenetic studies and clinical trials.

In time, with help of optogenetics (and other techniques) we could move from the place where the idea of CNS is a neurotransmitter mix, to circuit engineering. Nevertheless, we should consider the complex brain connections and network interactions and not to freeze only on glutamate itself. Its influence on another neurotransmitter systems should be taken to serious consideration.

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