

**Neurobiological Bases of the use of Atypical Antipsychotics in
Treatment-Resistant Major Depressive Disorder**

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ABSTRACT

Only one third of depressed patients experience a beneficial therapeutic effect after using a first-line medication, leaving two-thirds of patients without effective treatment. It has been shown that a combination of two drugs with different modes of action result in an increase in the number of patients responding to treatment. One of the most effective strategies is the addition of low doses of an atypical antipsychotic. In-depth evaluation of the neurobiological properties of atypical antipsychotics have revealed that these agents produce antidepressant effects and enhance the therapeutic response of first-line medications through antagonism of the 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1B/D}, 5-HT₇ receptors and NET; agonism of the 5-HT_{1A} receptor; and/or D_{2/3} partial agonism. The present experiments focused on determining the mode of action of this combination of drugs to help design better antidepressant treatment in the future. A series of electrophysiological experiments were proposed to assess 5-HT and NE neurotransmission in the rat hippocampus, as well as DA transmission in the rat forebrain.

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LIST OF ABBREVIATIONS

5-HT	5-Hydroxytryptamine; serotonin
5-HTP	5-Hydroxytryptophan
7TM	Seven transmembrane
AADC	Amino Acid Decarboxylase
ACh	Acetylcholine
ARI	Aripiprazole
ACTH	Adrenocorticotrophic Hormone
ATP	Adenosine Triphosphate
BDNF	Brain-Derived Neurotrophic Factor
cAMP	Cyclic Adenosine Monophosphate
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	Cognitive Behavioural Therapy
CCK	Cholecystokinin
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
CPu	Caudate Putamen
CRH	Corticotropin-Releasing Hormone
CSF	Cerebrospinal Fluid
DA	Dopamine
DAT	Dopamine Transporter
DHMA	3,4-Dihydroxymandelic acid
DHPG	3,4-Dihydroxyphenylglycol
DNA	Deoxyribonucleic acid
DNB	Dorsal Noradrenergic Bundle
DOPA	3,4-Dihydroxyphenylalanine
DRN	Dorsal Raphe Nucleus
ECF	Extracellular fluid
ESC	Escitalopram
FKBP5	FK506 Binding Protein 5
GABA	Gamma-Aminobutyric Acid (γ -Aminobutyric acid)
GPCR	G-Protein Coupled Receptor
GTP	Guanosine-5'-triphosphate
HPA	Hypothalamic-Pituitary-Adrenal
HVA	Homovanillic Acid
IFN- α	Interferon- α
IL-2	Interleukin-2
IL-6	Interleukin-6
L-DOPA	Dihydroxyphenylalanine
LC	Locus Coeruleus
MAO	Monoamine Oxidase
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder

MHPG	3-Methoxy-4-hydroxyphenylglycol
NAC	Nucleus Accumbens
NE	Norepinephrine
NET	Norepinephrine Transporter
NO	Nitric Oxide
NRI	Norepinephrine Reuptake Inhibitor
OT	Olfactory Tubercle
PFC	Prefrontal Cortex
SBP	Serotonin-Binding Protein
SERT	Serotonin Transporter
SN	Substantia Nigra
SSRI	Selective Serotonin Reuptake Inhibitor
TBZ	Tetrabenazine
TCA	Tricyclic Antidepressant
TNF	Tumor Necrosis Factor
TPH	Tryptophan Hydroxylase
TRD	Treatment Resistant Depression
VMAT2	Vesicular Monoamine Transporter 2
VNB	Ventral Noradrenergic Bundle
VTA	Ventral Tegmental Area
WHO	World Health Organization

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CHAPTER 1: INTRODUCTION

1.1 Major Depressive Disorder

1.1.1. Background

Major depressive disorder (MDD) is characterized by at least one discrete depressive episode lasting two or more weeks, involving depressed mood and/or diminished interests, with a total of at least five symptoms that include impaired cognitive function, sleep disturbances or changes in appetite, alterations of psychomotor activity, inappropriate guilt, and thoughts of death or suicide (American Psychiatric Association, 2013). It is one of the most increasingly common and debilitating psychiatric illnesses, affecting an estimated 350 million people worldwide (World Health Organization, 2014) with a lifetime prevalence of 10-15% (Lépine & Briley, 2011). The prevalence of an illness by itself, however, does not capture its burden on society. High levels of depression, globally, account for wide-ranging social and economic effects including, but not limited to, functional impairment, disability or lost work productivity, and increased use of health services (Simon, 2003). For these reasons, MDD is ranked as the leading contributor to chronic disease burden as measured by years lived with disability (Vos et al., 2015). Although the rate of suicide attempts is significantly higher, the incidence of mortality by suicide characterizes the course of illness in approximately 800,000 of those suffering from depression each year (World Health Organization, 2014). Moreover, an estimated 50% of the 800,000 suicides per year worldwide occur within a depressive episode and those who suffer from MDD are nearly 20 times more

likely to commit suicide than the general population (Chesney et al., 2014). Patients with MDD are at higher risk of developing comorbidities such as type II diabetes, heart disease, and stroke, thereby increasing its burden of disease (Penninx et al., 2013). When depression is comorbid with other medical conditions, it has adverse effects on their associated prognoses while creating additional impairment. Furthermore, patients with comorbid depression report worse overall health than those with arthritis, asthma, cardiovascular disease, or diabetes alone (Moussavi et al., 2007).

1.2.2. Etiology

The etiology of MDD is multifactorial and no single mechanism can explain all aspects of the disease. However, we have known for several years that the development of MDD is influenced largely by genetic factors, as indicated by family, twin, and adoption studies (Lohoff, 2010). First-degree relatives of MDD patients are three times more likely to develop the disease, and the heritability of this disorder is estimated to be 35% (Kendler et al., 2015). Still, large-scale analysis of genome-wide association studies fails to affirm consistent or replicated significant findings in the search for genetic effects of MDD (Bosker et al., 2011; Kendler et al., 2015). These difficulties may be attributed to a variety of causes, including those inherent to MDD itself, as it is a highly polygenic disorder involving genes with small effects, none of which are likely to impose significant risk (Fava & Kendler, 2000). To reduce heterogeneity, more stringent inclusion criteria were implemented (recurrent MDD requiring outpatient care) in a genome-wide association study in Chinese patients and two genetic loci were identified as contributors to risk of MDD (Converge Consortium, 2015). Furthermore, a meta-analysis of over

75,000 patients and 321,000 controls has identified 15 genetic loci associated with risk of major depression in individuals of European descent, some of which were also implicated in genome-wide association studies of related psychiatric traits (Hyde et al., 2016). Although genetic variants are expected to only have small effects on overall disease risk, and these genes may interact with each other and/or environmental risk factors to produce MDD, these findings hold promise for the identification of genetic variants that contribute to the development of the disorder.

It is well known that the interaction between genetic predisposition and the environment contribute to the development of psychiatric disorders. Investigation of molecular mechanisms underlying gene-environment interactions has shed light on the possible epigenetic regulation of stress-related psychiatric disorders (Torsten Klengel & Binder, 2015). For example, one study found that a functional polymorphism in the FK506 binding protein 5 (FKBP5) gene, an important regulator of the stress hormone system, leads to an increased risk of developing stress-related psychiatric disorders in adulthood by allele-specific DNA demethylation in glucocorticoid response elements of FKBP5. Furthermore, this demethylation was associated with an increase in stress-related gene transcription followed by a dysregulation of the stress hormone system and a global effect on the function of stress-regulating immune cells (Klengel et al., 2013). Epigenetic changes have also been observed in animal models of MDD and in post-mortem brain samples of patients with MDD. Although epigenetic changes have been implicated in genes involved in the stress response, limitations of this research lies in the

small magnitude of DNA methylation changes relative to those involved in other fields of research, such as cancer (Klengel & Binder, 2015).

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is one of the most enduring and replicated findings in depressed patients. Among the most frequently reported findings are increased levels of cortisol and corticotropin-releasing hormone (CRH), a blunted adrenocorticotrophic hormone (ACTH) response to CRH, a reduction in hippocampal volume, and non-suppression of the dexamethasone test (Varghese & Brown, 2001). Notably, alterations in the HPA axis are correlated with cognitive impairment in MDD patients, and are more pronounced in those with a more severe form of the disease (Nelson & Davis, 1997). Furthermore, several studies suggest cortisol as a predictor of MDD in high-risk populations (Goodyer et al., 2000; Harris et al., 2000). Further, data collected from a primary care database of 372,696 patients revealed that people treated with glucocorticoids have a twofold higher risk of developing depression and a nearly sevenfold higher risk of committing or attempting suicide compared to controls (Fardet et al., 2012). While the neuroendocrinology of MDD has been studied extensively, and a putative causal role has been established for alterations in the HPA axis, it has yet to generate new therapies for the disorder (Otte et al., 2016).

The bidirectional communication between the HPA axis and the immune system has been suggested as a pathophysiological mechanism implicated in the etiology of MDD (Lamers et al., 2012). The effect of HPA axis activation by pro-inflammatory cytokines is attributable to alterations in the production of CRH and vasopressin, neuropeptides involved in MDD symptomatology (Bao et al., 2008; Berkenbosch et al.,

1987; Grinevich et al., 2002; Holsboer, 2003). There are numerous animal studies that support a putative role for peripheral immune dysfunction and neuroimmunological mechanisms in depression. Animal models have also shed light on the direct and indirect effects of cytokines on brain circuits, behavior, and mood (Otte et al., 2016). Cytokines circulating in the blood are transported directly across the blood-brain barrier to act directly on CNS-resident cells such as microglia, astroglia, and neurons (Banks, 2005; Becher et al., 2000). Inflammatory signals can also be transmitted to the CNS through CNS infiltration by peripheral immune cells or via vagus nerve signaling (Otte et al., 2016). Increasing amounts of data suggest that similar mechanisms of inflammation may play an important role in the development of depression in humans. For example, up to half of patients treated with cytokines interleukin-2 (IL-2) and interferon- α (IFN- α) develop major depressive disorders (Raison et al., 2006). Likewise, depression is more prevalent in patients afflicted with autoimmune diseases, severe infections, cardiovascular disease, and type 2 diabetes than in otherwise healthy populations (Otte et al., 2016; Raison et al., 2006). It has been proposed that depression represents a maladaptive version of cytokine-induced sickness that would occur following an exacerbation of immune response activation or in the case of hyperactive CRH neuronal circuits (Nemeroff et al., 2005). Concordant with the hypothesis that CRF hypersecretion is partially responsible for HPA axis hyperactivity in MDD, increased CSF concentrations of cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) have been observed in depressed patients (Dowlati et al., 2010; Haapakoski et al., 2015). These

findings suggest that inflammation is an important biological process that contributes, at least in part, to an increased risk of the development of MDD.

More recently, it has been hypothesized that depression results from a decrease in the expression of brain-derived neurotrophic factor (BDNF), leading to neuronal atrophy, decreased hippocampal neurogenesis, and loss of glia. Moreover, this deficit is blocked by treatment with antidepressants, thereby reversing the neuronal atrophy and cell loss (Duman & Monteggia, 2006). Along the same lines, the role of BDNF has been explored in animal models of depression. Although a vast majority of behavioral studies have failed to produce evidence for depressive behavior in animals with reduced levels of BDNF (Wong & Licinio, 2004), it has been reported that site-specific knockdown of BDNF precipitates behaviors associated with depression (Taliaz et al., 2010).

Even though the idea of depressive illness has existed since the second century (Sartorius, 2001), effective antidepressant treatments were not made available until the late 1950s (Pinder, 2001). The nature of the biochemical changes evoked in the brain by the fortuitously discovered first-generation antidepressant drugs, the monoamine oxidase inhibitors (MAOI) tricyclic antidepressants (TCA), led to the development of the monoamine hypothesis of depression (Hindmarch, 2002). Specifically, the effectiveness of these drugs relied on their ability to increase levels of norepinephrine (NE) and serotonin (5-HT) at the synapse. The monoamine hypothesis of depression suggests that the underlying pathophysiologic basis of depression is a decrease in monoamine function in the central nervous system. Thus, increasing synaptic levels of the monoamine neurotransmitters, NE, 5-HT, and dopamine (DA), can alleviate the

symptoms of depression (Delgado, 2004). Moreover, reciprocal interactions between the monoamine systems give antidepressant drugs that target one system the ability to modify the function of the other two monoamine systems. These findings suggest a strong link between the functional deficiency of these three neurotransmitter systems and depression pathophysiology. Despite advances in our understanding of the neurobiological bases of MDD, many questions regarding the etiology of the disease remain unresolved.

1.2.3. Brain Systems Involved in Major Depressive Disorder

Despite extensive research focused on the identification of the neurobiological mechanisms underlying MDD, our understanding of such substrates is still incomplete. Several studies have found structural alterations in various subcortical brain regions in MDD. Furthermore, detection of subtle brain differences is limited by small sample sizes (Schmaal et al., 2015). One of the most thoroughly studied and consistently reported findings in structural studies in MDD is a reduced hippocampal volume in depressed individuals (Arnone et al., 2012). A meta-analysis of three-dimensional brain MRI data from over 1700 MDD patients and over 7100 controls from 15 research samples worldwide identified that MDD patients had significantly lower hippocampal volumes (Schmaal et al., 2015). In addition, a large-scale meta-analysis of 193 studies comprising almost 16000 individuals of structural neuroimaging studies across multiple psychiatric illnesses identified greater hippocampal grey matter loss than other internalizing, externalizing, or bipolar disorder groups (Goodkind et al., 2015). This correlation, however, is likely complex given the heterogeneous nature of MDD. For example, the

effect sizes of hippocampal volumetric changes may be modulated by disease stage, duration, severity, history, age of onset, and therapeutic intervention (Frodl & O'Keane, 2013; McKinnon et al., 2009). The pattern of structural abnormalities accounting for MDD remains unresolved, and it is unclear whether these alterations relate to depressive symptoms, are present in unaffected relatives of MDD patients, or whether these changes could help predict the onset of illness (Whalley et al., 2015).

1.2.4. Scope of the Problem

The effective treatment of patients with major depressive disorder (MDD) continues to challenge clinicians, despite widespread availability and advancement of antidepressant treatment over the past several decades. Even when treating from initiation at an adequate dose over a sufficient period of time, only one third of patients with MDD experience a beneficial therapeutic effect after using selective serotonin reuptake inhibitors (SSRIs), the current first-line treatment for depression. Furthermore, a broad range of residual symptoms, such as insomnia and difficulty concentrating, often persist after remission is achieved, and lead to psychosocial dysfunction (Trivedi et al., 2006, 2008).

1.2. Monoamine Systems

1.2.1. Serotonin

1.2.1.1. Neuroanatomy

Serotonin, otherwise known as 5-hydroxytryptamine (5-HT), is a molecule with diverse effects throughout the CNS and periphery, acting as a hormone, neurotransmitter, and mitogen (Mohammad-Zadeh et al., 2008). Serotonin was first

extracted in the 1930s from enterochromaffin cells in the gastrointestinal tract, where it is responsible for smooth muscle contraction (Erspamer & Asero, 1952). It was isolated and characterized in the 1940s, which came after decades of investigation to characterize a vasoconstrictor in platelets (Rapport et al., 1948a, 1948b). Following the discovery of 5-HT, many researchers sought to identify the localization of the compound as well as its function. The compound was identified as being present in many tissues including the brain, lung, kidney, platelets, and gastrointestinal tract. Based on studies demonstrating the localization of 5-HT receptors to specific vertebrate brain regions, 5-HT was identified as a neurotransmitter (Amin et al., 1954; Twarog & Page, 1953). Serotonin was found to be primarily located in the nerve endings of neurons in specific regions of the mammalian brain (Michaelson & Whittaker, 1963; Zeher & DeRobertis, 1963). Specific 5-HT-containing nuclei in the brain were mapped and these specific clusters are referred to as the serotonergic system (Dahlström & Fuxe, 1964).

Serotonergic neurons originate in the raphe nuclei of the brainstem, a collection of aggregates of neurons situated along the midline of the brain. While they project to nearly every region of the brain, the primary targets of serotonergic nerve terminals include the substantia nigra (SN), hypothalamus, thalamus, amygdaloid-hippocampal area, CPU, NAc, and cortical structures (Azmitia & Whittaker-Azmitia, 1991). This system of extensive innervation by serotonergic neurons of cortical and subcortical brain regions allows the serotonergic system to affect a variety of brain function and provides the anatomical basis for the role of the serotonergic system in many psychiatric disorders, including MDD.

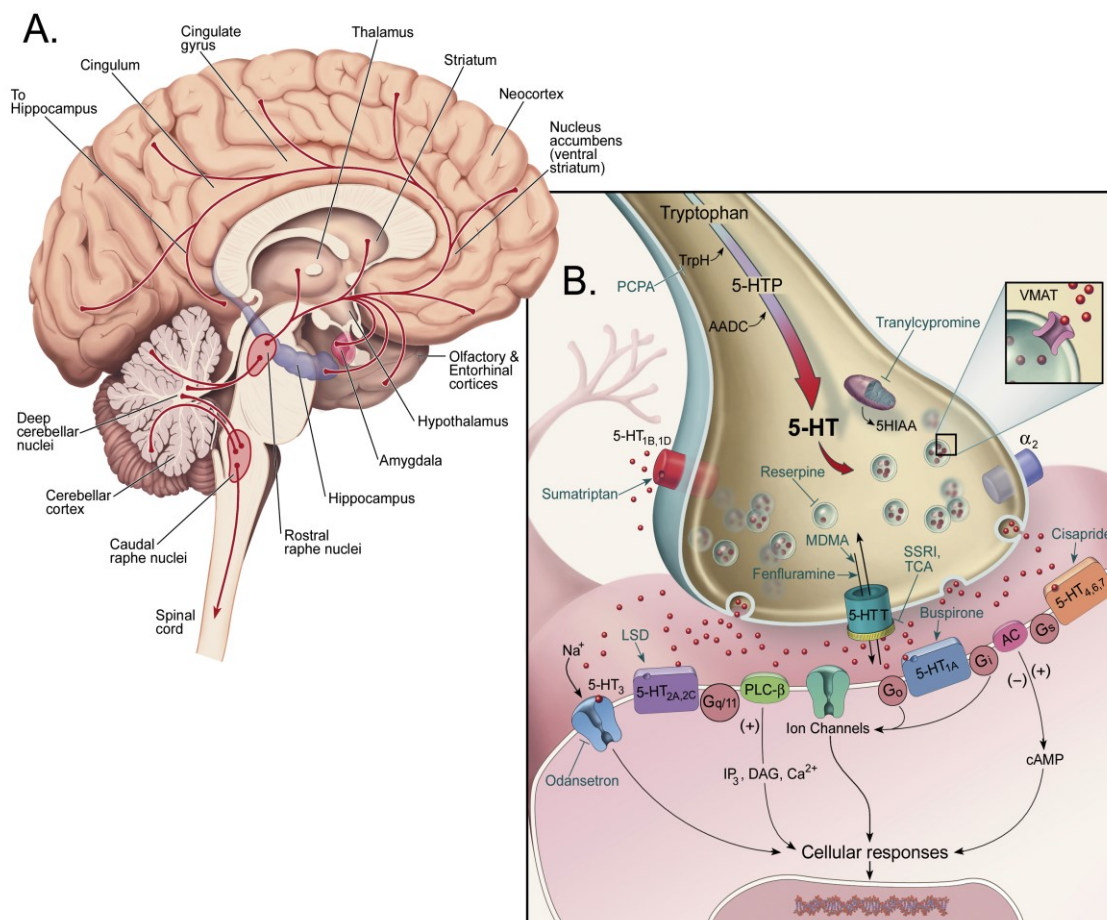


Figure 1. The Serotonin System. (A) Representation of the human brain with the main raphe nuclei giving rise to 5-HT projections. (B) Diagram of a serotonergic synapse with the various 5-HT receptors, their transduction mechanisms, and examples of specific ligands, both agonists and antagonists. Adapted from (Szabo, 2009).

1.2.1.2. Synthesis, Storage, and Release

Serotonin is a biogenic molecule, similar to the other two monoamine neurotransmitters NE and DA. It is produced in two steps, beginning with the hydroxylation of tryptophan to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase (TPH). This is considered the rate-limiting step, as TPH has relatively high affinity, but has little affinity for other amino acids, and its distribution is restricted to 5-HT-containing tissues (Noguchi et al., 1973; Tong & Kaufman, 1975; Tyce, 1990). More recent studies

have shed light on 5-HT alterations involving the neuronal isoform of the rate-limiting enzyme in CNS 5-HT biosynthesis, TPH2 (Bach-Mizrachi et al., 2008; Bach-Mizrachi et al., 2006; Boldrini et al., 2005). Tryptophan hydroxylase is a critical component in determining the amount of 5-HT synthesized in the brain (Patel et al., 2004; Zhang et al., 2004). In the second step, 5-HTP is decarboxylated by L-aromatic amino acid decarboxylase to form 5-HT (Gwaltney-Brant et al., 2000). Unlike TPH, tryptophan decarboxylase has affinity for many L-amino acids and is present in most tissues. Similarly to TPH, however, tryptophan decarboxylase has a relatively low affinity (Clark et al., 1954; Tyce, 1990). Since tryptophan decarboxylase is not a rate-limiting enzyme in the synthesis of 5-HT, it would be challenging to reduce 5-HT levels by its inhibition (Mohammad-Zadeh et al., 2008). The synthesis of 5-HT can increase markedly under conditions requiring a continuous supply of the neurotransmitter; the synthesis of 5-HT from tryptophan is increased in a frequency-dependent manner in response to electrical stimulation of a serotonergic cell body (Boadle-Biber, 1993). Short-term requirements for increased 5-HT synthesis can be met by changing kinetic properties of TPH, such as phosphorylation, without actually synthesizing more of the enzyme. In contrast, synthesis of TPH is prompted with long-term requirements for increased 5-HT synthesis and release (Frazer & Hensler, 1999).

As with other biogenic amine neurotransmitters, 5-HT is stored primarily in storage vesicles. The vesicular transporter uses an electrochemical gradient generated by a vesicular proton ATPase to drive transport, such that a cytoplasmic amine is

exchanged for a proton. In other words, storage of 5-HT in vesicles requires active transport in which the uptake of 5-HT is coupled to H⁺ efflux (Frazer & Hensler, 1999).

There is considerable evidence that the release of 5-HT occurs primarily by exocytosis. First, 5-HT is ionized sufficiently at physiological pH so that it is unable to diffuse across the plasma membrane. Second, 5-HT is contained in storage vesicles and released with other vesicular contents, including serotonin-binding protein (SBP). Finally, the release of 5-HT occurs by a calcium-dependent process in which Ca²⁺ stimulates fusion of the vesicle to the plasma membrane (Frazer & Hensler, 1999). The rate of 5-HT release is dependent on processes occurring at the somatodendritic region, where neuronal firing is regulated. This, in turn, influences the rate at which 5-HT molecules in nerve terminals are released. The amount of neurotransmitter available to be released is regulated by TPH or the availability of tryptophan. Increases in raphe cell firing are known to enhance the release of 5-HT, and decreases in raphe firing have the opposite effect (Frazer & Hensler, 1999). Thus, pharmacological tools used to change the firing rate of the serotonergic cell have the ability to alter the release of 5-HT.

Serotonin is processed in multiple ways following release into the synaptic cleft. It can either bind to postsynaptic 5-HT receptors or to presynaptic autoreceptors. Through a negative feedback mechanism, binding of 5-HT to presynaptic autoreceptors prevents further release of the neurotransmitter into the synapse. The activity of 5-HT in the synapse is terminated primarily by its re-uptake into serotonergic terminals by the highly selective serotonin transporter (SERT), located on the presynaptic membrane. The primary metabolic pathway for serotonin is by monoamine oxidase (MAO), an enzyme

that exists in two major forms: MAO-A and MAO-B within the cytosol (Frazer & Hensler, 1999). Alternatively, serotonin in the pineal gland is converted to melatonin (Klein et al., 1997).

1.2.1.3. Receptors

The function of serotonin is mediated by seven classes of 5-HT receptors (5-HT₁ to 5-HT₇), which permit a great diversity of signaling and therefore a great diversity of effects with the same neurotransmitter. All 5-HT receptors belong to the G-protein-coupled receptor (GPCR) family, except for the 5-HT₃ receptor, which is a ligand-gated ion channel. Importantly, alterations of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} levels have been linked to the development of psychiatric disorders, and thus are favourable pharmacological targets in the treatment of MDD.

The 5-HT₁ receptor family is comprised of six receptor subtypes (5-HT_{1A-F}), each of which is G_i-coupled receptors and their activation is transduced in target cells by various effector systems including modulation of adenylyl cyclase (AC) activity, inhibition or activation of phosphoinositide (PI) turnover, and changes in plasma membrane permeability to potassium (Peroutka, 1988). 5-HT_{1A} receptors are largely distributed throughout the CNS and are highly expressed both as presynaptic autoreceptors at the somatodendritic sites of the raphe nuclei and at the postsynaptic sites of limbic structures, primarily in the hippocampus (Hoyer et al., 2002). 5-HT_{1B} receptors function as terminal autoreceptors in the basal ganglia, striatum, and frontal cortex (Lin & Kuo, 2013). The stimulation of 5-HT_{1A} receptors is associated with an increase in the permeability of potassium channels in hippocampal neurons and inhibition of adenylyl

cyclase. Moreover, activation of the 5-HT_{1A} receptor subtype has been reported to be negatively coupled to PI phosphodiesterase activated by muscarinic receptors in the rat hippocampus (Claustre et al., 1988). The role of 5-HT_{1A} receptors in modulating anxiety-related behaviors is supported and 5-HT_{1A} receptor agonists, such as buspirone and gepirone, have been implicated in the treatment of anxiety and depressive disorders (Den Boer et al., 2000; Tunnicliff, 1991). Furthermore, the 5-HT_{1A} antagonist, pindolol, was found to accelerate/enhance the therapeutic effect of SSRIs in depressed patients (Artigas et al., 1996; Ballesteros & Callado, 2004). CNS 5-HT_{1B} receptors are expressed in the basal ganglia, striatum, and frontal cortex and function as terminal autoreceptors. In addition, 5-HT_{1B} receptors may behave as terminal heteroreceptors to control the release of other neurotransmitters, such as ACh, glutamate, DA, NE, and GABA (Pauwels, 1997). The 5-HT_{1D} receptor possesses a relatively high structural homology with the 5-HT_{1B} receptor, however, its level of expression is low compared to 5-HT_{1B} receptors (Hoyer et al., 2002). Although assigning a functional role for 5-HT_{1D} expression has been difficult due to a lack of antagonists that discriminate between the two subtypes, an increasing volume of evidence suggests that 5-HT_{1D} receptors govern 5-HT release in the dorsal raphe nucleus (DRN) (Davidson & Stamford, 1995; Hopwood & Stamford, 2001; Piñeyro & Blier, 1999). The 5-HT_{1E} receptor is highly expressed in the human brain and lacks polymorphisms, suggesting an important physiological role (Shimron-Abarbanell et al., 1995). While a greater understanding of the pharmacology, distribution, and function of the 5-HT_{1E} receptor is necessary, a functional link to memory has been speculated as it is expressed in the olfactory bulb, hippocampus, and frontal cortex (Bai

et al., 2004). The distribution and function of the 5-HT_{1F} receptor require further exploration, however, mRNA for the human receptor protein has been identified in the dorsal raphe, hippocampus, cortex, striatum, thalamus, and hypothalamus, suggesting a potential role as a 5-HT autoreceptor (Hoyer et al., 2002).

The 5-HT₂ class of receptors consists of the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes, which are preferentially coupled to G_q to increase cytosolic Ca²⁺ concentration (Hoyer et al., 2002). Centrally, the 5-HT_{2A} receptors are found in the cortex, claustrum and basal ganglia. Antagonists of this receptor, such as risperidone and olanzapine, have been indicated for the treatment of schizophrenia and have been shown to reduce extrapyramidal symptoms over the pure D₂ antagonism. The 5-HT_{2A} inverse agonist, pimavanserin, was approved for the treatment of psychosis associated with Parkinson's disease, and may be useful in the treatment of psychotic symptoms in schizophrenia, psychotic depression, psychotic mania, delirium, or drug-induced psychosis without the undesirable extrapyramidal side effects (Garay et al., 2015; Howland, 2016; Mills et al., 2016). Antipsychotic activity of most of these drugs appears to be explained by the combination of 5-HT_{2A} and DA D₂ receptor antagonism (Ichikawa et al., 2001; Schotte et al., 1996). Despite widespread distribution in the CNS, central 5-HT_{2B} receptor function remains unknown. Stimulation of the 5-HT_{2B} receptor results in cross-talk with the 5-HT_{1B/D} receptor subtypes via activation of phospholipase A₂ and nitric oxide (NO) synthesis (Diaz et al., 2011). Activation of 5-HT_{2B} receptors in the amygdala with the agonist, BW-723C86, produces an anxiolytic effect in the rat social interaction test, but has little effect on behavior in a punished conflict model of anxiety (Duxon et al., 1997).

Furthermore, 5-HT_{2B} receptors have been found to promote phosphorylation of SERT in primary neurons from the raphe nuclei, thereby governing the overall 5-HT transport system (Launay et al., 2006). Moreover, long-term behavioural and neurogenic SSRI effects are abolished after inactivation of 5-HT_{2B} receptors. Direct agonism of 5-HT_{2B} receptors, on the other hand, induces an SSRI-like response (Diaz et al., 2011). Thus, the 5-HT_{2B} receptor appears to positively modulate serotonergic activity and may be required for the therapeutic action of SSRIs. Notably, 5-HT_{2B} receptors are expressed by 5-HT neurons (Diaz et al., 2011) 5-HT_{2C} receptors are distributed throughout the corticolimbic system and have been localized to DRN GABAergic neurons (Boothman et al., 2006). These receptors are blocked by some atypical antipsychotics and are thus a target for pharmacological therapies in the treatment of depression. In the VTA, activation of 5-HT_{2C} receptors inhibits DA neurons, which contributes to a reduction in SSRI-enhanced DA transmission (Hamon & Blier, 2013).

Among the currently known 5-HT receptor subtypes, the 5-HT₃ receptor is structurally and functionally from the other six classes of 5-HT receptors. 5-HT₃ channels are non-selective, cationic ion channels activated directly by serotonin, and belonging to the Cys loop family of ligand-gated channels, which mediate fast excitatory neurotransmission (Panicker et al., 2002). Activation of 5-HT₃ receptors leads to membrane depolarization and Ca²⁺ influx (MacDermott et al., 1999). In the brain, 5-HT₃ receptors are located in several regions, including the cortex, hippocampus, nucleus accumbens, substantia nigra, ventral tegmental area, and brain stem and have been localized to both pre- and postsynaptic nerve terminals. Their activation enhances the

release of various neurotransmitters including DA, cholecystokinin (CCK), and GABA (Nayak et al., 1999).

While the 5-HT_{4,6,7} receptors all couple preferentially to G_s and promote formation of cAMP, they are classified distinctly because they have relatively limited sequence identities. In the CNS, 5-HT₄ receptors appear to modulate ACh, DA, 5-HT, and GABA release and enhance synaptic transmission (Hoyer et al., 2002). They play a major role in the expression of limbic and affective functions, constituting a potential involvement in mood control (Lucas, 2009). Indeed, it has been shown that 5-HT₄ receptors exert a tonic and phasic excitatory control on the firing rate of DRN 5-HT neurons (Lucas & Debonnel, 2002). Since the DRN is virtually devoid of 5-HT₄ mRNA and protein, it was found that this positive control is indirect and involves medial PFC 5-HT₄ receptors (Lucas et al., 2005). Studies on acute administration of 5-HT₄ agonists show that the 5-HT₄-mediated control reaches its maximal level after only three days, and this amplitude is maintained after sustained administration (Lucas et al., 2005). These findings raise the possibility for the use of 5-HT₄ receptor agonists as pharmacological tools in the treatment of depression. Several antipsychotic (clozapine, olanzapine) and antidepressant agents, (amitriptyline, nortriptyline) are high-affinity 5-HT₆ antagonists, suggesting a potential involvement of this receptor in psychiatric disorder pathology (Hoyer et al., 2002). Four 5-HT₇ receptor isoforms (5-HT_{7A-D}) have been identified, which differ in their C-termini. However, these isoforms are similar in their pharmacology, signal transduction, and tissue distribution (Heidmann et al., 1997; Heidmann et al., 1998; Jasper et al., 1997). The distribution of binding sites in the limbic and

thalamocortical systems suggests a role for 5-HT₇ receptors in the pathophysiology of mood disorders. Supporting evidence includes the observation that numerous atypical antipsychotics and antidepressants have high affinity for the 5-HT₇ receptor (Roth et al., 1994). Furthermore, sustained long-term antidepressant treatment results in down-regulation of 5-HT₇ receptors (Mullins et al., 1999). Furthermore, pharmacological blockade of 5-HT₇ receptors produces a more rapid antidepressant-like response than that of an SSRI (Mnie-Filali et al., 2011).

1.2.1.4. Dysfunction in MDD

At the neurochemical level, the most widely accepted hypothesis concerns the depletion of monoamines in the depressed brain. Most notably, the 5-HT hypothesis of depression states that a reduction in 5-HT level increases an individual's risk of being affected by MDD. Since the formulation of this hypothesis and the discovery of SSRIs as a leading class of psychotherapeutic drugs in the treatment of depression, a large amount of research has attempted to elucidate the role of the 5-HT system in the mechanisms that underlie MDD pathology. Deficiencies in 5-HT metabolism have long been associated with major depression and suicide (Kim & Park, 2013; Meltzer, 1990), validating the link between the 5-HT system and MDD. It has been shown that depressed patients have low levels of both blood platelet 5-HT and plasma 5-HT precursor L-tryptophan (Maurer-Spurej et al., 2007; Ogawa et al., 2014). Furthermore, acute tryptophan depletion induces depressive symptoms in MDD patients in remission (Booij et al., 2002; Smith et al., 1997). There is also evidence that altered serotonergic function persists in recovered depressed patients, suggesting that 5-HT dysfunction increases an

individual's risk of developing the disorder (Bhagwagar et al., 2004). More recently, it has been reported that the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase, is associated with suicide among depressed patients (Fudalej et al., 2010). In addition, it has been proposed that the increased density of tryptophan-hydroxylase-immunoreactive neurons in the DRN and expression of TH2 both reflect either a reduction in 5-HT or an upregulatory homeostatic response to decreased 5-HT neurotransmission (Bach-Mizrachi et al., 2006; Boldrini et al., 2005; Kim & Park, 2013). Together, this data illustrates the importance of physiological dysfunction at 5-HT targets in the pathophysiology of MDD.

1.2.2. Dopamine

1.2.2.1. Neuroanatomy

Many components of positive mood states, such as motivation, concentration, and the ability to experience pleasure are regulated by the brain's dopamine-containing circuitry (Dunlop & Nemeroff, 2007). The neural projection pathways essential for the behavioral effects mediated by DA are characterized based on the locations of the DA cell bodies in the ventral tegmental area (VTA) and substantia nigra (SN) and their projections to the nucleus accumbens (NAc), prefrontal cortex (PFC), and caudate putamen (CPu). These three distinct DA projection pathways are termed the mesolimbic, mesocortical, and nigrostriatal pathways, respectively (Meck, 2006).

The mesolimbic pathway innervates limbic structures including the nucleus accumbens (NAc), prefrontal cortex, amygdala, and ventral hippocampus. The NAc is the central node within this reward system, is integrated with circuits involved in emotion

and movement, and is a major modulator within the limbic-cortical-striatal-pallidal-thalamic circuitry (Lane, 2014). The mesolimbic system mediates reward-based drive and motivation, punishment, decision-making, cognition, and reward prediction and valuation (Aarts et al, 2011; Delgado et al., 2008; Dichter et al., 2012; Ernst & Fudge, 2009; Han et al., 2010; Knutson & Cooper, 2005; Rangel et al., 2008). The mesocortical pathway projecting from the VTA and innervates different regions of the frontal cortex plays a critical role in several emotional and cognitive processes (Gorelova et al., 2012). Specifically, the mesocortical pathway seems to be involved in some aspects of learning and memory (Le Moal & Simon, 1991). The nigrostriatal pathway originating from the SN is distinguished from the mesocorticolimbic pathway in that its projections are exclusively dopaminergic, while only 30-40% of the mesofrontal projections are dopaminergic (Swanson, 1982). The nigrostriatal pathway has long been associated with motor function and its degeneration results in Parkinson's disease, characterized by tremors, rigidity, and akinesia (Gerfen, 1992; Lang & Lozano, 1998). In addition, it is generally accepted that the nigrostriatal pathway contributes to attentional set switching, error prediction, timing, and time perception (Dreher & Grafman, 2002; Meck & Benson, 2002; Pastor et al., 1992). A fourth pathway, the tuberoinfundibular pathway, arises from cells of the periventricular and arcuate nuclei of the hypothalamus and projects to the median eminence of the hypothalamus (Vallone et al., 2000). Here, DA is released and transported to the anterior pituitary, inhibiting prolactin release (Vallone et al., 2000).

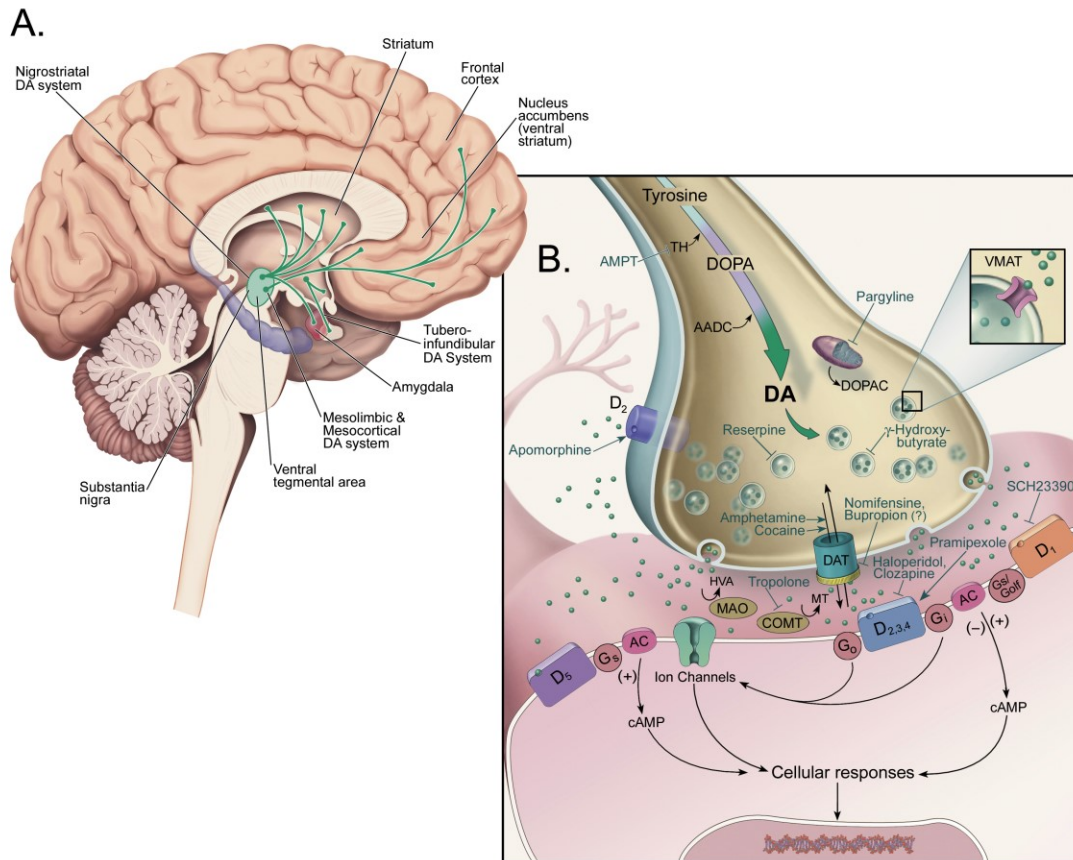


Figure 2. The Dopamine System. (A) Representation of the human brain with the DA nuclei located within the green area. (B) Diagram of a dopaminergic synapse with the various DA receptors, their transduction mechanisms, and examples of specific ligands, both agonists and antagonists. Adapted from (Szabo, 2009).

1.2.2.2. Synthesis, Storage, Release

The synthesis of dopamine begins with tyrosine, an amino acid abundant in dietary proteins. Tyrosine in the blood is taken up into the brain by a low-affinity amino acid transport system and then from the brain extracellular fluid (ECF) by high- and low-affinity amino acid transporters into DA neurons. Once in the dopaminergic neuron, tyrosine is converted into dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase, the rate-limiting enzyme of catecholamine biosynthesis. The activation of tyrosine hydroxylase involves phosphorylation of the regulatory domain by protein kinases and

perhaps also by alternative splicing. The activated form of tyrosine hydroxylase has a higher K_i for DA, effectively reducing end-product inhibition, and a lower K_m for its pterin cofactor. In addition, dihydropteridine reductase activity is indirectly involved in DA biosynthesis, by catalyzing the recycling of dihydrobiopterine to tetrahydrobiopterine, an essential cofactor of tyrosine hydroxylase. Tetrahydrobiopterine synthesis is dependent on the activity of GTP-cyclohydrolase-1. The cytosolic conversion of L-DOPA to DA is accomplished by aromatic amino acid decarboxylase (AADC, DOPA-decarboxylase). D-DOPA, in the periphery, is unidirectionally converted to L-DOPA by D-amino acid oxidase, followed by DOPA transaminase (Wu et al., 2006).

Immediately after synthesis, DA is transported by the vesicular monoamine transporter 2 (VMAT2) from the cytoplasm into specialized storage vesicles in DA neurons. Here, the neurotransmitter is concentrated to a level 10-1000 higher than that in the cytosol (Elsworth & Roth, 1997). In contrast to the cytoplasmic environment, where DA is highly prone to enzymatic and spontaneous degradation, the synaptic storage sites hinder DA breakdown by virtue of their low pH and MAO-free environment (Lotharius & Brundin, 2002).

The arrival of an action potential triggers a change in membrane protein conformation, which allows for the influx of calcium ions, an event important to the stimulus responsible for vesicle fusion with the neuronal cell membrane (Elsworth & Roth, 1997). Secretory vesicle contents are then released into the synapse via exocytosis (Eiden et al., 2004). The extent of mesolimbic dopamine release is regulated by a number of factors. Synaptic or phasic levels of dopamine are mediated primarily by

burst-firing and appear to lead to an increased dopamine release than when these neurons fire in a single spike mode (Gonon, 1988; Grace, 1991; Ungless & Grace, 2012).

The time course and localization of DA released by burst-firing is restricted by a high-affinity rapid reuptake system localized in the dopaminergic nerve terminal (Floresco et al., 2003). Under normal conditions, however, the transporter recycles DA that has been released into the synapse by actively pumping it back into the nerve terminal, thereby occluding detection of a sustained and measurable increase in extracellular DA (Elsworth & Roth, 1997; Floresco et al., 2003).

1.2.2.3. Receptors

Dopamine exerts its action by binding to receptors belonging to the family of seven transmembrane (7TM) G-protein coupled receptors (GPCRs) (Vallone et al., 2000). To date, five distinct DA receptors (D₁-D₅) have been identified and characterized. These receptors have been subdivided into two categories based on their biochemical and pharmacological properties. The cloned D₁ and D₅ receptors belong to the D₁-like subfamily of DA receptors, whereas the D₂-like subfamily is comprised of D₂, D₃, and D₄ receptors (Sealfon & Olanow, 2000). Phosphorylation and palmitoylation sites are present at the C-terminus of all DA receptors, and are involved in agonist-dependent receptor desensitization (Bates et al., 1991; Ng et al., 1994). Although most dopaminergic ligands do not clearly differentiate between members of the same subfamily, they discriminate easily between the two receptor families. For example, the DA agonist, risperidone, has similar affinity for both the D₃ and D₄ receptors (Vallone et al., 2000).

The D₁ and D₂ receptor genes are the most highly expressed and have the most widespread expression of the DA receptors (Vallone et al., 2000). The D₁ receptors are expressed primarily in the CPU, NAc, olfactory tubercle (OT), cerebral cortex, and amygdala (Jackson & Westlind-Danielsson, 1994). Compared to the D₁ receptor, the D₅ receptor gene has a more restricted pattern of expression. D₅ receptors have been detected in the hippocampus, lateral mammillary nucleus, and thalamus (Jackson & Westlind-Danielsson, 1994). D₂ receptor mRNA distribution has been studied by *in situ* hybridization, and the highest levels are observed in the striatum, NAc, OT, and midbrain dopaminergic neurons, where they likely encode autoreceptors (Sealfon & Olanow, 2000). This receptor is also expressed in the SN and VTA, suggesting that D₂ receptors are located presynaptically, in contrast to the exclusively presynaptically located D₁ and D₅ receptor subtypes (Civelli et al., 1991; Vallone et al., 2000). Compared to D₂ receptor mRNA levels, D₃ receptor mRNA levels are lower in the striatum and higher in the NAc (Sealfon & Olanow, 2000). The D₃ receptor shares 75% similarity with the D₂ receptor in terms of transmembrane domains, but differs significantly in its pharmacological profile, signal-transduction coupling, and distribution (Sokoloff et al., 1990). The D₄ is expressed highly in the frontal cortex, amygdala, olfactory bulb hippocampus, hypothalamus, and mesencephalon (Jackson & Westlind-Danielsson, 1994). In humans, it is highly polymorphic with a specific amino-acid repeat that has been correlated with novelty-seeking personality traits in humans (Ebstein et al., 1996). In addition, a high number of D₄ repeat segments may constitute a liability factor for development of delusional symptomatology in patients with major psychoses (Kapur et al., 2006).

1.2.2.4. Dysfunction in MDD

It is largely known that positive mood is correlated with reward-related responsiveness of the mesocorticostriatal system in both healthy individuals and those with a history of depression (Admon & Pizzagalli, 2015). Recently, researchers have been interested in elucidating a role for the brain's reward regions in the pathophysiology of MDD. One of the most important anatomical substrates for reward is the NAc and its dopaminergic inputs from the VTA of the midbrain (Koob & Le Moal, 2001). While the amygdala and hypothalamus also influence positive responses to rewarding stimuli, these various brain regions function as parts of highly interfaced circuits, and must be thought of as a functionally connected unit (Nestler & Carlezon, 2006). For example, the VTA and NAc receive glutamatergic inputs from the frontal cortex, hippocampus, amygdala, and hypothalamus. In turn, these regions are innervated by VTA DA neurons.

Decreased functioning of the mesocorticolimbic DA system may contribute to decreased positive mood in MDD by loss of motivation, psychomotor slowing, decreased concentration, loss of interest, and anhedonia (Dunlop & Nemeroff, 2007). Positive affect, on the other hand, has been linked to increased functional dopaminergic activity (Depue & Collins, 1999). Furthermore, diseases characterized by deficiencies in DA neurotransmission are associated with a high prevalence of mood disorders with marked anhedonia and blunted reward-related behavior (Lane, 1998). Decreased striatal dopaminergic function has been reported in depressed patients with affective flattening and psychomotor delay, but not in depressed patients without these symptoms (Bragulat et al., 2007). Additionally, homovanillic acid (HVA), a metabolite of DA, has

been found in low concentrations in the CSF of depressed suicide attempters (Sher et al., 2006). Moreover, a reduction in brain DA levels may potentiate anhedonic symptoms in depressed patients and induce decreased positive mood in individuals unaffected by MDD (Hasler et al., 2008; Jimerson, 1984). Taken together, these results suggest that dopamine dysfunction plays a major role in the pathophysiology of MDD.

1.2.3. Norepinephrine

1.2.3.1. Neuroanatomy

Norepinephrine is the principle sympathetic neurotransmitter in the periphery and is one of the brain's most abundant neurotransmitters, playing a role in selective attention, general arousal, and defense reactions in stressful environments (Aston-Jones & Cohen, 2005; Berridge & Waterhouse, 2003; Levine et al., 1990). Within the CNS, NE-containing nerve cell bodies are located primarily within the LC, however, the noradrenergic system is comprised of two main ascending projections (Ressler & Nemeroff, 1999). The dorsal noradrenergic bundle (DNB) arises from the LC catecholaminergic A6 cell group, and innervates the hippocampus, cerebellum, and forebrain whereas the ventral noradrenergic bundle (VNB) originates in the A1, A2, A5, and A7 cell groups of the pons and medulla, and projects to the hypothalamus, midbrain, and amygdala (Szabadi, 2013).

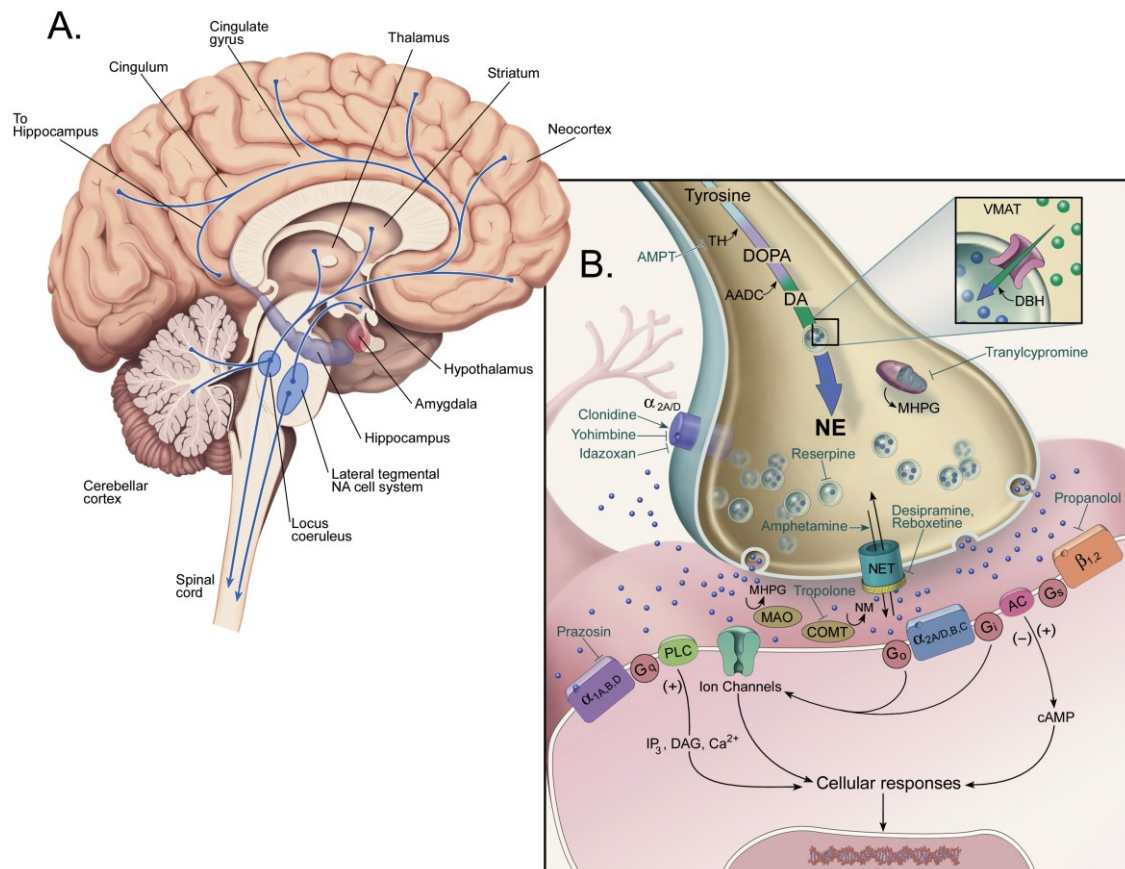


Figure 3. The Norepinephrine System. (A) Representation of the human brain with the NE nuclei located within the blue area in the pons; the locus coeruleus is a bilateral structure that is located just below the floor of the fourth ventricle. (B) Diagram of a noradrenergic synapse with the various NE receptors, their transduction mechanisms, and examples of specific ligands, both agonists and antagonists. Adapted from (Szabo, 2009).

1.2.3.2. Synthesis, Storage, and Release

Along with the catecholamine epinephrine, NE is synthesized along an enzymatic cascade beginning with the amino acid tyrosine. The rate of production of NE is limited by the enzyme tyrosine hydroxylase, which converts L-tyrosine to L-DOPA in the cytosol of the neuronal cell body and its nerve terminals. DOPA-decarboxylase, an enzyme with a high affinity for L-DOPA, rapidly converts L-DOPA to DA, the immediate precursor for NE. Amine-specific transporters then function to transport DA into storage vesicles in NE-producing neurons (Szabadi, 2013). These neurons contain membrane-bound

dopamine- β -hydroxylase, which catalyzes the hydroxylation of DA to NE (Weinshilboum et al., 1971). Norepinephrine is subsequently released into the synapse via vesicle fusion and exocytosis upon the arrival of an action potential. NE release onto target neurons in the cortex and subcortical regions is not a simple function of LC firing rate. At baseline, LC neurons fire at a slow, tonic rate. As LC neuron firing rate increases, there is also an increase in postsynaptic responsivity. However, the amount of NE released per impulse is decreased at elevating firing rates due to terminal α_2 -adrenergic autoreceptor activation (Curet & De Montigny, 1989).

Following its release into the synaptic cleft, NE is rapidly returned to the synaptic terminals by the NE transporter (NET), a specific carrier located on the outer membrane of the terminal (Szabadi, 2013). Once inside the terminal, the neurotransmitter is either rapidly returned to the storage vesicles or biochemically degraded via one of two mechanisms: the MAO pathway or the 3-Methoxy-4-hydroxyphenylglycol (MHPG) breakdown pathway. Monoamine oxidase is present on the mitochondrial outer membrane, and exerts its action by deaminating free catecholamines in the cytosol (Szabadi, 2013). In the MHPG breakdown pathway, NE is converted to its aldehyde form and then to 3,4-Dihydroxyphenylglycol (DHPG) or 3,4-Dihydroxymandelic acid (DHMA) by dehydrogenase or reductase enzymes. Catechol-O-methyltransferase (COMT) finally transforms these compounds into MHPG or 3-Methoxy-4-hydroxy-mandelic acid (VMA), respectively (Eisenhofer et al., 2004).

1.2.3.3. Receptors

Adrenergic receptors are the targets of endogenous NE and epinephrine. Not only are they important in mediating sympathetic activation to peripheral organs, but also in the CNS. α_1 -Adrenoreceptors are divided into α_{1A} -, α_{1B} -, and α_{1D} -subtypes, and α_2 -adrenoreceptors are divided into α_{2A} -, α_{2B} -, and α_{2C} -subtypes, whereas β -adrenoreceptors are divided into β_1 -, β_2 -, and β_3 -subtypes based upon functional studies with agonists and antagonists, radioligand binding, and cloning techniques (Cottingham & Wang, 2012; Koshimizu et al, 2003; Pytka et al., 2016). Some adrenoreceptors are located both pre- and post-synaptically. The stimulation or inhibition of those located presynaptically modulates NE release from synaptic vesicles, while stimulation or blockade of postsynaptic adrenoreceptors causes a variety of physiological and pharmacological effects (Pytka et al., 2016).

The α_1 -adrenoreceptors are widely distributed in the CNS and are involved in a variety of actions in CNS neurons and glial cell (Docherty, 2010). These receptors are expressed in high levels in the olfactory system, the hypothalamic nuclei, brainstem, spinal cord, pineal gland, thalamus nuclei, amygdala, and raphe nuclei (Pytka et al., 2016). Behavioral studies on rodents suggest a role for α_1 -adrenoreceptors in an antidepressant-like response. In addition, chronic antidepressant treatment has been shown to enhance α_1 -adrenergic responsiveness in the facial motor nucleus and lateral geniculate nucleus (Menkes et al., 1980; Menkes & Aghajanian, 1981). Furthermore, NE burst activity in the LC is increased following electroconvulsive shocks (ECS), and, in the facial motor nucleus, facilitation of electrophysiological activity by NE was determined to be through α_1 -adrenoceptor activity (Tsen et al., 2013). Locally administered NE, but not

5-HT, facilitates glutamate-induced firing following ECS. Therefore, ECS may enhance NE transmission in the facial motor nucleus, contributing to the alleviation of depressive symptoms by ECT.

While α_1 -adrenoreceptors activate phospholipase C, producing inositol triphosphate and diacylglycerol as second messengers, α_2 -adrenoreceptors inhibit adenylyl cyclase, in turn decreasing cAMP levels (Langer, 2015). The α_2 -adrenoreceptors appear to play a critical role in the regulation of noradrenergic transmission and have been studied extensively for their role in MDD (Cottingham & Wang, 2012). All presynaptic autoreceptors in noradrenergic neurons correspond to the α_2 subtype, and, through a negative feedback mechanism, are responsible for the release of NE from noradrenergic terminals (Hein et al., 1999; Langer, 2015). In contrast, α_2 -heteroreceptors are located on non-adrenergic neurons, including serotonergic, cholinergic and glutaminergic neurons, and are responsible for neurotransmitter release (Hein et al., 1999; Langer, 2015). Activation of α_2 -heteroreceptors is known to induce sedation, analgesia, and hypothermia (Hein et al., 1999). Long-term treatment with the non-selective α_2 -adrenoreceptor antagonist, mirtazapine, increases 5-HT neurotransmission as a result of a sustained increase in the firing activity of 5-HT neurons with a decrease in 5-HT terminal α_2 -heteroreceptor activity (Hadjjeri et al., 1997). Moreover, mirtazapine treatment results in an earlier increase in 5-HT transmission than with an SSRI and, therefore, may have a more rapid onset of action than an SSRI (Besson et al., 2000; Thase et al., 2010).

β_1 -adrenoreceptor mRNA has been found in the rat anterior olfactory nucleus, cerebral cortex, lateral intermediate septal nucleus, reticular thalamic nucleus, oculomotor complex, vestibular nuclei, deep cerebellar nuclei, trapezoid nucleus, abducens nucleus, ventrolateral pontine and medullary reticular formations, the intermediate grey matter of the spinal cord and in the pineal gland, whereas β_2 mRNA was predominantly found in the olfactory bulb, piriform cortex, hippocampal formation, thalamic intralaminar nuclei and cerebellar cortex (Nicholas et al., 1993). In the human brain, however, β_3 -adrenoreceptor mRNA was found in the brain stem, temporal and frontal cortices, cerebellum, hippocampus, striatum, and SN (Rodriguez et al., 1995).

Repeated administration of antidepressant drugs characteristically diminishes β -adrenergic responsiveness in the brain as measured by catecholamine-induced increases in cAMP (Weiss et al., 1982). This reduction of responsiveness is often attributable to a decrease in β -adrenergic receptor density, an effect produced by antidepressants (Sarai et al., 1978). In fact, sustained treatment with the β_2 -adrenergic receptor agonist, clenbuterol, has been shown to reduce β -adrenergic responsiveness in the rat cerebral cortex (O'Donnell & Frazer, 1985). Studies have demonstrated that the modulation of β -adrenergic receptors by salbutamol and clenbuterol increases 5-HT synthesis in the rat brain. The antidepressant properties of β -adrenergic receptor agonists may be attributable to their capacity to increase the plasma levels of tryptophan (Nimgaonkar et al., 1983). In fact, a controlled study comparing salbutamol to clomipramine in depressed inpatients revealed that, while both treatments were effective on depressive symptomatology, the onset of action of salbutamol was more rapid (Lecrubier et al.,

1980). Clinical studies have confirmed the rapid onset of antidepressant activity in both salbutamol and clenbuterol in the treatment of bipolar and unipolar depression (Lecrubier et al., 1981; Simon et al., 1984). Furthermore, prolonged administration of flerobuterol enhances 5-HT neurotransmission, suggesting that β -adrenergic agonists may be useful in the treatment of major depression (Bouthillier et al., 1991).

Likewise, the selective β_3 -adrenoreceptor agonist, amibegron, possesses a profile of antidepressant activity in rodents similar to that of classical $\beta_{1/2}$ adrenoceptors agonists (Simiand et al., 1992). Amibegron has been shown to increase both 5-HT and NE neurotransmission in the rodent brain after acute administration (Claustre et al., 2008). Its effect on 5-HT transmission is likely due to an activation of peripheral β_3 -adrenoreceptors, leading to an increase of central 5-HT synthesis via an elevation of tryptophan levels and inducing 5-HT release without altering the firing activity of raphe neurons (Claustre et al., 2008). Its effect on NE transmission, in contrast, results from central stimulation of β_3 -adrenoreceptors and a subsequent increase in LC NE neurons (Stemmelin et al., 2008). Unlike most β -adrenergic receptor agonists, however, amibegron seems to be devoid of undesirable side effects such as tachycardia, alteration of locomotor activity, sedation, myorelaxation, sleep disturbances, or memory impairment (Simiand et al., 1992; Stemmelin et al., 2008). Therefore, the antidepressant effects of amibegron may involve activation of 5-HT and NE transmission through a mechanism distinct from those known for SSRI and SNRIs and the stimulation of β_3 -adrenoreceptors may represent a novel approach in the treatment of depressive disorders.

1.2.3.4. Dysfunction in MDD

There are several lines of evidence indicating that dysfunction of the NE system contributes to the pathophysiology of depression. Some of the first studies suggesting that the NE system plays a crucial role in depressive disorders occurred in the mid-1950s. Reserpine, a compound that reduces sympathetic activity by depleting amines in the central and peripheral nervous systems, was found to cause profound depression in some patients taking the drug for hypertension (Freis, 1954). Likewise, tetrabenazine (TBZ), a compound used to treat hyperkinetic movement disorders, exerts its action by depletion of the monoamines in the CNS by inhibiting VMAT2 and preventing monoamine uptake into presynaptic neurons. Treatment with TBZ is associated with numerous adverse effects including depression and suicidality (Guay, 2010). Moreover, when these medications were discontinued, these patients returned to their normal affective state (Ressler & Nemeroff, 1999). Numerous studies have investigated the relationship between altered NE or its metabolites and depression, however the findings are inconsistent. For example, short-term depletion of NE by administration of α -methylparatyrosine to healthy subjects does not produce a significant change in mood (Salomon et al., 1997). On the other hand, pharmacologic depletion of NE in patients on noradrenergic antidepressant treatment results in a rapid return of depressive symptoms (Delgado, 2000). In addition, it has been shown that catecholamine depletion in euthymic patients with a history of MDD caused a relapse of depression (Berman et al., 1999). Taken together, these findings are consistent with the hypothesis that, while

NE depletion alone is insufficient to induce depressive symptoms, it has the potential to induce depressive symptoms in at-risk individuals.

There are also reports that identify changes in the density of adrenergic receptors in individuals with depression. Postmortem studies on the brains of depressed suicide victims revealed an increase in cortical α_1 - and α_2 -adrenergic receptors, and in hypothalamic α_2 -adrenergic receptors (Arango et al., 1993; Meana et al., 1992; Meana & García-Sevilla, 1987). Studies on the biochemistry of the locus coeruleus (LC) of suicide victims revealed elevated tyrosine hydroxylase and upregulation of α_2 -adrenergic receptors as compared to control subjects (Ordway, 1997). These biological abnormalities are consistent with those observed in the rodent LC following repeated activation of the LC or administration of NE depleting pharmacological agents (Melia et al., 1992; Nestler et al., 1990). These results support the hypothesis that suicide victims have experienced chronic activation of the LC through exposure to chronic stress or by abnormal overresponsiveness of the LC to normal daily stressors, resulting in depletion of synaptic NE, compensatory changes in TH expression, and upregulation of LC α_2 -adrenergic receptors (Ordway, 1997). Elevated LC activity in people with MDD may be secondary to elevated excitatory glutamatergic input to the LC. Given that excitatory glutamatergic input is a major modulator of LC activity, there is also strong evidence of astrocyte dysfunction in the LC, implicating a deficit in the regulation of glutamatergic action in this region (Chandley et al., 2013). It is well-known that MDD is commonly precipitated by stress and that stress increases glutamate release in the LC (Valentino et al., 2001). Hence, it is possible that dysfunctional glutamate uptake by compromised

astrocytes in the LC could exacerbate the detrimental effects of increased glutamate release in the LC at the level of neurons as well as astrocytes. Furthermore, recent studies demonstrate that the destruction of astrocytes in the prefrontal cortex can induce depressive-like behaviours in rats (Banasr & Duman, 2008). Therefore, there is strong evidence for a direct role of NE in depression pathophysiology.

1.3. Functional Interactions

It is noteworthy to mention that multidirectional structural and functional relationships exist among the monoamine neurotransmitter systems (Figure 4). The primary origins of 5-HT, NE, and DA are the raphe nucleus, LC, and VTA, respectively and they project to the limbic structures, striatum, and cortical areas. The serotonergic and noradrenergic systems project more diffusely through the cortex and hindbrain in comparison to the dopaminergic system. For example, pharmacologic activation of α_1 or α_2 adrenergic receptors respectively increases or decreases the firing rate of dorsal raphe 5-HT neurons (Marwaha & Aghajanian, 1982; Svensson et al., 1975). There is also considerable interaction between the serotonergic and dopaminergic systems in the brain. A tonic inhibitory effect of the serotonergic system on DA activity is seen with administration of 5-HT_{2C} antagonists (Millan et al., 1998). In addition, 5-HT_{2C} antagonists reverse DA agonist-induced inhibition of DA neurons (Shi et al., 1995). Finally, LC firing with NE release has been shown to potentiate firing of DA neurons in the VTA (Guiard et al., 2008). Moreover, this excitation is decreased with the α_1 -adrenergic antagonist, prazosin (Grenhoff et al., 1993). The extensive reciprocal interactions between these three neurotransmitter systems give pharmacological agents that target one system the

ability to modify the function of the other two systems. This finding supports a strong link between the functional deficiency of the monoamine neurotransmitter systems and the pathophysiology of MDD.

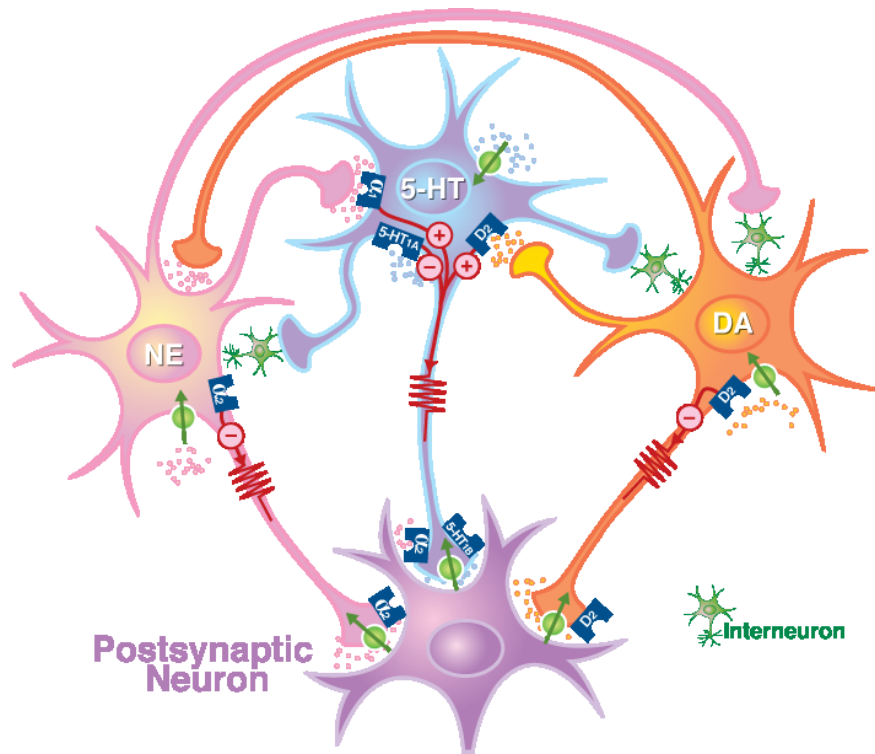


Figure 4. Functional Connectivity of Monoaminergic Neurons. Direct and indirect interconnections between 5-HT, NE and DA neurons mediated through various receptor types which act both as autoreceptors controlling the activity of respective neuronal phenotype and heteroreceptors controlling the activity of the other two monoaminergic neuronal phenotypes. Adapted from Blier (2014).

1.4. Treatment Strategies

1.4.1. Non-Pharmacological

There is a wide variety of non-pharmacological techniques for the treatment and management of depression. Cognitive Behavioral Therapy is can be defined as a comprehensive system of psychotherapy, which combines behavior theory with cognitive learning theory and implements strategies to change the way a patient thinks. CBT appears to alleviate symptoms of depression and reduce the risk of relapse (Fava et al., 1998; Paykel et al., 1999, 2005; Scott et al., 2000). It has been suggested, however, that combined treatment with antidepressant pharmacotherapies and psychotherapy is more effective than psychotherapy alone (De Jonghe et al., 2001). More recently, the field of non-pharmacological therapies for treatment resistant depression (TRD) has been rapidly evolving, and new somatic therapies have proven to be valuable for patients who have failed numerous treatment trials. The efficacy of electroconvulsive therapy (ECT) is well established in TRD (The UK ECT Review Group, 2003; Trivedi & Daly, 2008). There has been growing interest in the application of vagus nerve stimulation (VNS) as an adjunct therapy for TRD patients who have failed 4 or more medications, however, it is not indicated for management of acute illness (Cusin et al., 2013). A 5-year observational study of patients with TRD provides additional evidence that adjunctive VNS has better clinical outcomes and higher remission rate compared with treatment as usual (Aaronson et al., 2017). Similarly, repetitive transcranial magnetic stimulation (rTMS) has been investigated in patients with TRD, often in combination with pharmacotherapies (Fitzgerald et al., 2006; Kozel & George, 2002). Based on published

data, the magnitude of the efficacy of rTMS in TRD patients is not sufficiently robust and further investigation with double-blind randomized controlled trials is required.

1.4.2. Pharmacological

1.4.2.1. Tricyclic Antidepressants

The history of antidepressants dates back to the 1950s with the discovery of the TCAs and MAOIs, marking the commencement of pharmacotherapy in the treatment of MDD and prompting the first monoaminergic theories in the pathogenesis of depression. TCAs were named after their basic three-ring structure and, much like the serotonin norepinephrine reuptake inhibitors (SNRIs), act by increasing 5-HT and NE levels by inhibiting their reuptake. However, the utility of TCAs is limited as they also produce unfavourable side-effects via muscarinic ACh receptor antagonism (Santarsieri & Schwartz, 2015). Furthermore, a TCA overdose has the potential to cause sudden cardiac death (Sicouri & Antzelevitch, 2008). Due to their safety profile, this class has fallen out of favour as first-line treatment for major depressive disorder.

1.4.2.2. Monoamine Oxidase Inhibitors

In contrast, MAOIs act by inhibiting monoamine oxidase activity to prevent breakdown of monoamine neurotransmitters. It was previously shown that subacute administration of MAOIs decreases both 5-HT and NE firing rates. The firing rate of 5-HT neurons, but not NE neurons, recovers after prolonged administration of MAOIs, due to 5-HT_{1A} autoreceptor desensitization (Blier & de Montigny, 1985). More recent investigation suggests that long-term administration of MAO-A inhibition has an indirect

effect on the firing of VTA DA neurons (Chenu et al., 2009). Since the introduction of MAOIs, their use in psychiatric practice has decreased due to safety and tolerability restrictions and the potentially lethal interaction with tyramine-rich foods (Thase, 2012). The selective MAO-A inhibitor, moclobemide, is also effective in the treatment of depressive disorders (Angst, et al., 1995; Bonnet, 2006). The drug is well tolerated by most patients and, compared with SSRIs, moclobemide causes fewer gastrointestinal side effects and no sexual dysfunction (Lotufo-Neto et al., 1999).

1.4.2.3. Selective Serotonin Reuptake Inhibitors

SSRIs have become the most commonly prescribed antidepressant pharmacotherapy since FDA approval of the first SSRI in 1987 (Wong et al., 1995). The serotonin transporter (SERT) is inhibited when SSRIs cross the blood brain barrier, and the blockade of the 5-HT reuptake increases the amount of neurotransmitter available at the synapse. The increased levels of 5-HT lead to enhanced activation of the 5-HT_{1A} autoreceptors, and the 5-HT firing rate falls significantly. With sustained administration of SSRIs, the desensitization of the 5-HT_{1A} autoreceptors results in the firing rate to be restored to baseline levels (Chaput et al., 1986). This SSRI-induced desensitization also affects terminal 5-HT_{1B} autoreceptors that control 5-HT release, dampening the effect of 5-HT_{1B} antagonists and allowing for greater release of 5-HT (Blier & De Montigny, 1983; Piñeyro & Blier, 1999). The responsiveness of postsynaptic 5-HT_{1A} receptors, however, remains unchanged following sustained blockade of 5-HT reuptake (Béique et al., 2000). Together, these effects lead to an accumulation of synaptic 5-HT and, thus, an increase in 5-HT neurotransmission. Through 5-HT_{2A} and 5-HT_{2C} receptors respectively, an

increase in 5-HT transmission acts to decrease the spontaneous firing of NE and DA (Dremencov et al., 2007, 2009; Szabo et al., 2000). Despite substantial progress in the study of MDD, there is a continuing warrant for more effective and better-tolerated depression therapies.

1.4.2.4. Norepinephrine Reuptake Inhibitors

A substantial body of data exists to support the hypothesis that noradrenergic mechanisms play an important role in antidepressant activity. Norepinephrine reuptake inhibitors (NRIs) can therefore be considered valuable tools in the treatment of depression. The potent and highly selective NRI, reboxetine, for example, inhibits firing of LC NE neurons by blocking NET, thereby increasing extracellular levels of NE. This inhibition is attributed to α_2 adrenergic receptors as α_2 -receptor antagonists reverse this inhibition (Millan et al., 2001; Szabo & Blier, 2001a).

1.4.2.5. Serotonin-Norepinephrine Reuptake Inhibitors

The SNRI's, such as venlafaxine, desvenlafaxine, and duloxetine, function to dually inhibit 5-HT and NE reuptake, allowing treatment of a variety of symptoms associated with MDD. This pharmacological mechanism is similar to that of the TCAs, however, the SNRIs are not associated with anticholinergic side effects. With respect to their effect on neurotransmission, long-term administration of SNRIs produces a marked decrease in the firing rate of NE neurons and an acute decrease in dorsal raphe 5-HT neurons with complete recovery after sustained administration (Béïque et al., 2000).

1.4.2.6. Other Antidepressant Therapies

Antidepressants such as mirtazapine, trazodone, bupropion, vilazodone, and vortioxetine do not belong, structurally or mechanistically, to any of the above-defined classes. Mirtazapine is one such agent that functions by inhibiting NE α_2 -autoreceptors and α_2 -heteroreceptors, thereby allowing a greater amount of NE to be released from the terminal (Haddjeri et al., 1998). Mirtazapine also inhibits 5-HT_{2A/C} receptors, allowing for more 5-HT, DA, and NE modulation in the cortex (Santarsieri & Schwartz, 2015). A meta-analysis of individual patient data from 15 controlled trials revealed that mirtazapine monotherapy produces a faster onset of efficacy, but equal efficacy, compared to SSRIs (Thase et al., 2010). Like the SSRIs, trazodone was an early “second generation” antidepressant therapy. Trazodone’s mechanism of action is multifaceted, with mixed serotonergic agonist-antagonist activity functioning to increase CNS 5-HT via a combined effect on 5-HT reuptake and 5-HT_{2A/C} receptors (Ghanbari et al., 2010, 2012).

Vilazodone and vortioxetine are two recently approved drugs for the treatment of MDD. Both agents possess a core mechanism of 5-HT reuptake inhibition, while interacting with various other receptors. Vilazodone is both a pre- and postsynaptic 5-HT_{1A} partial agonist. Vortioxetine, like vilazodone, possesses multimodal activity with mixed agonist-antagonist effects on 5-HT receptors. For example, vortioxetine is a 5-HT₃, 5-HT₇ and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} receptor partial agonist, a 5-HT_{1A} receptor full agonist and a SERT inhibitor (Mørk et al., 2013).

1.4.2.7. Combination and Augmentation Strategies

Where there is failure of patients with MDD to achieve full remission after first-line treatment with SSRIs, the Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines consider augmentation therapies among the most effective pharmacological treatments (Kennedy et al., 2016). While the classic approach to overcoming treatment-resistant MDD is switching the patient to another antidepressant with either a different or additional mechanism of action, the therapeutic effectiveness of this strategy remains controversial (Bschor & Baethge, 2010). This approach necessitates the same duration as the initial treatment, and evidence suggests that the risk of treatment resistance increases with the number of trials required to achieve it (Trivedi & Daly, 2008). Furthermore, the recommendation to switch from one antidepressant agent to another dismisses the possibility that a therapeutic biological action was triggered, even without a marked clinical improvement (Blier & Blondeau, 2011; Nelson et al., 2014). To maintain the beneficial therapeutic response to the initial treatment, the addition of a second agent with a different mechanism of action (i.e. an antidepressant from another class or a non-antidepressant medication) to the existing antidepressant treatment is suggested. Among such treatment options is the addition of low doses of an atypical antipsychotic, such as risperidone, olanzapine, aripiprazole, and quetiapine, which may act synergistically with an antidepressant to produce a more rapid and robust response (Ostroff & Nelson, 1999; Shelton et al., 2001). The key to this strategy is to administer doses lower than those typically used to treat psychosis as to mediate their antidepressant effects and avoid undesirable physiological effects of diminishing D₂ receptor activation (Blier & Blondeau, 2011). Given that these agents

function as antidepressants at doses that would be sub-therapeutic for patients with psychosis, the term *atypical antipsychotic* does not adequately reflect their therapeutic potential in the treatment of mood disorders. To date, there have been seven placebo-controlled trials of atypical antipsychotics as adjuncts in unipolar depression with a total of over 6,400 subjects (Durgam et al., 2016; Kamijima et al., 2013; Lenze et al., 2015; Papakostas et al., 2015; Shelton & Papakostas, 2008; Thase et al., 2015). This thesis will examine the neurobiological properties of properties of atypical antipsychotics that may account for their efficacy in treatment-resistant depression.

The approval of olanzapine, aripiprazole, and quetiapine alone and/or in combination with antidepressants for the treatment of depression was motivated by observed clinical improvement among depressed patients receiving olanzapine in addition to an SSRI regimen (C. Shelton et al., 2001). Most atypical antipsychotics can be characterized by their ability to block 5-HT_{2A} receptors more potently than D₂ receptors, presumably contributing to their low propensity to produce extrapyramidal side effects through an increase in DA release in the striatum *via* 5-HT_{2A} receptor blockade (Ichikawa et al., 2001; Schotte et al., 1996).

1.5. Rationale

The clinical characterization component has opted to study the SSRI, escitalopram as the antidepressant to treat patients with major depressive disorder. This choice is justified by its exquisite selectivity for the 5-HT transporter, as well as its high capacity to promote its own binding through an allosteric site, a feature unique to escitalopram (Zhong et al., 2012). We have extensively studied the effects of both acute

and sustained administration of escitalopram on monoamine neurons. It produces a rapid decrease of the firing rate of 5-HT neurons followed by a gradual recovery to normal after 2 to 3 weeks, due to the desensitization of the 5-HT_{1A} autoreceptor (El Mansari et al., 2005; Guiard et al., 2012). This leads to a net and sustained increase in 5-HT_{1A} transmission in the hippocampus (Figure 5) (El Mansari et al., 2005). In contrast, escitalopram produces a decrease in the firing activity of NE and DA neurons (Figure 6,7) (Dremencov et al., 2007; Dremencov et al., 2009). This dampened catecholamine activity is the result of increased activation of 5-HT_{2A} receptors in the case of NE neurons and of 5-HT_{2C} receptors for DA neurons, as indicated by the restoration of normal firing by 5-HT_{2A} and 5-HT_{2C} antagonists, respectively.

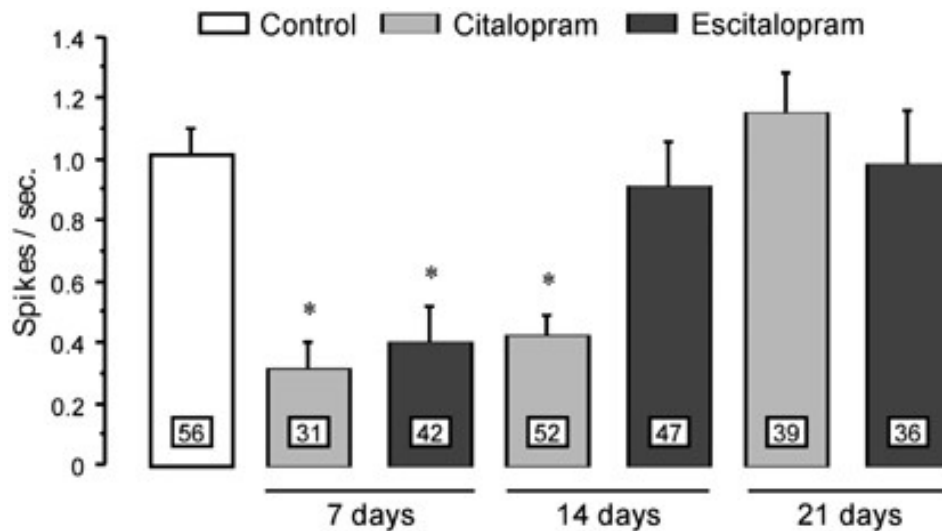
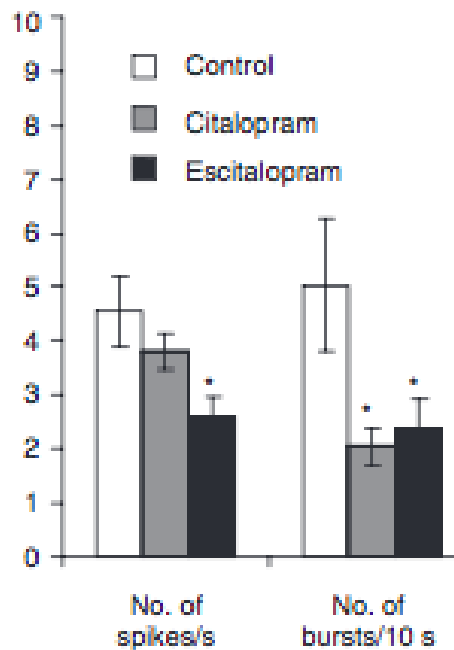
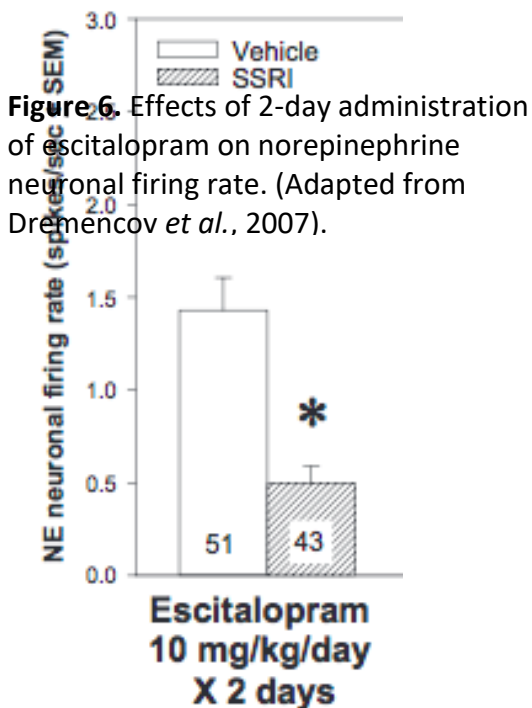


Figure 5. Mean firing rate of dorsal raphe 5-HT neurons in control rat and rats treated with escitalopram (10 mg/kg/day, s.c.) or citalopram (20 mg/kg/day, s.c.), for 7, 14, and 21 days. (Adapted from El Mansari *et al.*, 2005).

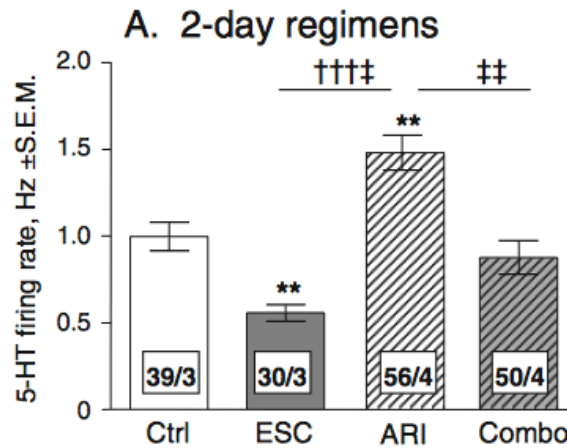
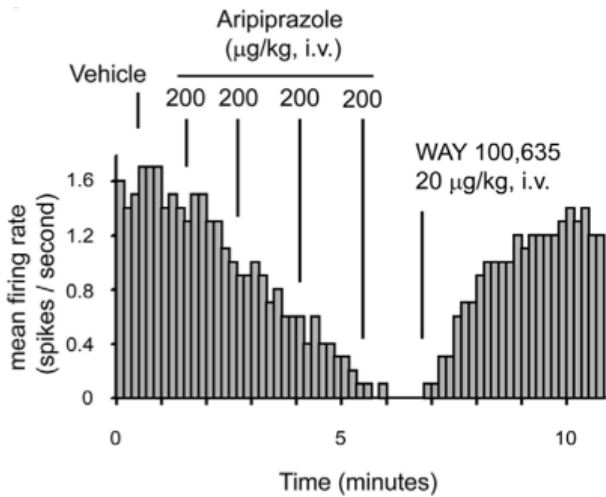


Aripiprazole was the first antipsychotic to be approved by the FDA as an adjunct in patients with MDD having an inadequate response to antidepressants. It has been

used as an augmentation strategy in escitalopram-resistant patients. This is deemed to be a very effective strategy based on five positive double-blind studies (Berman et al., 2007, 2009; Kamijima et al., 2013; Lenze et al., 2015; Marcus et al., 2008). Despite this proven clinical efficacy, the precise neurobiological mechanism underlying its mode of action is not entirely understood.

It is further justified based on studies on the impact of sustained administration of aripiprazole alone, and in combination with escitalopram, on monoaminergic neurons (Berman et al., 2009; Chernoloz et al., 2009). Acute aripiprazole injection suppresses the firing of 5-HT neurons through its potent 5-HT_{1A} agonistic activity (Figure 8) (Dahan et al., 2009). Strikingly, however, aripiprazole markedly increases the firing rate of 5-HT neurons after only 2 days of repeated administration, due to rapid desensitization of the 5-HT_{1A} autoreceptor, thereby unveiling the excitatory action of aripiprazole on D₂ receptors on 5-HT neurons (Chernoloz et al., 2009). The combination of aripiprazole with escitalopram prevents the initial decrease in firing of 5-HT neurons, suggesting that the combination could produce a rapid and marked increase in 5-HT transmission in the forebrain (Chernoloz et al., 2009). However, this has yet to be investigated.

Repeated aripiprazole administration does not alter the firing activity of NE and DA neurons (Chernoloz et al., 2009). When combined with escitalopram, however, aripiprazole reverses the inhibitory action of escitalopram on NE and DA neurons, presumably through its functional antagonism of 5-HT_{2A} and 5-HT_{2C} receptors (Dremencov et al., 2007, 2009). These results suggest that aripiprazole could restore a potentially reduced NE and DA transmission by escitalopram in forebrain structures.



Indeed, prolonged administration of citalopram has been shown to reduce extracellular NE in the rat amygdala (Kawahara et al., 2007). We have yet to examine the effect of escitalopram on extracellular DA levels in forebrain experiments.

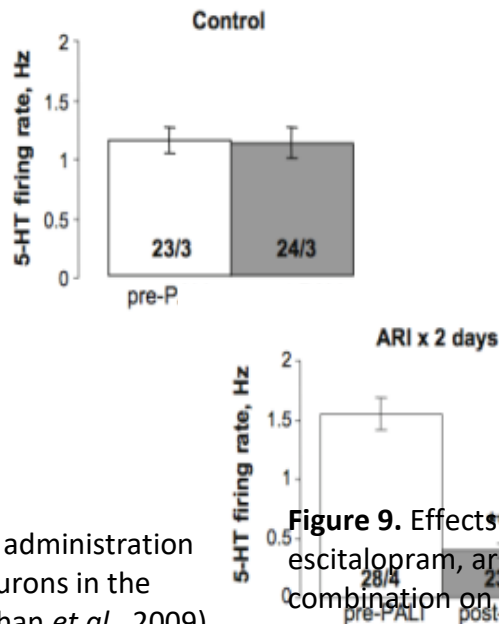


Figure 8. Effects of aripiprazole administration on the firing activity of 5-HT neurons in the dorsal raphe (Adapted from Dahan *et al.*, 2009).

Figure 9. Effects of acute administration of escitalopram, aripiprazole, and their combination on 5-HT spontaneous firing rate. (Adapted from Chernoloz *et al.*,

Figure 10. Effect of D₂ antagonist PALI on 5-HT neuronal firing in control rats and rats treated with aripiprazole treated for 2 days. (Adapted from Chernoloz *et al.*, 2009).

One of the most effective combination treatments is the addition of low doses of the antipsychotic, aripiprazole, to the SSRI, escitalopram (Mohamed et al., 2017). The present work will focus on determining the mode of action of this combination of drugs. Elucidating the neurobiological mechanisms leading to normal monoamine function will help to design better antidepressant treatment in the future, thus, providing clinicians with more options to treat patients suffering with depression.

CHAPTER 2: OBJECTIVES & HYPOTHESES

Objective 1: Electrophysiological assessment of 5-HT neurotransmission in the rat hippocampus.

Hypothesis: Tonic activation will increase with escitalopram + aripiprazole.

Objective 2: Electrophysiological assessment of NE neurotransmission in the rat hippocampus.

Hypothesis: Tonic activation will not increase with escitalopram + aripiprazole.

Objective 3: Assessment of DA neurotransmission in the rat forebrain.

Hypothesis: Tonic activation will increase with escitalopram + aripiprazole.

CHAPTER 3: MATERIALS & METHODS

3.1 Proposed Experiments

3.1.1 Electrophysiological assessment of 5-HT neurotransmission in the rat hippocampus

The degree of tonic activation of postsynaptic 5-HT_{1A} receptors on CA₃ pyramidal neurons will be examined in rats treated with escitalopram alone, and aripiprazole alone for 2 and 14 days. Aripiprazole will also be administered for 2 days concomitantly with escitalopram and from day 13 of a 14-day regimen of escitalopram. These experiments also allow assessment of the sensitivity of postsynaptic 5-HT_{1A} receptors, as well as the degree of 5-HT reuptake inhibition from the direct iontophoretic application of 5-HT and the 5-HT_{1A} agonist 8-OH-DPAT. Finally, by applying aripiprazole and 5-HT through the microelectrode, it will be possible to determine in vivo the intrinsic activity of aripiprazole (partial to full agonistic) and also to determine if, given systemically, aripiprazole competes or synergizes with postsynaptic 5-HT_{1A} receptor (Blier & de Montigny, 1990).

3.1.2 Assessment of NE neurotransmission in the rat hippocampus

The degree of tonic activation of postsynaptic α_1 - and α_2 -adrenoreceptors on CA₃ pyramidal neurons will be examined in rats administered escitalopram alone, aripiprazole alone, and their combination for 2 and 14 days (Ghanbari et al., 2011). These experiments will also allow assessment the sensitivity of α_2 -adrenoceptors located on cell body of the pyramidal neurons.

3.1.3 Assessment of DA transmission in the rat forebrain

In a first series of experiments, we will assess the levels of extracellular DA in the nucleus accumbens and frontal cortex, following prolonged administration of escitalopram. This brain region will be studied, as the hippocampus is only sparsely innervated by DA terminals. We will then assess the degree of tonic activation of postsynaptic DA₂ in the frontal cortex, a paradigm in which previously showed an enhanced tonic activation of these receptors by prolonged administration of the DA_{3/2} agonist pramipexole (Chernoloz et al., 2012b). The same treatments regimens as above will be used.

3.2 Treatments

Escitalopram was delivered via subcutaneously implanted osmotic minipumps at a dose of 5 mg/kg/day. Aripiprazole was injected subcutaneously at a dose of 2 mg/kg/day. Both drugs were administered for 2 or 14 days alone and in combination.

3.3 Extracellular unitary recordings

All animals, regardless of treatment, underwent the electrophysiological recording experiment, a non-recovery procedure. Animals were anesthetized with chloral hydrate injections (400 mg/kg, i.p.). To maintain anesthesia, chloral hydrate supplements were given as needed (100 mg/kg, i.p.). Extracellular recordings of hippocampal CA3 neurons were obtained using multi-barrelled glass micropipettes.

3.4 Tool Compounds

Treatment	Administration	Dose*	Volume
8-OH-DPAT	i.v.	10 µg/kg	100 µl
WAY100635	i.v.	100 µg/kg	100 µl
Clonidine	i.v.	10 µg/kg	100 µl
Idazoxan	i.v.	1 mg/kg	100 µl
Apomorphine	i.v.	50 µg/kg	100 µl
Haloperidol	i.v.	200 µg/kg	100 µl

* Doses are based on previous successful studies

3.5 Data Analysis

The data are presented as mean values \pm standard error of the mean (SEM).

Statistical comparisons are to be performed using the Student t-test, Mann-Whitney U test, or Wilcoxon signed rank test when a parameter is studied in control and treated rats. For the tonic activation, statistical comparisons will be carried out using a two-way analysis of variance (ANOVA) with repeated measures (treatment as the main factor) followed by the Tukey *post hoc* analysis. Statistical significance to be taken at $p < 0.05$.

CHAPTER 4: PRELIMINARY RESULTS

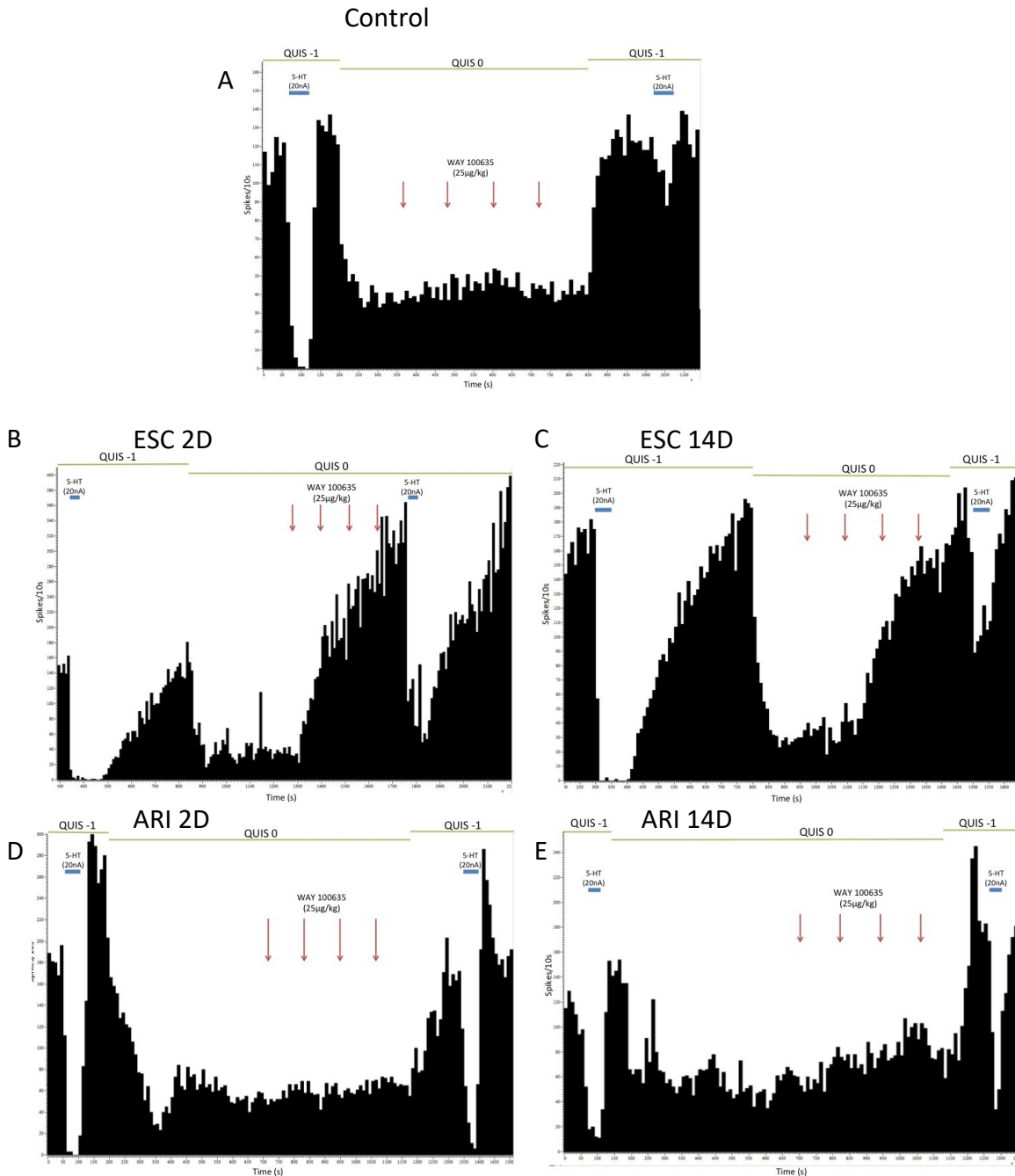


Figure 11. Firing rate of hippocampus CA3 pyramidal neurons in response to microiontophoretic application of 5-HT in control (A); rats treated with escitalopram (5 mg/kg/day) for 2 days (B); rats treated with escitalopram (5 mg/kg/day) for 14 days (C); rats treated with aripiprazole (2 mg/kg/day) for 2 days (D); and rats treated with aripiprazole (2 mg/kg/day) for 14 days (E).

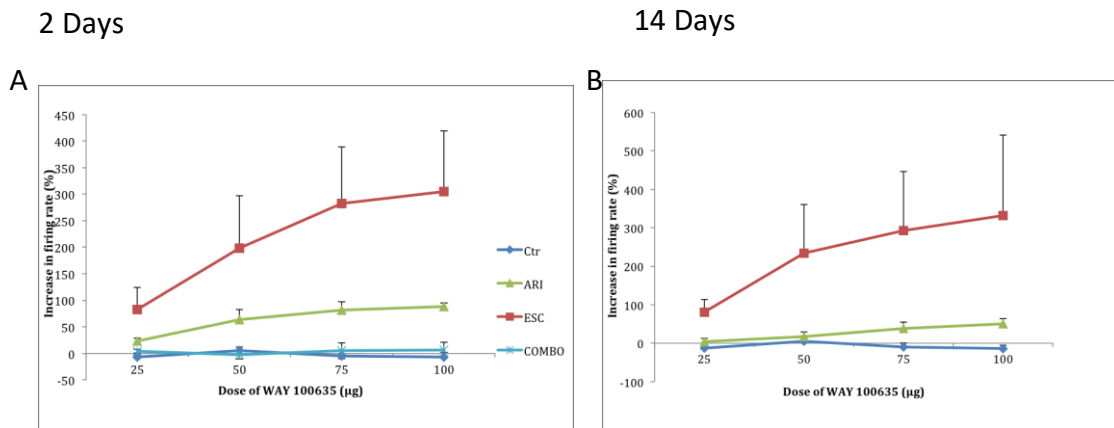


Figure 12. Assessment of tonic activation of 5-HT_{1A} receptors in hippocampus CA3 pyramidal neurons with systemic administration of WAY 100635 in four incremental doses of 25 µg/kg (n=3-7).

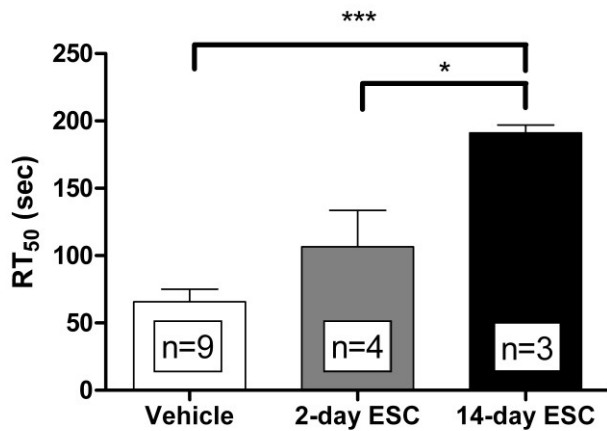


Figure 13. RT₅₀ values calculated from microiontophoretic application of 5-HT (20nA) in control, and rats treated with escitalopram for 2 and 14 days. Data were analyzed with a one-way ANOVA and Bonferroni *post hoc* analysis.* illustrates significant effect of escitalopram administration; *p<0.05; ***p<0.001

These results indicate that the SSRI, ESC, is more potent than paroxetine because the former enhanced 5-HT_{1A} receptor transmission after only 2 days (Figure 11B; Figure 12A). ARI on its own enhanced tonic activation of 5-HT_{1A} receptors after 2 days, but not 14 days, in normal rats (Figure 12B). The combination of ESC + ARI enhanced 5-HT_{1A} receptor transmission to a lesser extent than ESC alone (Figure 12A), as was the case with ESC + Quetiapine. Together, these results suggest that the combination is not acting primarily through 5-HT_{1A} receptors in projecting areas such as the hippocampus.

These preclinical studies document whether aripiprazole acts like other antidepressants in increasing 5-HT transmission in the hippocampus. Positive results could justify studying aripiprazole monotherapy in unipolar major depressive disorder. Examining the potential synergy between subacute aripiprazole and subacute and long-term escitalopram administration on 5-HT, NE, and DA transmission could help determine whether the combination could be used from treatment initiation for a more rapid and/or robust antidepressant response. Indeed, if the addition of short-term aripiprazole produces the same effects after subacute and long-term administration of escitalopram on these systems, the combination could be highly beneficial in the short-term. Noradrenergic and dopaminergic transmissions remain to be evaluated. Similar studies need to be done in rats first subjected to models producing depression-like features.

In fact, the recent study investigating postsynaptic neurotransmission of the monoamine systems revealed that 14 day escitalopram and combined escitalopram +

aripiprazole administration significantly inhibits 5-HT transporter activity (Blier et al., 2017). While neither escitalopram nor aripiprazole administration alone altered the tonic activation of 5-HT_{1A} receptors, 14 day administration of escitalopram and aripiprazole in combination significantly increased tonic activation of pyramidal 5-HT_{1A} receptors (Blier et al., 2017). In contrast, noradrenergic neurotransmission was unchanged by either of the treatment regimens (Blier et al., 2017). These results, on the other hand, suggest a synergistic effect between escitalopram and aripiprazole in increasing hippocampal 5-HT_{1A} receptor tonic activation after long-term administration of the drugs in combination.

CHAPTER 5: DISCUSSION

5.1 Properties of atypical antipsychotics accounting for their use in treating major depressive disorder

5.1.1 5-HT_{2A} Receptors

Given that pure D₂ receptor blockers (formerly denoted as first-generation atypical antipsychotics) do not possess antidepressant properties, the blockade of dopamine D₂ receptors does not appear to explain these properties. Additionally, antidepressant potential is unlikely, given the dosage of D₂ blockers utilized in the treatment of depression is lower than the dosages used in psychotic states and may not significantly occupy D₂ receptors beyond the commonly accepted threshold of about 60% (Kapur et al., 2006). Low doses of atypical antipsychotics that block the 5-HT_{2A} receptor display antidepressant effects, and are deemed among the most effective augmentation agents in depressed patients with inadequate response to SSRIs (Nelson &

Papakostas, 2009), suggesting that the main determinants of the antidepressant response of antipsychotic drugs in SSRI-resistant depression are the 5-HT₂ receptors.

We have extensively studied the effects of acute and sustained administration of SSRIs on monoaminergic neurons. Escitalopram produces a rapid decrease of the firing rate of 5-HT neurons, followed by a gradual recovery to normal after 2 to 3 weeks, due to the desensitization of the 5-HT_{1A} autoreceptor, leading to a net and sustained increase in 5-HT_{1A} transmission in the hippocampus (El Mansari et al., 2005; Guiard et al., 2012). In contrast, sub-acute administration of escitalopram or sustained administration of paroxetine, citalopram, or fluoxetine produces a marked decrease in the firing activity of NE neurons (Szabo & Blier, 2001b; Szabo et al., 1999). This inhibitory activity is the result of increased activation of 5-HT_{2A} receptors present on GABA neurons controlling the activity of the LC neurons, as indicated by the restoration of normal firing by 5-HT_{2A} antagonists (Dremencov et al., 2007; Seager et al., 2004). Indeed, stimulation of the 5-HT_{2A} receptor reduces dorsal raphe 5-HT activity via the noradrenergic system and increased cortical NE outflow contributes to enhancement of the acute antidepressant-like effect of escitalopram by the 5-HT_{2A} antagonist MDL100907 (Quesseveur et al., 2013). Therefore, potent blockade of the 5-HT_{2A} receptor with an atypical antipsychotic in the presence of 5-HT reuptake inhibition could explain the robust therapeutic response of atypical antipsychotics in patients with MDD who fail to achieve remission with SSRIs alone.

5.1.2 5-HT_{2C} Receptors

In addition to their high affinity for 5-HT_{2A} receptors, atypical antipsychotics have a high affinity for 5-HT_{2C} receptors (Schotte et al., 1996), a property that may also contribute to the antidepressant effects of atypical antipsychotics by increasing extracellular levels of DA in the prefrontal cortex. For example, the atypical antipsychotics olanzapine and quetiapine are 5-HT_{2C} antagonists which have proven antidepressant action (Nelson & Papakostas, 2009; Stahl et al., 2013). Olanzapine, in combination with fluoxetine, showed a rapid, robust, and sustained antidepressant effect in treatment-resistant depressed patients (Shelton et al., 2005). In contrast to olanzapine, asenapine has an upregulating effect on D₁-like receptors, suggesting that, in addition to theoretic potential for antidepressant effect, it may be associated with a decreased likelihood of producing extrapyramidal side effects (Stoner & Pace, 2012). Aripiprazole, a 5-HT_{2C} partial agonist, when combined with escitalopram, reverses the inhibitory action of escitalopram on DA neurons, presumably through its functional antagonism of 5-HT_{2C} receptors (Chernoloz et al., 2009; Dremencov et al., 2009). These results suggest that atypical antipsychotics could restore potentially reduced DA transmission by SSRIs in forebrain structures.

5.1.3 α_2 -adrenergic Receptors and NET blockade

In addition to common properties, most atypical antipsychotics are heterogeneous in terms of high relative affinities. For example, risperidone has a high affinity for α_2 -adrenergic receptors similar to its affinity for D₂ receptors (Arnt & Skarsfeldt, 1998). This antagonism of α_2 -adrenergic receptors may also contribute to the antidepressant response of atypical antipsychotics in treatment-resistant patients with

MDD. Blockade of the α_2 receptors NE neuron cell bodies and their terminals by atypical antipsychotics may enhance NE transmission by increasing synaptic availability of neurotransmitter at the synapse. Likewise, NE release may be increased directly by α_2 antagonists at the level of NE terminals because of its inhibitory action on α_2 -adrenergic autoreceptors in projection areas (Blier & Szabo, 2005). Like the antidepressant mirtazapine, for example, risperidone may also enhance 5-HT transmission directly through blockade of α_2 -adrenergic receptors on 5-HT terminals (Blier & Blondeau, 2011; Haddjeri et al., 1997). Also similar to mirtazapine, asenapine blocks α_2 -adrenergic autoreceptors on LC neurons acutely, whereas the function of these receptors is restored after long-term asenapine administration (Ghanbari et al., 2009; Oosterhof et al., 2015). Unlike mirtazapine, however, sustained asenapine administration reduces the inhibitory response of iontophoretically applied NE, suggesting that post-synaptic α_2 -adrenoceptors are blocked incompletely by the drug (Oosterhof et al., 2015). Despite the increased firing rate of LC NE neurons after treatment with asenapine, NE tone on α_2 -adrenoceptors is not enhanced by sustained asenapine administration (Oosterhof et al., 2015). Because of these similarities, it is conceivable that asenapine monotherapy would be effective in the treatment of MDD. Similarly, brexpiprazole has been shown to block terminal α_2 -adrenergic heteroreceptors, thereby increasing 5-HT release in the presence of enhanced NE transmission (Oosterhof et al., 2015; Oosterhof et al., 2014). This provides further insight into the neural mechanisms by which α_2 -adrenoceptor antagonists exert antidepressant effects. Moreover, adjunctive brexpiprazole therapy demonstrated clinical efficacy in patients with MDD and inadequate response to

antidepressants (Thase et al., 2015). Furthermore, quetiapine is a potent α_2 -adrenoreceptor antagonist, and its systemic administration has been shown to increase the concentration of extracellular NE in the rat prefrontal cortex and caudate nucleus, thereby enhancing NE transmission (Pira et al., 2004). A synergistic effect on extracellular NE levels has been observed previously upon blockade of NET together with α_2 -adrenoreceptor antagonism (Dennis et al., 1987). N-Desalkylquetiapine (norquetiapine), the active metabolite of quetiapine, exhibits a distinct pharmacological profile from quetiapine, which contributes to its antidepressant effect. In addition to its affinity for several 5-HT receptors, norquetiapine acts as a potent NET blocker with an affinity similar to that of other antidepressants such as nortriptyline, amitriptyline, and duloxetine (Jensen et al., 2008). This feature may help to explain the robust antidepressant action of quetiapine and quetiapine extended release (XR) in bipolar depression (Jensen et al., 2008). Furthermore, norquetiapine indirectly increases dopamine levels in the prefrontal cortex by NET inhibition (Jensen et al., 2008; Möller, 2005). The apparent antidepressant actions of norquetiapine and quetiapine are therefore a possible result of potent NET inhibition. Quetiapine has also been shown to enhance tonic activation of postsynaptic α_2 -adrenergic receptors in the hippocampus (Chernoloz et al., 2012).

A 2015 meta-analysis on the efficacy and tolerability of augmentation agents in treatment-resistant depression concluded that, along with aripiprazole, quetiapine appears to be the most robust evidence-based options for augmentation therapy in treatment-resistant depressed patients (Zhou et al., 2015). Furthermore, quetiapine is

not only efficacious as adjunctive therapy with antidepressants, but also displays clinically significant efficacy in treating unipolar depression as a monotherapy (López-Muñoz & Álamo, 2013).

5.1.4 5-HT_{1A} Receptor Activation

As previously mentioned, prolonged administration of SSRIs produce a desensitization of presynaptic 5-HT_{1A} autoreceptors. However, an approach in which a more rapid desensitization of these autoreceptors is produced is critical to effective treatment of depression. This can presumably be achieved via the combination of agents that block serotonin reuptake with 5-HT_{1A} receptor agonists. This approach will also stimulate postsynaptic 5-HT_{1A} heteroreceptors, further enhancing 5-HT mediated antidepressant efficacy (Dawson & Watson, 2009).

5-HT_{1A} partial agonists, such as buspirone, are known to produce immediate and selective effects at presynaptic 5-HT_{1A} autoreceptors. The addition of such agents to SSRIs has the ability to potentiate extracellular 5-HT concentrations in the rat frontal cortex, an effect that is contingent on SERT blockade (Dawson & Nguyen, 1998). Furthermore, direct agonism of 5-HT_{1A} receptors can lead to a more rapid and robust downregulation and desensitization of 5-HT_{1A} autoreceptors (Stahl et al., 2013). Moreover, buspirone has shown to be equally as effective as bupropion as an augmentation strategy in SSRI-resistant MDD patients (Trivedi et al., 2006). In addition, buspirone produced a rapid antidepressant effect when used with pindolol in a study of 30 depressed patients, providing further evidence that the selective activation of postsynaptic 5-HT_{1A} receptors plays an important role in the antidepressant response

(Blier et al., 1997). Pharmacologically similar to SSRI plus buspirone, the antidepressant, vilazodone, has both SERT inhibiting and 5-HT_{1A} partial agonistic properties, a combination known to enhance therapeutic efficacy of antidepressant compared to an SSRI alone (de Paulis, 2007).

Many atypical antipsychotics, such as aripiprazole and ziprasidone, are potent 5-HT_{1A} agonists, which may explain in part their antidepressant effects when used as augmentation agents in SSRI-resistant patients (Nelson et al., 2014; Papakostas et al., 2015). Prolonged administration of 5-HT_{1A} agonists have been shown to enhance 5-HT neurotransmission in the rat hippocampus (Haddjeri et al., 1998). In the clinic, aripiprazole is deemed to be an effective augmenting agent for the treatment of depression in SSRI-resistant patients based on five positive double-blind studies (Berman et al., 2007, 2009; Fava et al., 2012; Kamijima et al., 2013; Lenze et al., 2015; Marcus et al., 2008).

5.1.5 D_{2/3} Receptor Agonism

MDD is also associated with an increase in binding sensitivity to D_{2/3} receptors and a decrease in dopamine transporter (DAT) activity, likely a compensatory change to impairment of the mesolimbic dopaminergic pathway in patients (Allard & Norlen, 2001; Klimek et al., 2002; Meyer et al., 2001). The dopamine D₃ receptor has a specific distribution in areas of the brain regulating motivation and reward, and has been studied as a potential pharmacological target by which dopaminergic function can be enhanced (Leggio et al., 2008; Mah et al., 2011). These observations justified the development of dopamine D₃ receptor partial agonists to increase DA release from

presynaptic terminals, enhancing DA transmission, and finally, producing a more enhanced antidepressant response in MDD patients. Pramipexole is a dopamine receptor agonist with high specificity for the D₂ receptors; it is a full agonist with a greater affinity for the D₃ receptor than for the D₂ receptor (Mierau et al., 1995). A randomized, double-blind, placebo-controlled trial of pramipexole augmentation provides support for the efficacy of pramipexole as an adjunct to SSRIs in patients with a history of insufficient response to antidepressants (Cusin et al., 2013). In addition, pramipexole monotherapy produces a similar or more statistically consistent improvement in depression than fluoxetine when both groups were compared to placebo (Corrigan et al., 2000). Despite their high affinities for D₃ receptors, some atypical antipsychotics, such as risperidone and olanzapine, fail to achieve sufficient D₃ receptor occupancy to conclude a D₃ receptor-mediated antidepressant effect (Gross & Drescher, 2012).

While antagonism at the 5-HT₂ and D₂ receptors is common to antipsychotics in the class, aripiprazole is the exception. In contrast to these D₂ receptor antagonists, aripiprazole acts as a partial D_{2/3} receptor agonist. In addition, aripiprazole has a high affinity for D₃ receptors and is among the most effective atypical antipsychotics to enhance the therapeutic response of SSRIs in treatment-resistant depressed patients. Under conditions in which DA transmission is enhanced, such as in the case of schizophrenia, high doses of aripiprazole competes for D₂ receptors to decrease DA transmission. On the other hand, where DA transmission is diminished, such as in the

case of depression, low doses of aripiprazole may work to enhance DA transmission (Blier & Blondeau, 2011).

Like aripiprazole, the more recently approved atypical antipsychotic brexpiprazole functions as partial $D_{2/3}$ receptor agonist. Compared to aripiprazole, however, brexpiprazole has double the affinity and approximately 20% the intrinsic activity at the D_2 receptor (Bruijnzeel & Tandon, 2016; Stahl, 2016). This distinct pharmacological feature allows an intermediate level of dopaminergic tone such that it remains below the threshold in which development of positive symptoms induced by excessive dopamine occurs, but high enough to avoid extrapyramidal side effects. Several clinical trials investigating brexpiprazole in the treatment of depression have been completed or initiated. Among them, two multicenter, randomized, double-blind, placebo-controlled trials support the use of brexpiprazole as an effective agent over placebo in treatment-resistant MDD (Thase et al., 2015a; 2015b).

Similarly, cariprazine, a novel drug with partial agonist activity at dopamine $D_{3/2}$ receptors, has been shown to evoke lesser inhibition of DA neurotransmission in the dorsal striatum than in the limbic region in comparison to other antipsychotics, suggesting a lower propensity for extrapyramidal side effects with cariprazine (Kiss et al., 2010; Veselinovic et al., 2013). Moreover, its activity on the dopamine system depends on the *in vivo* functional status of the dopamine system such that $D_{3/2}$ partial agonist properties are predominant under conditions with low DA transmission and, under conditions of high DA transmission, its $D_{3/2}$ receptor agonist efficacy exceeds that of aripiprazole (Kiss et al., 2010). In contrast to aripiprazole, however, cariprazine is a less

potent D₂ receptor agonist, but a more potent D₃ receptor agonist with higher selectivity for D₃ receptors than D₂ receptors (Gyertyán et al., 2011; Kiss et al., 2010; Roman et al., 2013). In the clinic, a double-blind, randomized, placebo-controlled study on the efficacy and safety of cariprazine as adjunctive therapy in MDD concluded that cariprazine produces significantly greater improvement in depressive symptoms compared with placebo (Durgam et al., 2014). In addition, cariprazine monotherapy demonstrated significant improvement across outcomes when compared with placebo in adult patients with acute bipolar I depression (Durgam et al., 2016).

5.1.6 5-HT_{1B/D} Autoreceptors

The 5-HT_{1B/D} receptor is a terminal autoreceptor that, in the presence of synaptic 5-HT, inhibits 5-HT neuron activity. Pharmacological agents that occupy these receptors typically block them, inhibiting negative feedback, thereby enhancing presynaptic 5-HT release (Moret & Briley, 2000). Through this mechanism, a number of atypical antipsychotics with 5-HT_{1B/D} antagonistic properties, such as iloperidone, ziprasidone, and asenapine, could theoretically produce antidepressant effects (Köhler et al., 2015; Pehrson et al., 2012). Vortioxetine possesses a unique multimodal pharmacological profile with the ability to agonize or antagonize several serotonin receptors in addition to its core mechanism of serotonin reuptake inhibition (Santarsieri & Schwartz, 2015). For example, *in vitro* studies indicate that vortioxetine is a 5-HT₃, 5-HT₇, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, and a 5-HT_{1A} receptor agonist (Llorca et al., 2014; Pehrson et al., 2012; Stahl et al., 2013). In the clinic, vortioxetine has shown efficacy in the treatment of MDD in seven short-term, randomized, placebo-

controlled trials in a dose range from 5-20 mg/day (Alvarez et al., 2012; Baldwin et al., 2012; Boulenger et al., 2014; Henigsberg et al., 2012; Jain et al., 2012; Katona et al., 2012; Mahableshwarkar et al., 2013). Moreover, a meta-analysis of both published and unpublished short-term randomized clinical trials concluded that vortioxetine is comparable or favourable in efficacy to other antidepressants (MADRS/HAM-D), and is ranked higher than desvenlafaxine, sertraline, and venlafaxine in tolerability (Llorca et al., 2014). Furthermore, long-term efficacy of vortioxetine has been established in a double-blind, randomized, placebo-controlled study in patients with recurrent MDD (Boulenger et al., 2012). These results support the probability that 5-HT_{1B/D} receptor antagonists may be useful pharmacological tools in the treatment of depressive disorders.

5.1.7 5-HT₇ Receptors

Through potentiation of SERT inhibition, antagonism of the 5-HT₇ receptor by atypical antipsychotics may contribute to their antidepressant action in MDD (Mnie-Filali et al., 2011). When 5-HT binds the 5-HT₇ receptor on GABA interneurons, 5-HT release is decreased. Pharmacological blockade of these receptors would thus increase 5-HT release and produce an antidepressant response. It has been suggested that selective 5-HT₇ receptor antagonists might be of therapeutic benefit in the treatment of depressive symptoms. Several atypical antipsychotics effective in the treatment of major depressive disorder, such as aripiprazole, quetiapine, and olanzapine possess 5-HT₇ antagonistic properties (Köhler et al., 2015; Stahl et al., 2013). Furthermore, the more potent 5-HT₇ receptor antagonist, lurasidone, used in the treatment of bipolar depression, not only

exhibited antidepressant-like properties in both acute and chronic mouse models of depression, but is equally potent to citalopram in behavioral models of depression (Cates et al., 2013). There is also evidence of a synergistic relationship between the SERT and the 5-HT₇ receptor in studies that combined administration of sub-therapeutic doses of an SSRI and the 5-HT₇ receptor antagonist, SB-269970 (Sarkisyan et al., 2010).

In the clinic, treatment with lurasidone is associated with improved MADRS scores in bipolar depression and major depressive disorder presenting with mixed features (Citrome, 2011; Loebel et al., 2014; Loebel et al., 2014; Nakamura et al., 2009; Suppes et al., 2015). Taken together, these findings suggest that 5-HT₇ antagonism could play a role in the antidepressant effect of atypical antipsychotics, and an atypical antipsychotic with high 5-HT₇ receptor affinity can act synergistically with an SSRI to produce a more robust antidepressant response.

In summary, there is a growing body of evidence that supports the use of low doses of atypical antipsychotics in treatment-resistant depression. The neurobiological effects associated with the use of these agents in treatment-resistant depression have been the subjects of in-depth evaluation and it has been demonstrated that they contribute a measurable increase in the availability and transmission of monoamines. This strategy, therefore, should be considered as a valuable pharmacological tool in the treatment of major depressive disorder as a second-line augmentation strategy in treatment-resistant patients, from treatment initiation, or even as a monotherapy.

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