Transcriptomic changes following chronic administration of selective serotonin reuptake inhibitors: a review of animal studies

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The review focuses on transcriptomic changes following treatment with serotonin reuptake inhibitor (SSRI) antidepressants. We aimed to overview results of the most established methods for the investigation of the gene expression alterations including northern blotting, in situ hybridization, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), microarray and RNAseq in various brain regions and after chronic treatment protocols. In spite of some measurable changes in serotonin system mRNA expression, serotonin transporter levels remained mostly unaltered following various treatment protocols. In contrast, tryptophan hydroxylase 2 appeared to be downregulated in serotonergic nuclei, and upregulated in the midbrain regions. Alterations in serotonin receptors lack clear conclusions and changes probably reflect animal strain/substance related- and brain region dependent effects. Brain derived neurotrophic factor was upregulated following many, but not all chronic treatment regimens. GABA and glutamate genes also showed heterogeneous changes, with a surprising NMDA receptor downregulation in areas including the striatum and amygdala, known to be involved in depressive states and stress reactions. The review of the above studies suggests alterations in multiple processes, reflecting the heterogeneity of the action depending on brain area and type of SSRI, and raises the possibility of a novel grouping of antidepressant medications based on their chronic molecular profile rather than on their initial actions.

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INTRODUCTION

Antidepressants (ADs) are on the market since the 1950s and in wide use since the 1960s for the treatment of depression. Following tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors as the first antidepressants, selective serotonin reuptake inhibitors (SSRIs) have been introduced towards the end of the 1980s in an attempt to employ antidepressants with more selective action mechanisms to limit burdensome side effects, but retaining therapeutic efficacy. Subsequently several other groups of antidepressants were introduced based on the monoamine theory of depression aimed at selectively targeting one or more of such systems, including for example serotonin–norepinephrine reuptake inhibitors (SN-

RIs) and norepinephrine reuptake inhibitors (NRIs). Nevertheless, SSRIs remain the most prescribed medications for the treatment of major depressive disorders (Bobo et al. 2019).

Major depressive disorder (MDD) is a complex and heterogeneous disorder both in its manifestation and in its neurobiology, and accordingly, the pathogenesis can't be easily determined. Genetic, environmental and biological factors together play a role in the development of depression (see for review (Gonda et al. 2019).

The acute mechanism of action of the SSRIs constitutes the blockade of the serotonin transporter directly elevating serotonin concentration in the synaptic cleft which, together with a similar blockade of noradrenaline reuptake, was thought to be the primary mechanism responsible for antidepressant effects ever since the observation that tricyclic antidepressants block these transporters (Coppen 1967; Schildkraut 1965). While this theory is not up to date, the monoaminergic systems remained in the focus of antidepressant pharmacotherapy, and a more complex mechanism of how monoaminergic antidepressants influence neurotransmitter function have been described.

Functional effects after the administration of SSRIs are diverse and biphasic, also reflected in the temporal development of both side effects and therapeutic effects in the course of treatment. The molecular changes underlying these functional effects can be measured by gene expression analysis (Volle et al. 2018). Four common methodical approaches are used to identify alterations of gene expression including northern blot, in situ hybdridization (ISH), quantitative reverse transcription polymerase chain reaction (qRT-PCR), RNA microarrays and RNA sequencing (RNA-Seq).

In this review, after a short overview on current methods in gene expression analysis we summarize animal studies assessing transcriptomic changes following chronic SSRI administration.

METHODS FOR GENE EXPRESSION ANALYSIS

Northern blot

Northern blotting is one of the oldest methods in analyzing gene expression. Electrophoresis is used to separate the RNAs of the sample by size with a very low throughput, usually after separation of those with a polyA tail (mRNAs) from the other RNA content (Kevil et al. 1997). Then, the mRNA containing gel has to be transferred onto a nylon membrane with the help of the electrophoretic blotter. Under UV light, the RNAs of different sizes will be covalently bound to this membrane. Afterwards, oligomers, usually of complementary DNA sequences (transcribed from RNA with reverse transcriptase) will be used for hybridization to the RNA of interest. After washing out, the hybridization, which is from the labelled oligonucleotides sequences or probes being complementary to the target transcript, will be detected by X-Ray. In this way, northern blot is useful to determine the RNA transcript size and also its sequence through the probes (VanGuilderet al. 2008). In northern blotting, a larger amount of RNA compared to qRT-PCR is required and is much less sensitive with respect to mRNA expression compared to qRT-PCR (Fehr et al. 2000).

In situ hybridization

In situ hybridization is a method using labelled DNA or RNA probes which can attach selectively to the nucleic acid of interest even in a cellular environment, thus, for example in a brain sample. Advantage of the method is the information about the specific cellular localization of the transcript and the fine (or even manual) evaluation of the signals that can provide additional details about the expression patterns (see e.g. Kirilly et al. 2008). The method is, nevertheless, unfeasible for transcriptional analysis on a larger scale.

qRT-PCR

Real-Time Quantitative Reverse Transcription PCR (polymerase chain reaction) is a method based on PCR. First RNA will be converted to cDNA with the use of reverse transcriptase. After this step the exponential amplification of cDNA takes place with PCR. A specific primer, or probe, will be attached on the template cDNA strand in order to start the replication trough polymerase enzyme. A probe is a modified primer with for example a fluorescent molecule (Heid et al. 1996), allowing relative quantification of specific genes, through sensors at a certain wavelength, during each PCR cycle (Cooper 2000).

Thus with this method, it is possible to quantify multiple genes with a high throughput single reaction. Trancriptome-wide gene expression analysis is however difficult (in case of some animal species), or even absolutely unfeasible (e.g. in humans) to realize (Teo et al. 2016).

Microarray

In differential expression analysis RNA is purified, extracted and is transcribed to cDNA. After transcription, cDNA samples are labeled with different fluorescent colors and applied on the microarray chip. The microarray chip is already printed with short, complementary probes of genes of interests and, thus, the cDNAs hybridize with these complementary sequences on the chip. Gene expression can be identified and compared through the different fluorescent intensity on the chip (Trevinoet al. 2007). Microarrays has been the technology of choice for large-scale studies of gene expression, since it is possible to measure the gene expression of thousands of known or putative transcripts or even genome-wide transcription simultaneously (Teo et al. 2016).

RNA-seq

RNA sequencing is the newest method for gene expression analysis and uses the next generation sequencing (NGS) platform. The main advantage of this method is the massively parallel sequencing and thus the possibility of detailed and transcriptome-wide analysis. There are several methods to perform RNA-seq that are different in their sequencing and amplification steps. From RNA, cDNA will be transcribed and will be cut randomly into more or less equally sized fragments. Fragments are ligated with sequence adaptors and amplified. For example, in case of Illumina platforms, amplification is made through bridge amplification on so-called flow cells, which create clusters of the same DNA fragments on the flow cell (www.illumina.com). After amplification the fragments are sequenced to produce reads. Again, in Illumina platforms this is based on the sequential addition of labelled bases that upon integration in the synthesis of the strand emit light, which is detected by a camera after each step. Thus, millions of cDNA copies are sequenced by synthesis in parallel. The number of cycles determines the read length. Afterwards in silico analysis is performed by various tools, the first step in the analysis pipeline is to map reads to a known reference genome. Which software exactly has to be used to map and align the reads depends on the sequencing protocol (sequencing data type). In RNA-seq for example the tool Tophat is used for the alignment (D'Antonio et al. 2015; Al Seesi et al. 2016). The next step depends on the scientific question. With different tools it is possible for example to identify chimeric transcripts, splicing junctions or alternate splicing in addition to differential gene expression analysis. The advantage of RNA-seq is that the whole transcriptome can be analyzed and discovery of novel transcripts is also possible (Teo et al. 2016).

TRANSCRIPTOMIC CHANGES FOLLOWING SSRI ADMINISTRATION

There have been several studies focusing on transcriptomic changes following SSRI administration. Since antidepressants are taken long-term and not acute for their therapeutic effects to manifest, an investigation with a single dose may not reflect the long-term gene expression changes. Therefore, in our review we confined our research on transcriptomic changes after chronic in vivo treatments in animals (rats, if not stated otherwise). Genetically modified animals were excluded (except one study for a particular serotonin receptor) as they could not represent the whole spectrum of targets.

Effects of chronic SSRI administration on expression of genes involved serotonin synthesis and serotonin transport

The prime acute target of SSRIs is the serotonin transporter (5-HTT). Nevertheless, 5-HTT mRNA levels were unaffected in the hippocampus after four weeks of citalopram (CIT) (10mg/kg) and fluoxetine (FLX) (10mg/kg) treatments (Cardamone et al. 2014). The same result was demonstrated after 12 d FLX (10mg/kg) treatment in the dorsal raphe (DRN) (Volle et al. 2018), after 21d treatment with FLX (3mg/kg) (Neumaier et al. 1996) and 4 week-long CIT (30mg/kg) treatment in the same region (Abumaria et al. 2007). Another study reported different results in the midbrain and brainstem after 2, 4 and 8 week-long treatments with FLX (7,5mg/kg), showing decreased 5-HTT expression (Shishkina, Kalinina, and Dygalo 2007).

Other studies focused on tryptophan hydroxylase 2 (TPH2) expression, which is the rate limiting enzyme in serotonin synthesis. A recent human study reported significantly decreased TPH2 mRNA expression in MDD patients who also attempted suicide (Zhang et al. 2015). The authors linked decreased TPH2 expression with DNA methylation of the TPH2 promoter region in MDD patients. In rat studies, FLX (7,5mg/kg) administration normalized the mRNA expression of TPH2 in the midbrain of stressed rodents (Shishkina et al. 2007). In the rat studies, following four-week CIT (30mg/kg) treatment downregulation

Table 1 Expression changes in serotonin transporter and synthesis

Medication	Region	Species	Method	Time	Daily dose	Result	Reference
FLX	HC	Wistar rat	PCR	28 d	10mg/kg	5-HTT Ø	(Cardamone et al. 2014)
CIT	HC	Wistar rat	PCR	28 d	10mg/kg	5-HTT Ø	(Cardamone et al. 2014)
FLX	DR	Sprague Dawley rat	ISH	12 d	10mg/kg	5-HTT Ø	(Volle et al. 2018)
CIT	DRN	Wistar rat	PCR	28 d	30mg/kg	5-HTT Ø	(Abumaria et al. 2007)
FLX	DRN	Sprague Dawley rat	ISH	21 d	3mg/kg	5-HTT Ø	(Neumaier et al. 1996)
FLX	Midbrain	Wistar rat	PCR	14, 28 and 56 d	7,5mg/kg	5-HTT ↓	(Shishkina et al. 2007)
FLX	Brainstem	Wistar rat	PCR	14, 28 and 56 d	7,5mg/kg	5-HTT ↓	(Shishkina et al. 2007)
CIT	DRN	Wistar rat	PCR	28 d	30mg/kg	TPH2 ↓	(Abumaria et al. 2007)
FLX	Midbrain	Wistar rat	PCR	4 and 8 weeks	7,5mg/kg	TPH2 ↑	(Shishkina et al. 2007)
CIT	DRN	Wistar rat	PCR	28 d	30mg/kg	TPH2 ↓	(Abumaria et al. 2007)
FLX	Brainstem	Wistar rat	PCR	14 d	25mg/kg	TPH2 ↓	(Dygalo et al. 2006)

HC: Hippocampus; DR: Dorsal raphe; DRN: Dorsal raphe nucleus; Ø: no changes observed; ↑: upregulation observed; ↓: downregulation observed

of TPH2 in the DRN was reported (Abumaria et al. 2007) and decreased expression in the brainstem was also observed in case of a two week long FLX (25mg/kg) treatment (Dygalo et al. 2006). Based on the above, changes in TPH2 expression following chronic SSRI treatment appear to be heterogeneous and no clear conclusions can be drawn. For detailed results see Table 1.

Effect of chronic SSRI administration on expression of serotonin receptor genes

While mainly the 5HT1A receptor has been emphasized in the action of SSRIs, the serotonin receptor family includes 14 receptors (Segi-Nishida 2017), some of which showed expression changes following chronic SSRI administration. During SSRI treatment the negative feedback mechanism limiting the serotonin release is inactivated due to the desensitization of the raphe 5-HT1A (and partially the 5-HT1B) autoreceptors that changes the discharge of serotonergic neurons (Hamon and Blier 2013). This process is assumed to take several weeks. Cardamone et al. (2014) reported no change in 5-HT1A expression after a four week long FLX treatment in the HC of rats while 5HT1A receptor upregulation was observed in the same time period and region following CIT (10mg/kg) treatment. We have to note that in this study rats underwent kindling to investigate kindling epileptogenesis and the effects of ADs in this process, which might have influenced mRNA expression (Cardamone et al. 2014).

Surprisingly, no expression changes were detected in the raphe nuclei after FLX (10mg/kg) for 12 days (Volle et al. 2018), while 5-HT1A mRNA was downregulated after 28 day-long treatment with CIT (30mg/kg) (Abumaria et al. 2007). Thus, studies show contradictory results on 5HT1A expression both in the HC and DRN. It is possible that different medications, treatment protocols, strains, and methodologies used to identify gene expression are responsible for these contradictory findings. Interestingly, desensitized 5HT1A receptors in the DRN, without a change in the receptor levels after FLX (Le Poul et al. 1995) and sertraline (SER) (Rossi et al. 2008) treatment, were observed in healthy rodents (Le Poul et al. 1995; Rossi et al. 2008).

The serotonin 1B receptor (5-HT1B) is located mainly presynaptically locally regulating 5-HT release [for review see (Sari 2004)]. It is possibly implicated in the pathophysiology of MDD. For example, a combination of a 5HT1B antagonist and a SSRI showed a rapid antidepressant effect (Sari 2004). 5-HT1B mRNA expression of rats in DRN was downregulated following 21 days of FLX (3mg/kg) treatment while no changes were observed in the raphe nuclei after 12 days of FLX (10mg/kg) treatment (Neumaier et al. 1996; Volle et al. 2018). The experiment from (Neumaier et al. 1996) also reported no significant 5-HT1B expression changes in the frontal cortex, striatum or HC. Another research team investigating this receptor in rats found decreased levels of 5-HT1B mRNA in the DRN with FLX (5mg/kg) and SER (10mg/kg) after eight week-long administrations,

Table 2 Expression changes in the serotonin transporter and its receptors

Medication	Region	Species	Method	Time	Daily dose	Result	Reference
FLX	HC	Wistar rat	PCR	28 d	10mg/kg	5HT1A Ø	(Cardamone et al. 2014)
CIT	HC	Wistar rat	PCR	28 d	10mg/kg	5HT1A ↑	(Cardamone et al. 2014)
FLX	Raphe nuclei	Sprague Dawley rat	ISH	12 d	10mg/kg	5HT1A Ø	(Volle et al. 2018)
CIT	DRN	Wistar rat	PCR	28 d	30mg/kg	5HT1A ↓	(Abumaria et al. 2007)
FLX	Raphe nuclei	Sprague Dawley rat	ISH	12 d	10mg/kg	5HT1B Ø	(Volle et al. 2018)
FLX	DRN	Sprague Dawley rat	ISH	21 d	3mg/kg	5HT1B ↓	(Neumaier et al. 1996)
FLX	DRN	Sprague Dawley rat	ISH	56 d	5mg/kg	5HT1B ↓	(Anthony et al. 2000)
SER	DRN	Sprague Dawley rat	ISH	56 d	10mg/kg	5HT1B ↓	(Anthony et al. 2000)
PXT	DRN	Sprague Dawley rat	ISH	56 d	5mg/kg	5HT1B Ø	(Anthony et al. 2000)
FLX	P/FC	Sprague Dawley rat	PCR	21 d	10mg/kg	5HT2C ↓	(Barbon et al. 2011)
FLX	HC	Sprague Dawley rat	PCR	21 d	10mg/kg	5HT2C ↑	(Barbon et al. 2011)

DR: Dorsal raphe; HC: Hippocampus; DRN: Dorsal raphe nucleus; P/FC: Prefrontal cortex; ISH: In situ hybridization; Ø: no changes observed; ↑: upregulation observed; ↓: downregulation observed

while paroxetine (PXT) (5mg/kg) treatment for 56 days didn't contribute to any significant decrease in 5-HT1B expression in this region. All three SSRIs failed to alter 5-HT1B expression in the HC (Anthony et al. 2000).

The serotonin 2C receptor (5-HT2C) has been implicated as a potential target of therapeutic efforts for various psychiatric disorders (Higgins and Fletcher 2003). Elevated protein levels of 5-HT2C in suicide victims was demonstrated in the prefrontal and frontal cortices when compared to controls (Pandey et al. 2006). MRNA levels were postmortem increased in patients with schizophrenia and bipolar disorder (Castensson et al. 2003; Iwamoto and Kato 2003). In a rat experiment using FLX (10 mg/kg) administration, 5-HT2C showed a downregulation in the prefrontal cortex (P/FC) and elevated mRNA levels were detected in the HC (Barbon et al. 2011).

A (partial) agonism at the serotonin 4 receptors (5HT4) showed rapid effects on depression-related behaviors and on hippocampal neurogenesis suggesting a possible role in MDD (Mendez-David et al. 2014; Vidal et al. 2014). Since transcriptomic changes are lacking in the literature, we discuss here, as an exception a study with transgenic mice. This experiment revealed that chronic treatment in transgenic mice with FLX elevated 5HT4 receptor expression levels in cortical neurons (Schmidt et al. 2012). P11 is a protein product of the S100a10 gene and has been involved in the mediation of antidepressant responses and depression-like states (Svenningsson 2006). Cortical neurons express p11 and 5HT4 receptors and may have behavioral effects in concert with SSRIs [we recommend reading (Schmidt et al. 2012) for further information about the connection between p11 and 5-HT4].

Besides the ones described above, there are other serotonin receptors with possible roles in depression and antidepressant pharmacotherapy that lack transcriptomic data following SSRI treatments, which is not to say that they couldn't be of etiological or therapeutic importance. Some papers, for example, mention the 5HT6 and 5HT7 receptors as useful targets in the treatment of affective disorders (Carr et al. 2011; Nikiforuk 2015). For an overview of the studies discussed above see Table 2.

Effect of chronic SSRI treatment on expression of neuroplasticity factors

Brain-derived neurotrophic factor (BDNF) is widely implicated both in the etiopathology of depression and in the mechanism of its treatment. BDNF stimulates neuroplasticity during development and also in adulthood (Huang and Reichardt 2001; McAllister et al. 1999). Deficits in neuroplasticity factors can lead to depression (Fossati et al. 2004). Decreased BDNF levels may be a factor for depression, and in a meta-analysis decreased serum BDNF was suggested to be a relevant biomarker in MDD patients (Polyakova et al. 2015). Several studies showed an upregulation while others showed no effect on BDNF levels with different SSRIs [for a review see (Duman and Monteggia 2006)].

Table 3 Expression changes of neuroplasticity factors

Medication	Region	Species	Method	Time	Daily dose	Result	Reference
FLX	HC	Sprague Dawley rat	ISH	21 d	10mg/kg	BDNF Ø	(Larsen et al. 2008)
FLX	HC	Wistar rats	PCR	14 d	5mg/kg	BDNF Ø	(Rogóż et al. 2017)
FLX	FC	Wistar rats	PCR	14 d	5mg/kg	BDNF ↑	(Rogóż et al. 2017)
ESCIT	HC	Wistar rats	PCR	14 d	10mg/kg	BDNF ↑	(Rogóż et al. 2017)
ESCIT	FC	Wistar rats	PCR	14 d	10mg/kg	BDNF Ø	(Rogóż et al. 2017)
FLX	HC	Sprague Dawley rat	PCR	21 d	10 mg/kg	BDNF ↑	(Musazzi et al. 2009)
FLX	P/FC	Sprague Dawley rat	PCR	21 d	10 mg/kg	BDNF ↑	(Musazzi et al. 2009)
SER	FC	Sprague Dawley rat	Northern blot	21 d	10 mg/kg	BDNF ↑	(Nibuya et al. 1995)
SER	HC	Sprague Dawley rat	Northern blot	21 d	10 mg/kg	BDNF ↑	(Nibuya et al. 1995)
FLX	HC	Sprague Dawley rat	ISH	21 d	11 mg/kg	BDNF Ø	(Hanson, Nemeroff, and Owens 2011)
SER	FC	Sprague Dawley rat	Northern blot	21 d	10 mg/kg	trkB ↑	(Nibuya et al. 1995)
SER	HC	Sprague Dawley rat	Northern blot	21 d	10 mg/kg	trkB ↑	(Nibuya et al. 1995)

HC: Hippocampus; P/FC: Prefrontal cortex; FC: Frontal cortex; ISH: In situ hybridization; Ø: no changes observed; ↑: upregulation observed; ↓: downregulation observed

Considering findings from studies focusing on the effect of chronic SSRI treatment on BDNF expression, FLX failed to alter BDNF levels in a 3-week long chronic treatment in rats in doses of 10 and 11 mg/kg (Hanson et al. 2011; Larsen et al. 2008), but another study showed elevations with FLX (10mg/kg) treatment following a similar treatment protocol in the HC and P/FC and after a one-week washout period the expression level was still significantly higher than basal levels (Musazzi et al. 2009). At the same time, the lower dose of 5 mg/kg in rats administered for 2 weeks induced elevated BDNF expression in the frontal cortex (FC), but not in the HC (Rogóż et al. 2017). The same study examined the effects in the same time period of escitalopram (ESCIT) (10mg/kg) and demonstrated an upregulation in the HC but no changes in the FC (Rogóż et al, 2017). Another study showed an upregulation following 3-week FLX (10mg/kg) treatment (Musazzi et al. 2009). SER, after treatment for 3 weeks with a 10 mg/kg dose in rats, increased mRNA levels of both BDNF and its receptor trkB, in the HC and FC (Nibuya, Morinobu, and Duman 1995). See Table 3 for a summary of the reviewed studies.

Effects of chronic SSRI administration on the expression of genes related to GABA neurotransmission

Dysfunctions of the GABAergic system are proposed to be associated with mood disorders. The GABAergic hypothesis by Emrich (Emrich et al. 1980) proposes a lack of GABA in the brain as a potential contributing factor in the background of mood disorders suggesting that elevated levels in the brain might be of therapeutic relevance in affective symptomatology. We only found one study reporting on mRNA expression of glutamic acid decarboxylase (GAD), the enzyme involved in GABA synthesis, which fulfilled our search criteria. SER in rats with a dose of 10 mg/kg downregulated the expression of GAD in the P/FC, nucleus accumbens (NAcc), olfactory tubercle (OT) and the thalamic reticular nucleus (TRN) (Giardino et al. 1996), suggesting decreased GABA synthesis in these regions following treatment. This result, however, is contradictory because in depressed humans GABA deficits normalized after SSRI intake (Sanacora et al. 2002) and it also opposes the original hypothesis. We didn't find any further transcriptomic studies that could confirm or debate these findings, suggesting that studies would be needed to deepen our understanding concerning the involvement of GABA in mood disorders and their treatment. See Table 4 for an overview of the discussed result.

Effect of chronic SSRI administration on the expression of genes related to the glutamate system

Glutamate is rising as a prime target of interest in the treatment of several psychiatric disorders including major depression, especially considering the approval

Table 4 Expression changes related to the neurotransmitter GABA and glutamate

Medication	Region	Species	Method	Time	Daily dose	Result	Reference
SER	P/FC	Sprague Dawley rat	ISH	28 d	10 mg/kg	GAD ↓	(Giardino et al. 1996)
SER	NAcc	Sprague Dawley rat	ISH	28 d	10 mg/kg	GAD ↓	(Giardino et al. 1996)
SER	OT	Sprague Dawley rat	ISH	28 d	10 mg/kg	GAD ↓	(Giardino et al. 1996)
SER	TRN	Sprague Dawley rat	ISH	28 d	10 mg/kg	GAD ↓	(Giardino et al. 1996)
CIT	HC	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR1 Ø	(Boyer et al. 1998)
CIT	HC	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR2A-C Ø	(Boyer et al. 1998)
CIT	Amygdala	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR1 ↓	(Boyer et al. 1998)
CIT	Amygdala	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR2A-B ↓	(Boyer et al. 1998)
CIT	Amygdala	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR2C Ø	(Boyer et al. 1998)
CIT	Thalamus	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR1 ↓	(Boyer et al. 1998)
CIT	Thalamus	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR2A ↓	(Boyer et al. 1998)
CIT	Striatum	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR1 ↓	(Boyer et al. 1998)
CIT	Striatum	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR2A ↓	(Boyer et al. 1998)
CIT	Striatum	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR2B Ø	(Boyer et al. 1998)
CIT	Cerebellum	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR1 ↓	(Boyer et al. 1998)
CIT	Cerebellum	NIH-Swiss mice	ISH	16 d	20 mg/kg	NR2A-C Ø	(Boyer et al. 1998)

P/FC: Prefrontal cortex; NAcc: Nucleus accumbens; HC: Hippocampus; OT: Olfactory tubercle; TRN: Thalamic reticular nucleus; ISH: In situ hybridization; Ø: no changes observed; ↑: upregulation observed; ↓: downregulation observed

of esketamine as a treatment in treatment resistant depression (www.jnj.com, accessed on the 28th of February, 2019). In contrast to the selective serotonin and noradrenalin reuptake blocker venlafaxine, which upregulated NR2A and NR2B subunits of NMDA glutamate receptors after chronic treatment in the FC (Tamási et al. 2014), CIT (20mg/kg) for 16 days downregulated the mRNA expression of almost all NMDA-R subunits in many regions with the exception of the HC in mice, where its levels remained unchanged (Boyer et al., 1998). In detail, in the amygdala NR1 and NR2A-B subunits were downregulated, whereas NR2C showed no change. NR1 and NR2A subunits showed downregulation in thalamus. Investigations in the striatum reported downregulation of NR1 and NR2A subunits but no changes in NR2B. Furthermore, in the cerebellum NR1 was downregulated and NR2A-C showed no significant alterations. In summary, surprisingly, no upregulations of NMDA receptor subunits could have been observed in any of the relevant regions following chronic SSRI treatment (Boyer, Skolnick, and Fossom 1998). All this suggests that upregulation of glutamatergic genes is not the main mechanism through which SSRIs exert their antidepressant properties. See Table 4 for detailed results.

CONCLUSIONS

Transcriptomic changes after chronic treatment could be orientating in uncovering the hidden mechanism of action of SSRI antidepressants. The current studies, however, rather demonstrate just how broad the spectrum of molecular mechanism of chronic SSRI treatments may be, in contrast to their similar initial effects. In the serotonergic system, 5-HTT expression showed mostly no change, while TPH2 mRNA was downregulated in some brain regions including the DRN. Serotonin receptor gene expression was variable. Chronic CIT treatment downregulated 5-HT1A receptors, which corresponds to the desensitization of the autoregulatory feedback mechanism, but FLX and SER downregulated 5-HT1B, with the former lacking effects at 5-HT1A in the DRN. FLX and CIT seemed to complement each other's effect in the HC and FC, with FLX more reliably inducing BDNF expression elevations in the FC and CIT in the HC at least in the discussed transcriptomic studies. Only SER was able to induce upregulations of both BDNF and its receptor in the two regions. With GAD and NMDA receptor expressions unchanged or rather downregulated, GABAergic and glutamatergic mechanisms also seem to be contradictory to the many

theories involving these neurotransmitter systems in depression. While we have to mention among the many limitations that the reviewed studies employed different rat strains, and that mRNA levels not necessarily represent protein levels, these results point to the enormous heterogeneity of action mechanisms behind the seemingly "homogeneous" class of SSRI ADs. In addition, the results of this review also underline the need for the development of novel ADs with more reliable clarity in their actions on a molecular level and raises the possibility of a novel grouping of antidepressants based rather on their chronic molecular changes, than on their initial effects.

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Krónikus szelektív szerotoninvisszavétel-gátló kezelés hatására bekövetkező transzkripciós változások: az állatkísérletek áttekintése

A közlemény a szelektív szerotoninvisszavétel-gátló (SSRI) antidepresszívumok hatására bekövetkező transzkriptomikai változásokat tekinti át. Célunk az volt, hogy összefoglaljuk a különböző agyterületeken krónikus kezelések hatására bekövetkező, a génexpressziós változások vizsgálatának leggyakrabban használt módszereivel – így Northern blottal, in situ hibridizációval, kvantitatív reverz transzkriptáz-polimeráz láncreakcióval (qRT-PCR), microarray-jel és a RNS szekvenálással – végzett kísérletek eredményeit. Annak ellenére, hogy a szerotonerg rendszer génjeiben krónikus SSRI kezelés hatására mRNS szinten mérhető változások voltak megfigyelhetők, a szerotonintranszporter szintje legtöbbször változatlan maradt. Ugyanakkor a triptofán-hidroxiláz-2 downregulálódott a szerotonerg magokban és upregulálódott a középagyi területeken. A szerotoninreceptorokat érintő változások nem mutattak egységes képet, és a leírt változások valószínűleg törzstől, hatóanyagtól, illetve a különböző vizsgált agyterületektől függő hatásokat is tükröznek. A legtöbb krónikus kezelés növelte az agy-eredetű neurotróf faktor expresszióját. A GABA- valamint a glutamátreceptorok génjei szintén heterogén változásokat mutatnak; meglepő módon az NMDA receptorok downregulációja volt megfigyelhető a depresszió és a stresszreakciók kialakításában részt vevő olyan agyterületeken, mint például a striatum és az amygdala területén. A fenti kutatások áttekintése számos eltérésre hívja fel a figyelmet, és hangsúlyozza a vizsgált agyterülettől és SSRI gyógyszertől is függő hatások heterogenitását. Mindeközben azonban az eredmények felvetik annak lehetőségét is, hogy az antidepresszívumokat – akut hatásmechanizmusuk helyett – talán célszerűbb volna krónikus molekuláris hatásaik alapján csoportosítani.

Kulcsszavak: SSRI, BDNF, patkány, transzkriptomika, 5-HTT