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# Depression and antidepressants: Insights from knockout of dopamine, serotonin or noradrenaline re-uptake transporters

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ABSTRACT

Major depressive disorder (MDD) which is supposed to result from a complex interaction of genetic and epigenetic, environmental and developmental factors is one of the most common debilitating public health problems. The molecular mechanisms underlying this disease are still largely unclear. Identifying common pathways for diverse antidepressants (ADs) as well as new drug targets and thereby developing more effective treatments are primary goals of research in this field.

Major targets of ADs are the serotonin transporter (SERT), the noradrenaline transporter (NAT) and also the dopamine transporter (DAT) located in the plasma membrane of corresponding neurons. These monoamine transporters (MATs) are important regulators of the extracellular neurotransmitter concentration. Among the clinically important ADs are tricyclic ADs (e.g. imipramine), selective serotonin re-uptake inhibitors (SSRIs, e.g. fluoxetine), selective noradrenaline (NA) re-uptake inhibitors (SNRIs, e.g. reboxetine) and NAT/DAT inhibitors like bupropion.

This review is focussing on brain changes in monoamine neurotransmitter systems, downstream targets of monoaminergic neurotransmission as well as of behaviours of mice with a conventional knockout (KO) of either the SERT, DAT or NAT.

MAT knockout induces changes in behaviour and brain neurochemistry. Although at least NATKO and SERTKO mice were expected to show a phenotype like AD-treated wild-type mice, this holds true only for the NATKO mice whereas SERTKO mice show an anxiety-like phenotype. Chronic social or restraint stress-induced depression-like behaviour and concomitant changes in brain neurotrophins are prevented by pharmacologically diverse ADs and by NATKO. Thus, NATKO mice are an interesting tool to investigate the mechanisms beyond monoamines responsible for depression as well as for AD actions.



**Contents**



*Abbreviations:* ADs, antidepressants; ADHD, attention deficit hyperactivity disorder; BDNF, brain-derived neurotrophic factor; CPP, conditional place preference; DA, dopamine; DAT, dopamine transporter; DATKO, DAT knockout; EPM, elevated plus maze; FST, forced swim test; GR, glucocorticoid receptor; LC, locus coeruleus; MA, monoamine; MAO, monoamine oxidase; MAT, monoamine transporter; MDD, major depressive disorder; NA, noradrenaline; NAT, noradrenaline transporter; NATKO, NAT knockout; SERT, serotonin transporter; SERTKO, SERT knockout; SNRIs, selective noradrenaline re-uptake inhibitors; SNSRIs, selective noradrenaline and serotonin re-uptake inhibitors; SSRIs, selective serotonin re-uptake inhibitors; TH, tyrosine hydroxylase; TST, tail suspension test.

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## 1. Introduction

Major depressive disorder (MDD) is one of the most common debilitating public health problems with a lifetime prevalence of about 15–20% (Berton & Nestler, 2006). According to the World Health Organization (WHO), MDD will be the most prevalent cause of illness-induced disability by the year 2030. MDD is supposed to result from a complex interaction of genetic and epigenetic, environmental and developmental factors. It is defined by episodes of depressed mood lasting for more than 2 weeks accompanied by additional symptoms, including e.g. hopelessness, worthlessness, disturbed appetite with weight gain or loss, disturbed sleep rhythm (insomnia or hypersomnia), reduced concentration, psychomotor agitation or retardation and recurrent suicidal thoughts (Mill & Petronis, 2007; Diagnostic and Statistical Manual of Mental Disorders, DSM-IV). However, the molecular mechanisms underlying this disease are still largely unclear. Identifying new drug targets and thereby developing more effective treatments are primary goals of research in that field. To achieve these goals a greater understanding of the aetiology of MDD is needed, which involves identifying the risk and resilience factors involved and the mechanisms by which these effects are mediated. To answer the question why some individuals develop depressive symptoms while others remain relatively unscathed by affective symptoms and to address the multifactorial causes probably involved, several factors have been supposed to contribute, including susceptibility genes, neurochemical imbalances, brain network dysfunction, false information processing, negative cognitions, and social or environmental sources of vulnerability as well as stressors. This review focuses on animal models used to study the aetiology of depression and the actions of antidepressants (ADs), in particular on mice in which a key target for important ADs, namely the neuronal transporter responsible for the re-uptake of dopamine, serotonin or noradrenaline has been knocked out.

## 2. Depression and antidepressants

Despite over 50 years of research in the field of major depressive disorder (MDD) the precise neurobiological processes and molecular mechanisms causing this heterogenous disease are still poorly understood. Although the knowledge of the aetiology and pathophysiology of MDD is limited, there are several effective treatments for depressed patients like psychotherapy, electroconvulsive therapy, light therapy and pharmacotherapy with ADs. Almost all clinically used ADs were developed after the by chance finding in the 1950s that the tricyclic compound imipramine and the antituberculosis drug iproniazid were effective in depression, and after it had become clear that both drugs cause elevation of extracellular monoamine levels by either blocking monoamine oxidase (MAO) (like iproniazide) or by inhibiting the neuronal serotonin and/or noradrenaline transporter (like imipramine and its active metabolite desipramine). This has led to the hypothesis of depression (affective disorders) due to CNS "catecholamine deficiency" (Schildkraut, 1965) and, after introduction into therapy of selective serotonin re-uptake inhibitors (SSRIs such as fluoxetine), of "monoamine deficiency" (Coppen, 1967).

Based on the acute mechanism of action of these drugs there is now compelling evidence that monoaminergic neurotransmission in the brain is disturbed in depressed patients. However, it is largely unknown why it takes between one and six weeks for antidepressant drugs to exert their clinical effects. The delayed onset of antidepressant action has been explained by the requirement of neuronal adaptive mechanisms, for example adaptation of presynaptic receptors. The latency in the onset of action of antidepressants is a problem in the therapy of MDD as depressive states are often associated with a high risk of committing suicide. Furthermore, only about 50% of patients with MDD show full remission while receiving currently available ADs, including trials on several medications with or without concurrent psychotherapy, but up to 80% show partial responses. Based on these facts, there is still a large need for more effective pharmacological treatments for MDD.

## 3. Animal models of depression

Diagnostic tools to decipher depressive states are almost exclusively based on observation of behaviour and interpersonal relations as well as on verbal reported feelings of the patients. Thus, the development of a valid animal model of depression seems to be difficult as typical symptoms of human depression like thoughts of death or suicide cannot be mimicked or evaluated in animals. Therefore, animal models of psychiatric diseases such as depression follow reductionistic criteria. In general, an ideal animal model should fulfil three criteria: face validity or isomorphism, i.e. the animal model reproduces symptoms of the disease observed in humans; predictive validity (pharmacological correlation), i.e. therapeutic drugs that are used in humans can be detected in the animal model; construct validity, i.e. the symptoms produced in the animal model are based on the same underlying neurobiological mechanism like in humans. At present, construct validity in animal models of depressive states is only of theoretic value as the exact pathophysiological processes of depression still have to be elucidated. Therefore, an animal model of depression should aim at having the same causative conditions, symptom profiles, and treatment responses seen in the human disease.

There are several kinds of animal models of depression (Willner & Mitchell, 2002; Duman, 2010). Diathesis models like the genetic model of Flinders Sensitive Line (FSL) rats (Overstreet et al., 1988) or the lesion model of olfactory bulbectomy (Kelly et al., 1997) include paradigms that involve a determined predisposition for depressive states. In stress models like restraint stress, learned helplessness, unpredictable chronic mild stress, resident–intruder models, maternal separation or adult isolation, external stress stimuli or natural social stressors are used to produce depressive behaviour. From the causes of developing depressive states in humans chronic stress is thought to be a key factor (de Kloet et al., 2005; Bale, 2006). Especially loss or fear of loss of a social status plays a major role in inducing depression. Therefore, social stress is supposed to be a very naturalistic animal model of depression that was shown to work in different species (e.g. rodents and tree shrews) (Kudryavtseva & Avgustinovich, 1998; Fuchs & Flügge, 2002). Thus, animal models of depression are important experimental models of translational medicine helping to develop new antidepressants and to unravel neurobiological mechanisms of depressive states. However, it must be taken into account that there are also species-specific differences in developing depressive-like states that can hardly be controlled for. In addition, genetic factors that might cause a predisposition for the disease have to be considered.

## 4. Importance of monoamine transporters

Monoamine (MA) transporters (MATs) including the noradrenaline transporter (NAT), the serotonin transporter (SERT), and the dopamine transporter (DAT) are located in the plasma membrane of the presynaptic nerve terminals from which the monoamine neurotransmitters are released. All three MATs belong to the SLC6 gene family of $Na^+$- and $Cl^-$-dependent neurotransmitter transporters (Masson et al., 1999), and the NAT was the first cloned MAT (Pacholczyk et al., 1991). The amino acid identity of the hNAT and hDAT is 66% (Giros et al., 1992), and that of hNAT and hSERT 48% (Ramamoorthy et al., 1993).

MATs in the brain are localized at the presynaptic membrane of monoaminergic neurones where they modulate the fate and concentration and curtail the lifetime of the released monoamine. All three MATs are targets of psychostimulant drugs/substances of abuse/