Paradoxical role of Serotonin in Depression

Towards a neuroplasticity theory of depression with a serotonin-glutamate-BDNF interplay

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Abstract

For decades, researchers have tried to clarify the paradoxical role of serotonin in depression and antidepressant drug effects. Early theories of depression mainly focused on the role of the serotonergic system and explained part of the behavioral pathology in depression and the action of antidepressants by elucidating processes like 5-HT1A somatodendritic autoreceptor desensitization. However, it soon became clear that an impaired serotonergic system could not fully explain behavioral, molecular and morphological aspects of depression and antidepressant drug effects. Acting via glutamate and brain-derived neurotrophic factor (BDNF), neuroplasticity proved to be a likely candidate involved in depression and the positive consequences of antidepressant drug treatments. Although serotonin-BDNF and serotonin-glutamate dualistic interactions are coined as causal relationships in the ontogeny of mood disorders, combining these three parts provides a model that is able to better resolve the paradoxical role of serotonin in depression. In this hypothetical model, serotonin and the activity of serotonergic neurons may act as a regulator of the glutamatergic transmission, which induces BDNF transcription, and will eventually lead to neuroplastic changes that can contribute to both the development of depression as well as the recovery after treatment with antidepressant drugs.

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Introduction

Soon after the discovery of the monoamines over 50 years ago, clinical observations led to a potential role for monoamines in depression, especially implicating noradrenaline and serotonin (5-Hydroxytryptamine, 5-HT). An acute increase of monoamines was described in pharmacological agents reducing depression, such as tricyclic antidepressants and monoamine oxidase inhibitors (Frazer, 1997). The observation that these antidepressant medications enhanced monoamine levels led to the monoamine hypothesis of depression. Initially, this hypothesis only focused on low levels of catecholamines (Bunney & Davis, 1965; Schildkraut, 1965), but quickly Coppen coined a potential role for reduced serotonin in depression (Coppen, 1967). A serotonin deficiency was put forward as the primary cause of depression. By increasing serotonin levels using antidepressant medication, normal functioning could be restored in depressive patients (Albert, Benkelfat, & Descarries, 2012; Coppen, 1967).

The serotonergic system is a complex network with projections from central nuclei to the entire brain, mediated by many receptor types (see figure 1) (Cools, Roberts, & Robbins, 2008). The simplistic view that serotonin is the only factor causing depression is now being revised, and it is generally accepted that many environmental, genetic and neurobiological factors underlie depression (Albert et al., 2012). Together with the serotonergic system, many factors have been implicated to be involved in depression, frequently proposed factors are: stress, hypothalamic–pituitary-adrenal axis (HPA-axis) malfunction, cytokines, the glutamatergic and GABA-ergic system, circadian fluctuations, epigenetic changes and

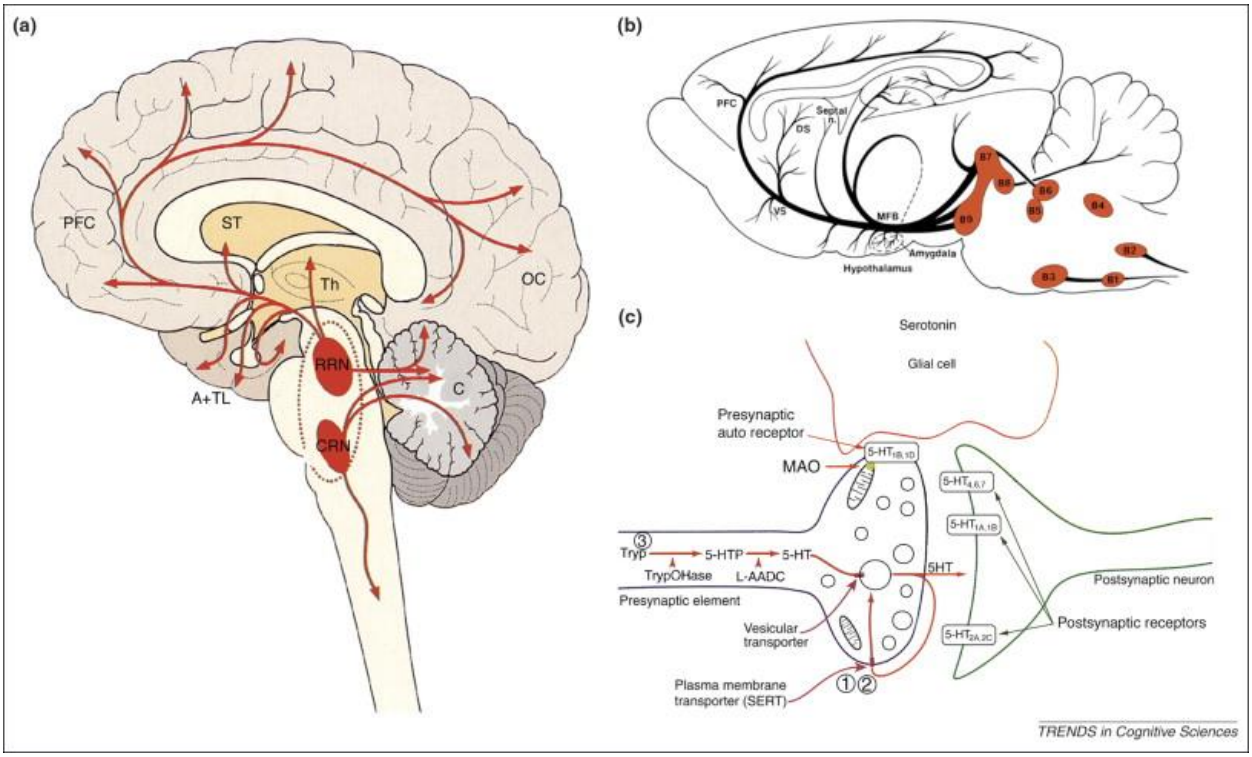

Figure 1 Serotonergic projections throughout the brain of a human (A) and rat (B). Serotonergic neurons project in both species from central nuclei to the entire brain. Serotonergic neuron (C), with localization of different 5-HT receptors and reuptake mechanism via serotonin transporter (SERT). Abbreviations in: (a) CRN, caudal raphé nuclei; RRN, one of the rostal raphé nuclei, i.e. the dorsal raphé nucleus, C, cerebellum; Th, thalamus; A, amygdala; TL, temporal lobe; ST, striatum; PFC, prefrontal cortex; OC, occipital cortex. (b) B7= dorsal raphé nucleus, B8= medial raphé nucleus, MFB, medial forebrain bundle; DS, dorsal striatum; VS, ventral striatum; PFC, prefrontal cortex; Septal n, septal nucleus. (c) Tryp, tryptophan; TrpOHase, tryptophan hydroxylase; 5-HTP, 5-hydroxytryptophan; L-AADC, l-amino acid decarboxylase; SERT, serotonin transporter; MAO, monoamine oxidase; 5-HT1A, 5-HT1B, 5HT2A,C, etc., pre- and postsynaptic 5-HT receptors. From Cools et al., 2008.

neuroplasticity involving Brain-Derived Neurotrophic Factor (BDNF) (Dale, Bang-Andersen, & Sánchez, 2015; Krishnan & Nestler, 2008; Massart, Mongeau, & Lanfumey, 2012). Although many factors besides serotonin are believed to be involved in depression, serotonin still plays a key role in depression research, especially concerning the development of antidepressants (Albert et al., 2012).

In the 1950s, studies already showed that serotonin enhancing drugs, for example Iproniazid and Imipramine, decreased depression symptoms (López-Muñoz, 2009). Increasing serotonin by blocking the reuptake mechanism of serotonin was further explored by creating drugs called selective serotonin reuptake inhibitors (SSRIs), that selectively block the serotonin transporter (SERT), a protein that is largely responsible for the reuptake of serotonin (Frazer, 1997). Although SSRIs increase serotonin levels in various brain regions within minutes to hours (Adell, Celada, Abellán, & Artigas, 2002; Giovacchini et al., 2005; Rutter & Auerbach, 1993), antidepressant effects are only seen after chronic treatment for three to four weeks. Many studies point to the fact that this therapeutic delay is caused by 5-HT1A autoreceptor desensitization after chronic administration of SSRIs (Albert, 2012; Artigas, Romero, de Montigny, & Blier, 1996; Blier & de Montigny, 1994). 5-HT1A autoreceptors are especially of interest in the proposed mechanisms of action of antidepressants that increase serotonin levels, but more serotonin receptors appear to play a role in depression and antidepressants (Artigas, 2013).

In contrast to serotonin increasing drugs like SSRIs, Tianeptine is a drug that is thought to decrease serotonin levels by enhancing serotonin reuptake. Nevertheless, Tianeptine is subject of many studies for its antidepressant properties (McEwen et al., 2009). It is suggested that by acting on the glutamatergic system, Tianeptine restores normal neuroplasticity and glutamatergic transmission, both factors that may underlie depression (Czéh et al., 2001; McEwen et al., 2009). Tianeptine research, combined with recent evidence of co-release of serotonin and glutamate in the raphe nucleus, indicates a potential interplay between glutamate and serotonin in depression (Fischer, Jocham, & Ullsperger, 2015).

Although experimental tools in human serotonin research are limited, results of tryptophan depletion studies and cerebral spinal fluid (CSF) measurements of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, indicate that altered serotonin levels play a role in depressive disorders.

Serotonin does not only seem to play a role in depression via pure neurotransmitting properties, but also through its neurotrophic function. Interacting with BDNF on genetic and molecular levels, serotonin is thought to regulate the neuroplastic processes that can underlie depression. On the one hand, BDNF is shown to be an important factor for development and survival of serotonergic neurons and on the other hand, evidence suggests that serotonin can regulate the expression of the BDNF gene and BDNF signaling (Martinowich & Lu, 2007). Besides the neurotrophic function later in life, serotonin is important in the development and wiring of the brain (Whitaker-Azmitia, 2001). Disturbed development caused by serotonergic dysfunction can result in lifelong alterations of the brain which may underlie (an increased risk of) depression (Homberg, Molteni, Calabrese, & Riva, 2014; Martinowich & Lu, 2007).

Research on polymorphisms in genes coding for the serotonergic system also reinforce the role of serotonin in depression. A polymorphism in the SERT promotor and 5-HT1A receptor promotor was found to be associated with depression (Caspi et al., 2003; Lemonde et al., 2003; Lesch et al., 1996).

Despite more than 40 years of research on the subject, the role of serotonin in depression is still not fully elucidated. Contradicting evidence to the scientific dogma, that low serotonin levels are associated with depression, is found in humans with the short allele for the SERT promotor and SERT knockout animals. While having high serotonin levels, they still appear to be associated with depression (Caspi et al., 2003; Holmes, Murphy, & Crawley, 2003; Olivier et al., 2008). Also serotonin reuptake enhancing drugs showed antidepressant effects (McEwen et al., 2009). The inconsistency that high serotonin levels increase the risk of depression and drugs influencing serotonin levels, increasing or decreasing, have antidepressant effects, is the paradox of serotonin. Although it remains open for discussion in what way, the fact that a dysfunctional serotonergic system contributes to depression is supported by an ever growing corpus of evidence. In this review, the paradoxical role of serotonin in depression will be evaluated by answering the following questions.

1. In what way does serotonin play a role in depression?

To discuss this question the long-standing hypothesis, that reduced serotonin levels are at the foundation of depression, is evaluated. Problems of the monoamine theory are described and an opposing theory, that increased serotonin levels are associated with depression is assessed.

2. Do neuroplastic changes lie at the foundation of depression and does an alteration in the serotoninergic system play a central role in this?

In this section, the neuroplasticity theory of depression will be evaluated. Mechanisms of the interaction of serotonin with BDNF and glutamate, two factors involved in neuroplastic changes, will be evaluated to determine to what extent these interactions can influence depression.

Serotonin and depression

The monoamine hypothesis of depression, referring to low serotonin levels as a primary factor in depression, has been studied for a long time and a comprehensive body of evidence supports this hypothesis. A lot of this evidence is derived from antidepressant research, for example tricyclic antidepressants, MOA inhibitors and SSRIs. Also evidence originating from tryptophan depletion studies, post mortem analysis and CSF measurements reflecting serotonin levels is in line with the monoamine hypothesis.

First evidence for the monoamine theory comes from studies of the drugs Iproniazid and Imipramine. The monoamine oxidase (MAO) A and B inhibiting drug Iproniazid was originally developed against tuberculosis, but showed improvement of depressive symptoms in depressed patients (Pare & Sandler, 1959; West & Dally, 1959). The tricyclic antidepressant Imipramine, a drug developed to treat schizophrenia, failed to be antipsychotic, but showed antidepressant properties (Kuhn, 1958). Studies in rats showed a role for serotonin in both drugs. Iproniazid, by inhibiting MAO A and B, enzymes which break down serotonin in the extracellular space, showed an increase in serotonin levels in rat brains (Bonnycastle, Giarman, & Paasonen, 1957). Imipramine was shown to inhibit serotonin reuptake in rats and therefore increase extracellular serotonin levels in vivo (Jordan, Kramer, Zukas, Moeller, & Petty, 1994; Langer, Moret, Raisman, Dubocovich, & Briley, 1980). Iproniazid or Imipramine treatment in humans also showed alterations in serotonin levels in blood platelets, which are thought to reflect serotonin levels in the brain (Marshall, Stirling, Tait, & Todrick, 1960). Depressed patients treated with MAO inhibitors showed enhancement of the antidepressant effect when receiving the amino acid tryptophan, which is a precursor of serotonin (Coppen, Shaw, & Farrell, 1963). Furthermore, depressed patients treated with MAO inhibitors and tricyclic antidepressants showed a relapse when a serotonin synthesis blocker was administered, indicating that these antidepressants act via the serotonergic system (Shopsin, Friedman, & Gershon, 1976).

Soon after the discovery of selective serotonin reuptake inhibitors , a new kind of antidepressant drug which blocks the serotonin reuptake mechanism, more evidence from antidepressant research was found supporting the monoamine hypothesis. In vivo studies in rats showed that after administration of SSRIs, extracellular serotonin and 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, were increased immediately (see figure 2) (Bel & Artigas, 1992; Invernizzi, Belli, & Samanin, 1992). Serotonin levels, measured as an acute response to SSRIs, in the raphe nuclei were significantly higher than in projected areas (Bel & Artigas, 1992; Invernizzi et al., 1992). Conversely, studies with chronic administered SSRIs only found higher serotonin levels in projected areas, thus at axon terminals, and not in the raphe nucleus (Bel & Artigas, 1993; Rutter, Gundlah, & Auerbach, 1994). Also after SSRI administration, serotonergic neurons in the raphe nucleus immediately showed reduced activity (figure 3A) (Gartside, Umbers, Hajos, & Sharp, 1995; Hajos, Gartside, & Sharp, 1995).

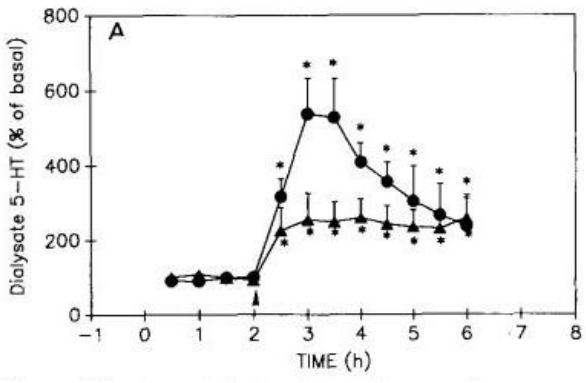

Figure 2 The effect of intraperitoneal injection of SSRI Fluvoxamine on extracellular 5-HT levels in freely moving rats in the raphe nuclei (circles) and the frontal cortex (triangles). A dose of 10mg/kg was administered at the time indicated by the arrow. Data are shown as means + S.E. of 4-6 animals. From Bel & Artigas, 1992.

A 5-HT1A receptor agonist was found to reduce cell firing in the dorsal raphe nucleus (Sprouse & Aghajanian, 1987). 5-HT1A receptors are found as serotonergic presynaptic autoreceptors and postsynaptic heteroreceptors (Albert, 2012). The 5-HT1A autoreceptor appeared

to be responsible for the autoinhibition of serotonergic neurons (Penington & Kelly, 1990). A selective 5-HT1A antagonist, WAY100635, was found to counteract the inhibiting effect of SSRIs in the raphe nucleus of rats (see figure 3A) and potentiated the extracellular serotonin increase in the forebrain (see figure 3B) (Gartside et al., 1995). Furthermore, co-administration of pindolol, a 5-HT1A/B receptor antagonist, in depressed patients using SSRIs accelerated antidepressant effects of SSRIs (Artigas et al., 1996).

Despite the immediate increase in serotonin levels after SSRI administration (Rutter & Auerbach, 1993), depressive symptoms do not immediately decrease. Sometimes symptoms, for example anxiety, increase after acute treatment before they improve after chronic SSRI administration (Burghardt, Sullivan, McEwen, Gorman, & LeDoux, 2004). The delayed therapeutic effects remained unclear for a long time. These micro dialysis studies in rats led to a theory that could explain the therapeutic delay of three to four weeks seen in SSRI use, suggesting a desensitization 5-HT1A autoreceptors which are responsible for the negative feedback on serotonergic neurons in the raphe nucleus (Blier & de Montigny, 1994; Charney, Menkes, & Heninger, 1981; Gardier, Malagié, Trillat, Jacquot, & Artigas, 1996; Stahl, 1998). Findings with pindolol in humans were consistent with this theory about antidepressants (Artigas et al., 1996).

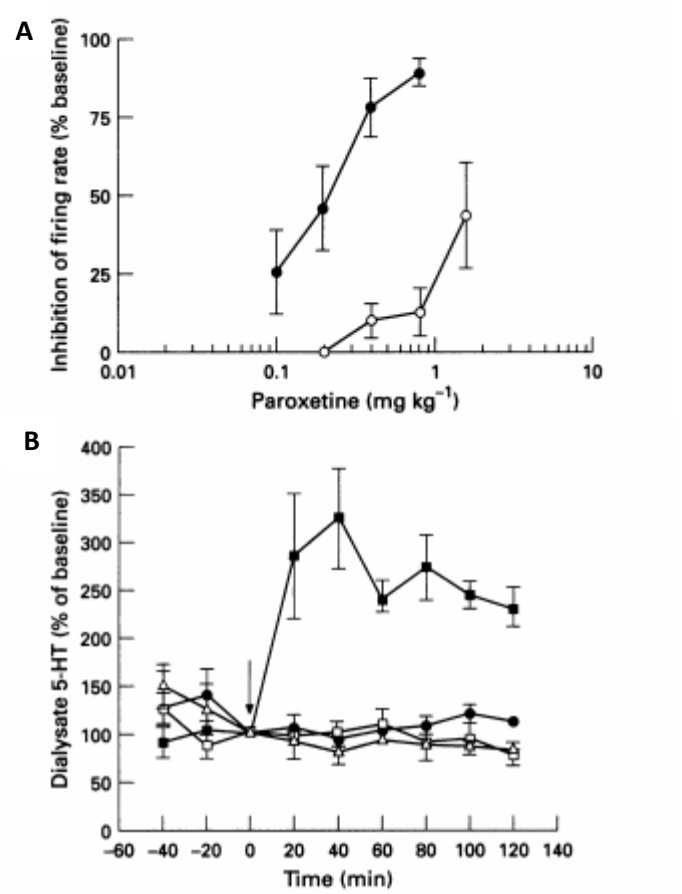

Figure 3. Effects of SSRI paroxetine and 5-HT1A antagonist WAY 100635 on the serotonergic system. (A) Mean percentage inhibition of 5-HT cells in the dorsal raphe nucleus induced by cumulative doses of paroxetine in naive rats (filled circles) and rats pretreated with WAY 100635 (0.1 mg/kg, i.v.) (open circles). Each point represents the mean ± s.e.m. of 5 - 7 measurements. (B) Time course of the effect on 5-HT in dialysates of the frontal cortex. Vehicle (open triangles), WAY 100635 (0.1 mg/kg, iv.) (open squares), paroxetine (0.8mg/kg, iv.) (filled circles), or WAY 100635 (0.1 mg/kg, iv.) followed by paroxetine (0.8mg/kg, i.v.) (filled squares). Paroxetine was given at t = 0. Data are mean ± s.e.m., n = 4- 7. From Gartside et al., 1995.

An increase of 5-HT1A autoreceptors in the dorsal raphe nucleus in depressive suicide victims was found in post mortem studies, using a radioactive labeled 5-HT1A agonist, suggesting reduced serotonergic transmission in these patients (Stockmeier et al., 1998). Furthermore, a reduction of 5-HT1A receptor binding was found using PET-scans in depressed humans (Drevets et al., 1999; Sargent et al., 2000). However, consistent with the monoamine hypothesis of depression, later studies showed an increase of 5-HT1A receptor binding in unmedicated depressed patients (Parsey et al., 2010; Parsey et al., 2006). Reduction of 5-HT1A binding potential after treatment of SSRI in unmedicated depressed patients was found suggesting a desensitization or down regulation, which conforms to the monoamine hypothesis based mechanism of SSRIs (Gray et al., 2013; Spindelegger et al., 2009). Also, a polymorphism was found that derepresses 5-HT1A receptors, presumably decreasing serotonin transmission and thereby causing a higher risk of depression and suicide (Lemonde et al., 2003).

Although 5-HT1A autoreceptor desensitization is most likely responsible for the delayed therapeutic effects of SSRIs, the mechanisms behind the desensitization are unclear. It is proposed that 5-HT1A autoreceptors were less able to activate G-proteins after SSRI treatment by uncoupling the G-protein

(Castro, Diaz, del Olmo, & Pazos, 2003; Hensler, 2002; Pejchal, Foley, Kosofsky, & Waeber, 2002). Acute desensitization of 5-HT1A receptors after 5-HT1A stimulation seems to be mediated by protein kinases (Wu, Kushwaha, Banerjee, Albert, & Penington, 2013; Yao, Bergold, & Penington, 2010). Others suggest a G-protein inactivation as mechanism for 5-HT1A receptor desensitization (Beyer et al., 2004). Also 5-HT1A receptor internalization was observed after acute administration of SSRI resulting in reduced 5-HT1A receptor on the plasma membrane, but this effect was not shown after chronic SSRI treatment (Riad et al., 2004; Riad et al., 2008). Comparable to the fact that 5-HT1A receptor internalization cannot explain chronic desensitization, G-protein related desensitization mechanisms are also quickly reversible (Albert, 2012). More likely is a desensitization mechanism involving transcriptional regulation, but more research needs to be done to unravel the precise mechanism of 5-HT1A desensitization (Albert, 2012).

While, supporting the monoamine hypothesis of depression, desensitization of the 5-HT1A autoreceptor causing an increase of terminal serotonin (see figure 4) is presumably the most important mechanism concerning serotonergic receptors in SSRI research, other serotonergic receptors are shown to be involved. An evaluation of all receptors involved in antidepressant treatments is beyond the scope of this review and is well described by Artigas (Artigas, 2013).

The monoamine hypothesis of depression is also supported by studies altering tryptophan levels. Tryptophan is a precursor of serotonin (see figure 1C). Administration of tryptophan caused an increase in brain serotonin levels in humans (Young & Gauthier, 1981) and depletion caused a decrease in serotonin (Nishizawa et al., 1997), both measured in CSF. Some studies showed that tryptophan administration was able to reduce depressive symptoms, most clearly in mild-depressive patients (Thomson et al., 1982; Young & Leyton, 2002). Tryptophan depletion showed to induce depressive symptoms in some circumstances (Porter et al., 2005; K. Smith, Fairburn, & Cowen, 1997), which would support the monoamine hypothesis of depression, but was only observed in people susceptible for depression (Young, 2013). Also many conflicting results are published concerning tryptophan depletion and a recent meta-analysis of tryptophan depletion studies concluded there is too little evidence that acute tryptophan depletion effects mood (Ruhe, Mason, & Schene, 2007).

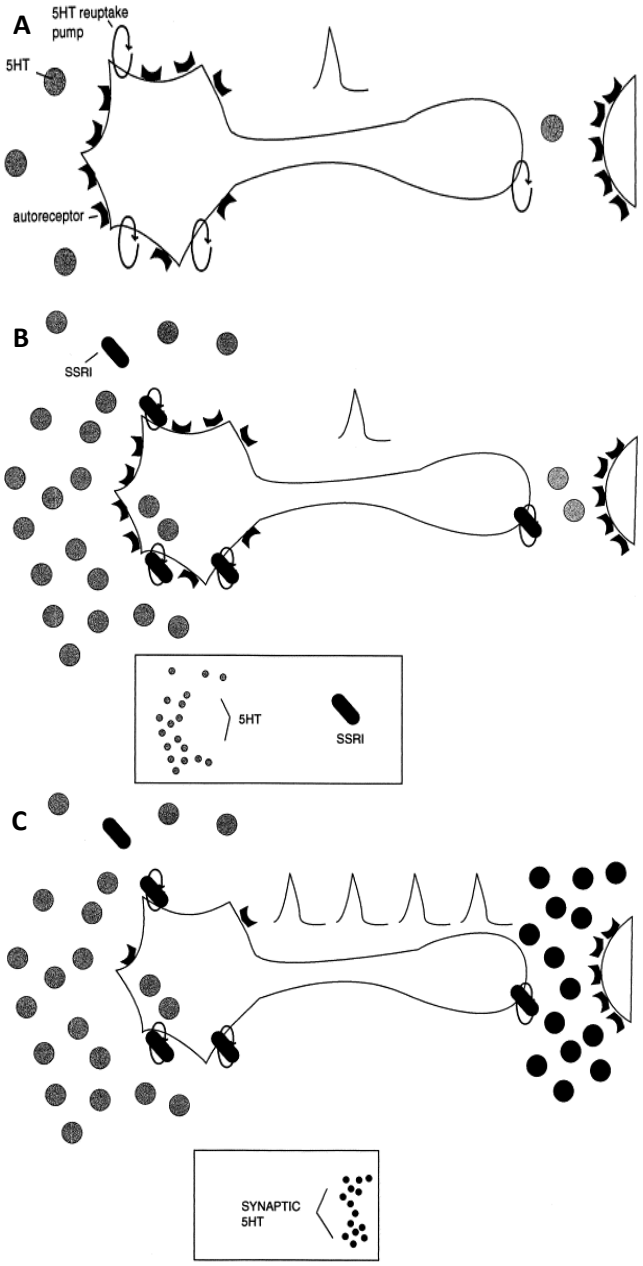

Figure 4 Adaptations of a serotonergic neuron to SSRIs. (A) a typical serotonergic neuron. Autoreceptor is 5-HT1A autoreceptor. (B) As acute reaction to SSRI administration, extracellular serotonin levels increase, with a stronger increase in the dorsal raphe nucleus than at axon terminals. (C) Desensitization or down-regulation of 5-HT1A autoreceptors reduces the inhibition on serotonergic neurons in the raphe nucleus resulting in an increased serotonin level at the axon terminal. From Stahl, 1999 .

Techniques to directly measure serotonin in the human brain are not yet developed. Therefore to get an indication of serotonin levels, post mortem brain analysis is performed, often on depressed suicide victims. Also in vivo measurements of 5-HIAA, the primary metabolite of serotonin, are done in CSF of humans. In the hindbrain tissue of depressive suicide victims, a decrease of serotonin levels was observed (Shaw, Eccleston, & Camps, 1967), but it is thought that tissue levels are not a precise indicator of extracellular serotonin levels (Jacobsen, Medvedev, & Caron, 2012). A more reliable reflection of brain serotonin levels are 5-HIAA levels in the CSF (Wester et al., 1990). Consistent with tissue serotonin levels, a decrease of 5-HIAA was found in depressive suicide victims (Åsberg, Träskman, & Thorén, 1976). Not all studies replicated this decrease in serotonin and 5-HIAA levels, but the majority did, supporting the monoamine hypothesis (Mann & Malone, 1997). While the association between low 5-HIAA levels and suicidal behavior is quite strong, no clear correlation between low 5-HIAA levels and depression alone is found (Åsberg, 1997; Jacobsen et al., 2012). However, due to the frequent comorbidity, suicide and depression may have similarities concerning neurobiology (Jacobsen et al., 2012; Malkesman et al., 2009).

Post mortem studies of depressed suicide victims showed that, besides an increase of 5-HT1A receptor binding, SERT binding was lower, indicating a less functional SERT. These changes were found in various regions of the prefrontal cortex (Arango, Underwood, Gubbi, & Mann, 1995; Austin, Whitehead, Edgar, Janosky, & Lewis, 2002; Mann et al., 2000). Furthermore, decreased volumes of brain areas were found in similar areas of the prefrontal cortex of depressed patients, suggesting that dysfunctions in the serotonergic system can lead to morphological changes in humans (Rajkowska, 2003). Yet, no causal relationship was established in these studies and the observed changes could also indicate adaptational changes to an altered serotoninergic system. Also more brain areas, for example hippocampus, showed decrease volume, while no direct link to serotonin could be made (Koolschijn, van Haren, Lensvelt-Mulders, Pol, & Kahn, 2009; Rajkowska, 2003; Sheline, Wang, Gado, Csernansky, & Vannier, 1996).

Taken together, evidence supporting the monoamine hypothesis of depression is quite substantive. Some evidence is strong, for example the mechanism of action of SSRIs, while other data, for example measurements of CSF 5-HIAA and tryptophan depletion studies, are inconsistent. Adding to the controversy of the monoamine hypothesis, many studies showed high serotonin is associated with depressive behavior or risk of depression. Studies focusing on rats and mice, using a knockout of the SERT gene, showed higher extracellular serotonin and depressive-like behavior (Holmes et al., 2003; Homberg et al., 2007; Olivier et al., 2008). SERT knockout mice also showed desensitization of 5-HT1A autoreceptors in the dorsal raphe nucleus (Li, Wichems, Heils, Lesch, & Murphy, 2000), a mechanism which is presumed to be involved in the antidepressant effect of SSRIs in humans. Moreover, genetic polymorphisms in the serotonergic system which increase serotonin levels in the brain are linked to an increased risk of depression. Carriers of the short allele for serotonin transporter promotor region, 5-HTTPR, showed a less efficient SERT transcription and therefore reduced SERT (Lesch et al., 1996). A short allele was associated with more anxiety and was found to be a risk factor for developing depression after experiencing stressful life events, establishing the link between SERT and depression (Caspi et al., 2003; Lesch et al., 1996).

In contrast to the monoamine theory, a theory was recently proposed, suggesting high serotonin levels are more likely to be involved in depression (Andrews, Bharwani, Lee, Fox, & Thomson Jr., 2015). Claiming serotonin levels are increased in depressive phenotypes, for example a SERT knockout in animals and SERT promotor polymorphism in humans, a high serotonin hypothesis was coined (Andrews et al., 2015). Looking from an evolutionary perspective, and supported by the existence of serotonin converting enzymes in mitochondria, serotonin is suggested to be evolved in mitochondria, and therefore is expected to be involved in energy regulation. Trying to explain the therapeutic delay of SSRIs, it is suggested that acute SSRIs administration disturbed energy homeostasis, and that therapeutic effects are achieved by restoring energy homeostasis rather than serotonin homeostasis (Andrews et al., 2015; Azmitia, 2010). The evidence in support of the high serotonin hypothesis is weak compared to findings supporting the

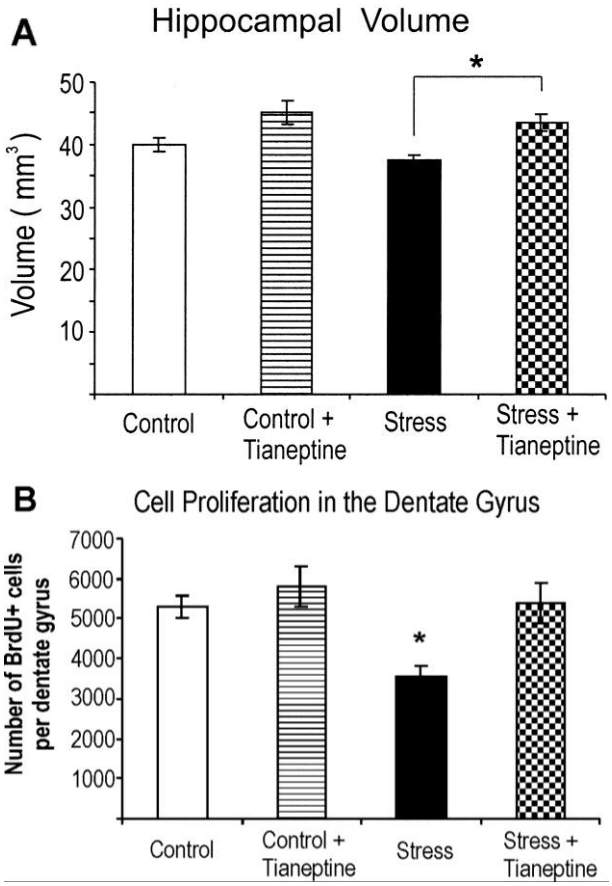

Figure 5 Effect of Tianeptine on hippocampal volume and cell proliferation in the dentate gyrus. (A) Tianeptine showed an significant increase in hippocampal volume after stress. (Stress + Tianeptine vs. Stress; *, $P < 0.05$). Tianeptine treatment alone slightly increased hippocampal volume, altough this was not significant. (B) Tianeptine prevented the stress-induced decrease of cell proliferation in the dentate gyrus. BrdUrd is a marker for cell proliferation. Results are given as mean ± SEM number of BrdUrd-positive cells in the hippocampal dentate gyrus. *, $P < 0.05$ vs. Controls. From Czéh et al., 2001.

monoamine hypothesis supporting findings. Nevertheless, it is an good indicator that there is more to depression than the monoamine hypothesis.

Perhaps the most convincing evidence against the monoamine hypothesis involves the antidepressant drug Tianeptine. Tianeptine proved to be an effective antidepressant drug in several clinical trials (Invernizzi et al., 1994; Lôo et al., 1999). But in contrast to SSRIs, Tianeptine increased serotonin reuptake and therefore lowered extracellular serotonin levels in vivo in rats, when given as acute treatment as well as chronic administration (Fattaccini, Bolaños-Jimenez, Gozlan, & Hamon, 1990; Mennini, Mocaer, & Garattini, 1987). However, a more recent study found no alterations in extracellular serotonin levels in response to Tianeptine (Malagié, Deslandes, & Gardier, 2000). Furthermore, Tianeptine treatment did not alter firing rate of serotonergic neurons in the dorsal raphe nucleus after chronic administration (Pineyro, Deveault, Demontigny, & Blier, 1995). An alternative mechanism needed to be found for Tianeptine, reducing depressive symptoms; the usual, serotonin increasing, mechanism of antidepressant did not apply for Tianeptine. As mentioned before, hippocampal volume loss is found in depressive patients (Koolschijn et al., 2009; Sheline et al., 1996). Antidepressant treatments in rats increased neurogenesis in the hippocampus, suggesting a new mechanism for antidepressants counteracting the reduced hippocampal volume, however this study did not include Tianeptine (Malberg, Eisch, Nestler, & Duman, 2000). It is even suggested that hippocampal plasticity is required for the effects of antidepressant (Santarelli et al., 2003). Although Tianeptine is does not appear to increase spontaneous neurogenesis, it is shown in tree shrews, a mammalian animal that is a model for depression when stressed, that Tianeptine could prevent stress-induced hippocampal volume loss (figure 5A) and decrease in proliferation rate in the dendate gyrus (figure 5B) (Czéh et al., 2001; McEwen et al., 2009).

Studies with Tianeptine showed the importance of neuroplasticity in depression, indicating serotonin and glutamate as a modulator (McEwen et al., 2009). Other studies suggested BDNF, a substance highly involved in neuroplasticity, to be involved in the neuroplastic changes that could underlie depression (Duman & Monteggia, 2006). It became clear that mechanisms underlying depression extend beyond the serotonergic neurotransmission alone. Alterations in serotonin levels nor the activity of the serotonergic system are able to fully clarify the paradoxical role of the serotonergic system in depression. In the following section interactions of serotonin with glutamate and BDNF are evaluated to see if they can shed some light on the role of serotonin in depression.

Neuroplasticity and depression

The serotonergic system on its own is not sufficient in explaining the mechanisms behind depression. The neurotrophic hypothesis of depression was coined, suggesting that neuroplastic changes are responsible for depression. It appears that serotonin, in interaction with glutamate or BDNF, can induce some neuroplastic changes associated with depression. Neuroplastic changes, presumably caused by a serotonin-glutamate/BDNF interplay, are for example: normalizing decreased hippocampal volume, neuroprotection and regulating cell proliferation. First, neuroplasticity in depression will be discussed in relation to glutamate and serotonin. Next, neuroplasticity in depression concerning BDNF will be evaluated, paying special attention to the interaction with serotonin.

Depressive patients showed an altered brain structure in areas including the prefrontal cortex, the limbic system and the hippocampus (Drevets, 2000; Koolschijn et al., 2009; McEwen & Chattarji, 2004; Sheline et al., 1996). Evidence indicated that antidepressants, increasing serotonergic activity, may have neuroprotective properties against hippocampal volume loss in rats (Malberg et al., 2000) as well as in humans (Sheline, Gado, & Kraemer, 2003). Yet, also serotonin reducing antidepressant Tianeptine showed neuroprotection in tree shrews, a mammalian model for depression research, presumably acting on the glutamatergic system (Czéh et al., 2001; McEwen et al., 2009).

Evidence from clinical studies suggested that alterations of the glutamatergic system are associated with depression. Especially ketamine, a fast acting N-methyl-D-aspartate (NMDA) receptor antagonist, showed a reduction of depressive symptoms within hours (Berman et al., 2000; Zarate et al., 2006). Ketamine rapidly increased extracellular glutamate levels via disinhibition of GABA-ergic interneurons by blocking NMDA receptors in the prefrontal cortex (Duman & Li, 2012). Mammalian target of rapamycin (mTOR) seems to be the most important regulator in the effects of Ketamine (Li et al., 2010; Li et al., 2011). mTOR is thought to be a modulator of synaptic plasticity and spine densities via BDNF and other neuroplastic proteins, influencing neuroconnectivity in various brain areas involved in depression. An increase of BDNF due to mTOR stimulation via glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor supports the neuroplasticity hypothesis of depression (figure 6) (Duman, Li, Liu, Duric, & Aghajanian, 2012; Duman & Li, 2012).

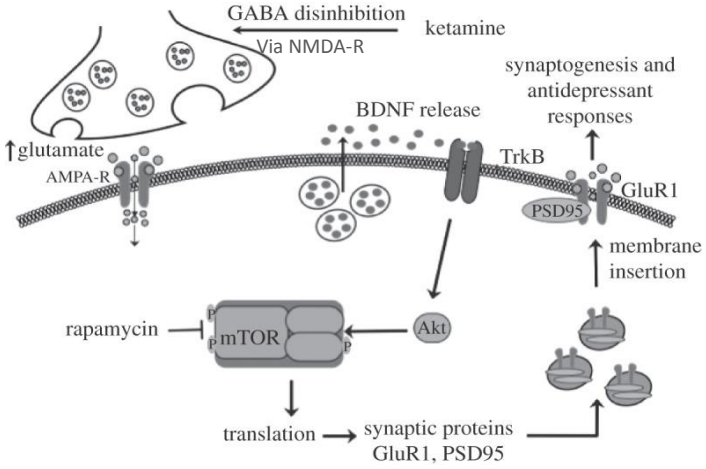

Figure 6 Regulation of neuroplasticity via glutamatergic modulation of ketamine. Ketamine increases extracellular glutamate by disinhibiting GABA-ergic interneurons via NMDA receptors. This leads to an increased transcription of BDNF and other proteins (GluR1 and PSD95) involving neuroplasticity, regulated by mTOR. Adapted from Duman & Li, 2012.

Besides the NMDA and AMPA receptor, the glutamatergic system has other receptors including the ionotropic kainite receptor. Moreover, there are metabotropic receptors named mGLU1-8 (Javitt et al., 2011). While NMDA and AMPA are presumably the most important receptors involved in neuroplastic mechanisms of depression and antidepressant effects, almost all glutamatergic receptors showed an association with antidepressants or depression (McEwen et al., 2009; Paul & Skolnick, 2003).

Generally, in vivo proton Magnetic resonance spectroscopy (^{1}H-MRS) measurements of glutamate levels showed to be reduced in depressed patients (Yüksel & Öngür, 2010). CSF measurements of

glutamate showed conflicting results (Sanacora, Treccani, & Popoli, 2012). While MRS reflects largely metabolites of glutamate and other evidence of altered glutamate levels is limited, it remains difficult to determine if glutamate transmission is reduced or increased in depression based on these findings. Nevertheless, glutamatergic alterations clearly play a role in depression. For example, reduction of NMDA receptors, as in line with the effects of Ketamine, is thought to improve mood. Metabolic glutamate receptors are presumably involved in neurogenesis (Paul & Skolnick, 2003; Sanacora et al., 2012).

Considering the great amount of evidence that serotoninergic alterations are associated with depression, the interaction between serotonin and glutamate is investigated to see if it can contribute to depression or antidepressant effects. Tianeptine, as described above, is an antidepressant drug that decreases serotonin levels. However, serotonin alone could not explain the proposed neuroplastic changes underlying the antidepressant effects of Tianeptine and glutamate was coined as interacting factor or even the main system through which Tianeptine acts (McEwen et al., 2009). Tianeptine showed to normalize the glutamatergic system in several ways after stress-induced changes in brain areas associated with depression. First, the increase in NMDA receptors after chronic stress in the hippocampus was reversed when rats were treated with Tianeptine (Kole, Swan, & Fuchs, 2002). Furthermore, Tianeptine caused normalization of increased extracellular glutamate levels after stress in the basolateral amygdala, with a possible regulatory role of glial-specific excitatory amino-acid transporter (GLT-1) (Reagan et al., 2004; Reznikov et al., 2007). Yet, there is no definitive answer if these effects on the glutamatergic system are caused via serotonin-reducing effects of Tianeptine. Nevertheless, serotonin appears to play a role in restoring stress-induced glutamatergic changes.

It is known stimulating several serotonin receptors may indirectly induce changes in glutamatergic transmission, suggesting an (glutamate-mediated neuroplasticity-based) explanation for the antidepressant effects of mono-amine based drugs (Pehrson & Sanchez, 2014). It is thought that stimulation of 5-HT1A receptors on GABA-ergic interneurons results in an inhibition of these interneurons, and therefore this stimulation of 5-HT1A receptors is able to stimulate glutamatergic pyramidal neurons in the prefrontal cortex (Lladó-Pelfort, Santana, Ghisi, Artigas, & Celada, 2012). 5-HT3 receptors are excitatory receptors that are located on GABA-ergic interneurons. Thus when they are stimulated they caused a reduction in the firing rate of glutamatergic pyramidal neurons in the prefrontal cortex (Ashby Jr., Minabe, Edwards, & Wang, 1991). Also the role of 5-HT7 receptors is not quite clear. It is thought they may increase or decrease glutamatergic transmission, depending on the localization of the receptor (Pehrson & Sanchez, 2014). Clearly, serotonergic effects on the glutamatergic system are dependent on many receptors and the complex regulation is not yet understood.

More evidence supporting the fact that serotonin and glutamate are intertwined in depression, comes from studies focusing on the co-release of these two substances. In serotonergic neurons of the raphe nucleus, expression of vesicular glutamate transporter 3 (VGLUT3) was found, suggesting storage of glutamate in these neurons (Gras et al., 2002). When serotonergic neurons were stimulated, they co-released glutamate, but while both systems act via their own receptors, a dissociation between glutamatergic and serotonergic effects could still be observed (Johnson, 1994; Liu et al., 2014; Varga et al., 2009). In light of the previous section, which described that serotonin enhancement after SSRI use inhibited serotonergic neurons in the raphe nucleus by 5-HT1A autoreceptors, glutamate release will also be inhibited and could contribute to the (delayed) antidepressant effects (Fischer et al., 2015). As shown in figure 7, after acute SSRI treatment, extracellular serotonin levels immediately increase and rapidly cause an autoinhibition via 5-HT1A autoreceptors. Inhibition of the serotonergic neuron will result in less release of neurotransmitter serotonin, as well as glutamate. Due to this reduction of neurotransmitter release, glutamate levels will decrease, while serotonin levels remains elevated by cause of blockade of SERT by SSRIs (figure 7B). When 5-HT1A receptors desensitize, inhibition of raphe neurons and therefore neurotransmitter release is restored to normal and serotonergic and glutamatergic co-release returns to baseline. Therefore, glutamate levels also return to baseline. Serotonin levels remains increased because,

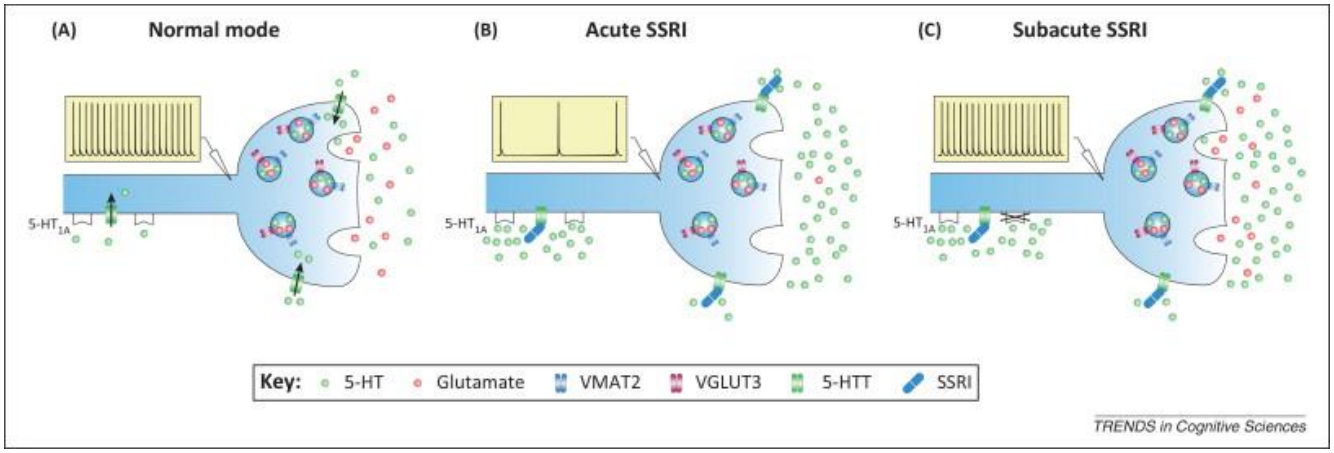

Figure 7 Proposed mode of action of SSRIs with regard to serotonergic and glutamatergic effects in a serotonergic neuron in the raphe nucleus. (A) In a normal condition, without SSRI. (B) Effects of acute SSRI treatment. An immediate increase of extracellular serotonin causes inhibition via 5-HT1A autoreceptors and thereby inhibits co-release of glutamate and serotonin. (C) Effects of chronic SSRI use. After 5-HT1A autoreceptor desensitization, co-release of serotonin with glutamate is restored to normal levels with a normalization for glutamate and a net increase of serotonin. Abbreviations: 5-HT, 5-hydroxytryptophan; 5-HTT, 5-HT transporter; SSRI, selective serotonin reuptake inhibitor; VMAT2, vesicular monoamine transporter 2; VGLUT3, vesicular glutamate transporter 3. From Fischer, Jocham & Ullsperger, 2015.

in addition to normal release, SSRIs block SERT and therefore also increase serotonin via another way (Fischer et al., 2015).

While changes in the glutamatergic system can cause neuroplastic changes, the glutamatergic system is a rather global system and the neuroplastic changes probably happen indirectly. As shown in figure 6, mTOR is a likely candidate to regulate this process. Besides the other neuroplastic proteins shown in figure 6, BDNF is released. BDNF is an, perhaps the most, important factor in neuroplasticity concerning depression and can act as an effector at the end of the chain of neuroplasticity (Duman & Monteggia, 2006; Duman & Li, 2012; Thompson et al., 2015).

BDNF is implicated in the neurotrophic theory of depression as it is a highly involved factor in neuroplasticity and is thought to be able to reverse morphological abnormalities in several brain regions. Also, altered levels of BDNF in serum of depressed patients are found. Furthermore, BDNF is proposed to regulate neuroplastic changes which may be the foundation of the actions of antidepressant drugs (Duman & Monteggia, 2006).

Stress, as described before, can induce reductions in brain volumes similar to depression. Together with this neuronal atrophy, decreased levels of BDNF mRNA are found in the hippocampus of chronically stressed animals in several studies (Duman & Monteggia, 2006; Smith, Makino, Kvetnansky, & Post, 1995). Direct administration of BDNF in the hippocampus of rats resulted in a reduction of depression-like behavior, but when BDNF was administered in the ventral tegmental area-nucleus accumbens (VTA-NAc) depression-like behavior increased (Eisch et al., 2003; Shirayama, Chen, Nakagawa, Russell, & Duman, 2002). Furthermore, a polymorphism in the BDNF promotor gene, where valine is substituted for a methionine (Val66Met), was found in humans. And while no direct association with depression could be observed, the Met allele is associated with worse performance on memory tasks and smaller hippocampal volume (Chen et al., 2006; Egan et al., 2003; Krishnan & Nestler, 2008). In post mortem studies in depressed humans, decreased BDNF levels were also found in the hippocampus, an effect mainly observed in untreated patients, suggesting BDNF involvement in antidepressants (Chen, Dowlatshahi, MacQueen, Wang, & Young, 2001; Karege, Vaudan, Schwald, Perroud, & La Harpe, 2005). A non-invasive way to measure BDNF was found, namely in serum, and alterations in BDNF were shown. Depressed patients showed reduced levels of BDNF and these increased to levels comparable to healthy subjects after chronic

administration of various types of antidepressants, including serotonin reuptake inhibitors (Karege et al., 2002; Sen, Duman, & Sanacora, 2008; Shimizu et al., 2003).

BDNF is, as described above, clearly involved in depression and antidepressants, possibly as downstream actor (Duman, Heninger, & Nestler, 1997). Due to the central role of monoamines, especially serotonin, in depression research, a reciprocal interaction between these substances may contribute to depression and antidepressant drug effects.

It is tempting to speculate that, as shown in figure 8, via stimulation of serotonergic receptors 4,6 and 7 (5-HT4, 5-HT6 and 5-HT7), the cAMP-PKA-CREB pathway is innervated, resulting in enhanced (promotor III-mediated) expression of BDNF (Martinowich & Lu, 2007). Consistent with this idea, a 5-HT4 receptor agonist (Pascual-Brazo et al., 2012) and a 5-HT6 agonist (de Foubert, O'Neill, & Zetterström, 2007) increased BDNF levels. Still, evidence for receptor types 4,6 and 7 is limited. Moreover, 5-HT1A, 5-HT2A and 5-HT2C seem to be involved in altering BDNF levels (Homberg et al., 2014). Not all data is consistent with this pathway, for example SERT knockout mice have high extracellular serotonin levels, but no difference in BDNF levels was found compared to wild type mice (Szapacs et al., 2004). As the authors suggested themselves, this could be due to adaptations in reaction to high serotonin levels throughout the development of an animal.

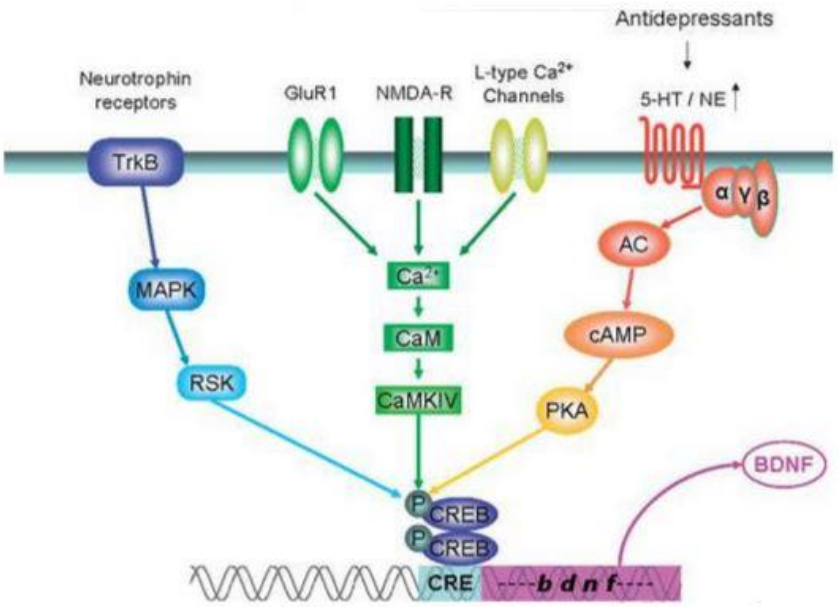

Figure 8 Signaling pathways important in mood regulation concerning phosphorylation of CREB. Activation of neurotrophic, glutamatergic and serotoninergic/adrenergic receptors result in phosphorylation of CREB and therefore transcription of BDNF. Abbreviations: 5-HT, serotonin; AC,adenylyl cyclase; BDNF, brain-derived neurotrophic factor; CaM, calmodulin; CaMKIV, Ca2þ/calmodulin-dependent kinase IV; CRE, cAMP response element; MAPK, mitogen activated protein kinase; NE, norepinephrine; PKA, cAMP-dependent protein kinase; RSK, ribosomal6 kinases; TrkB, neurotrophin tyrosine kinase receptor 2. From: (Gass & Riva, 2007)

BDNF is known to influence the development of serotonergic neurons. In vitro and in vivo experiments with embryonic raphe cells showed a survival and differentiation of serotonergic neurons after BDNF treatment (Djalali et al., 2005; Eaton & Whittemore, 1996). But also mature serotonergic neurons reacted to BDNF and showed axon sprouting after BDNF infusion in rats (Mamounas, Blue, Siuciak, & Altar, 1995). Consistently, mice heterozygous for BDNF ($BDNF^{+/-}$), thus having less BDNF, showed impairments in the serotonergic system, such as an altered expression of serotonergic receptors (Lyons et al., 1999). Yet, $BDNF^{+/-}$ mice showed no clear depression-like or anxious behavior (Chourbaji et al., 2004).

Double mutant mice (SERT knockout and BDNF heterozygous) did show more anxiety-related behavior and serotonergic impairment, than mice which had deficiencies in SERT or BDNF, which supports the idea of (genetic) interaction between serotonin and BDNF (Ren-Patterson et al., 2005). This is especially of interest because in humans, two polymorphisms were found in the SERT and BDNF promotor gene, as described earlier. While short variants of the SERT polymorphism showed an association with depression on its own, the met allele of BDNF polymorphism did not. A more robust connection to depression was made, when patients had both polymorphisms, two short alleles for SERT and the met allele for BDNF (Ignácio, Réus, Abelaira, & Quevedo, 2014; Kaufman et al., 2006). However, it must be noted that the association of previous polymorphisms and depression is highly dependent on environmental factors, for example stressful life events (Homberg et al., 2014).

Interestingly, mRNA levels of BDNF alter in antidepressant treatment. Following the therapeutic delay of many antidepressant drugs, including SSRIs, BDNF mRNA increased after chronic, but not acute, treatment with antidepressants, indicating a role for BDNF in the antidepressant drug effects after chronic use (Duman & Monteggia, 2006; Nibuya, Morinobu, & Duman, 1995; Nibuya, Nestler, & Duman, 1996). With the proposed mechanism involving co-release of serotonin and glutamate of chronic SSRI use (figure 7) (Fischer et al., 2015), co-released glutamate may be the factor linking serotonin and BDNF together. Consistent with this, is the fact that an acute glutamate increase by the NMDA antagonist Ketamine immediately increased BDNF levels or activated BDNF pathways (Garcia et al., 2008; Vásquez, Riener, Reynolds, & Britton, 2014). Nonetheless, more research needs to be done to determine the exact amount of co-released glutamate and whether this amount can contribute to neuroplastic mechanisms.

Neuroplastic mechanisms, via glutamate and BDNF, are most likely involved in depression and may be regulated by serotonin. However, a lot of work has to be done to fully understand of the mechanisms and pathways involved in depression and antidepressant effects.

Discussion

Theories about depression, focusing on serotonin and neuroplasticity, are described above and it is clear that none are singularly able to fully explain the underlying mechanisms of depression and antidepressant effects. Combining new insights of serotonin, glutamate and BDNF in depression, a theory based on serotonergic principles, as well as neuroplasticity might be able to clarify the paradoxical role of serotonin in depression.

A body of evidence suggests that serotonin levels, high or low, play a role in depression. Perhaps the most influencial evidence comes from the mechanism underlying antidepressant effects. Many antidepressants, SSRIs and Tianeptine, influence extracellular serotonin levels. While the effects on serotonin are acute, therapeutic effects are only occur after chronic administration of antidepressants. It is thought 5-HT1A autoreceptor desensitization is mainly responsible for this therapeutic delay (Albert, 2012; Artigas et al., 1996; Blier & de Montigny, 1994). Yet, inconsistent findings concerning serotonin levels in CSF or post mortem studies failed to establish a direction, high or low levels, to the role of serotonin (Massart et al., 2012).

It is generally accepted that serotonin is not the only factor involved in depression, and may indirectly contribute to depression, by influencing other mechanisms, like neuroplasticity (Duman & Monteggia, 2006; Massart et al., 2012). Besides a neurochemical impairment, depression is also associated with morphological changes, for example reduced hippocampal volume (Koolschijn et al., 2009). Therefore a theory including neuroplastic changes which normalize these morphological changes would be a likely candidate to explain a part of depression (Duman & Monteggia, 2006).

As discussed in previous sections, glutamate and BDNF, interacting with serotonin, appear to be involved in neuroplasticity. A recent study sugessted a dual-signaling of serotonin and glutamate in antidepressant effects (figure 7), proposing the interaction, or co-release, of these two substances (Fischer et al., 2015). Tianeptine, a serotonin decreasing drug, may act via the glutamatergic system invoking neuroplastic changes (McEwen et al., 2009). Glutamate increasing drugs such as Ketamine showed antidepressant effects, presumably by mTOR regulated transcription of BDNF and other neuroplastic molecules (Duman & Li, 2012).

BDNF is a neurotrophic factor which is, most likely, involved in restoring normal morphology in depressed patients after antidepressant treatment. It must be noted that BDNF is not the only neurotrophic factor implicated in antidepressants, for example FGF-2, IGF, VEGF and VGF are additionally thought to play a role (Homberg et al., 2014). However, BDNF is especially interesting in antidepressant and depression research because its close interaction with serotonin (Martinowich & Lu, 2007). Nevertheless, BDNF is regulated by such a complex system of transcriptional, translational and post-translational modifications, that the precise mechanism behind the influence of BDNF (interacting with serotonin) on depression is not fully understood (Homberg et al., 2014).

Although the neuroplastic changes in the hippocampus are well described and established, less is known about changes in other brain areas important concerning depression, for example the prefrontal cortex (Duman & Monteggia, 2006). On the other hand, many studies of serotonin levels in response to antidepressant treatments have been done, but often only focusing on the raphe nucleus and prefrontal cortex (Stahl, 1998). This led to the idea that antidepressants effects might by achieved in a brain area-specific mechanism or pathway. Examples of these mechanisms that may contribute to antidepressant drug effects are restoring normal morphology in the hippocampus with neuroplastic mechanisms, and normalizing serotonergic neurotransmission in the prefrontal cortex. While no clear distinctions are made, it is apparently generally accepted that, though based on a few studies, the principles of these processes are similar in the brain areas involved in depression. Although no clear distinction is made in processes between brain areas, I am convinced that a chemical as well as a morphological imbalance is underlying depression.

This review focused on serotonin and neuroplastic factors, although many other factors are implicated in depression. Stress and disturbances in the HPA-axis, cytokines and neuroinflammation, but also circadian fluctuations appear to play a part in depression. Besides these factors, other monoaminergic neurotransmitters such as dopamine and norepinephrine also play a role in depression, but were beyond the scope of this review (Hayley, Poulter, Merali, & Anisman, 2005; Krishnan & Nestler, 2008; Massart et al., 2012).

But even when all these factors will be included in a model to explain depression, I am not sure depression can be coined as a general phenomenon. Depression is very heterogeneous and is found in various forms, for example bipolar depression, seasonal affective disorder and major depressive disorder (Benazzi, 2006). Nevertheless, depressive disorders seem to show some similarities that could indicate a shared principle, for example energy saving. This review focused mainly on the most common variant of depression, major depressive disorder, and while the neurobiology of all depressive disorders may show similarities, it is doubtful if findings concerning one depressive disorder are applicable to all.

In depression, BDNF and serotonin are often described as a duo (Homberg et al., 2014; Martinowich & Lu, 2007; Mattson, Maudsley, & Martin, 2004). Serotonin and glutamate are also believed to be a signaling couple in depression (Fischer et al., 2015), but in light of described literature serotonin, glutamate and BDNF coupled together explain about depression and antidepressant effects better than when seen as separate duos. Two hypothetical models are proposed for antidepressant effects (figure 9) and depression (figure 10), including serotonin, glutamate and BDNF, regarding neuroplastic processes.

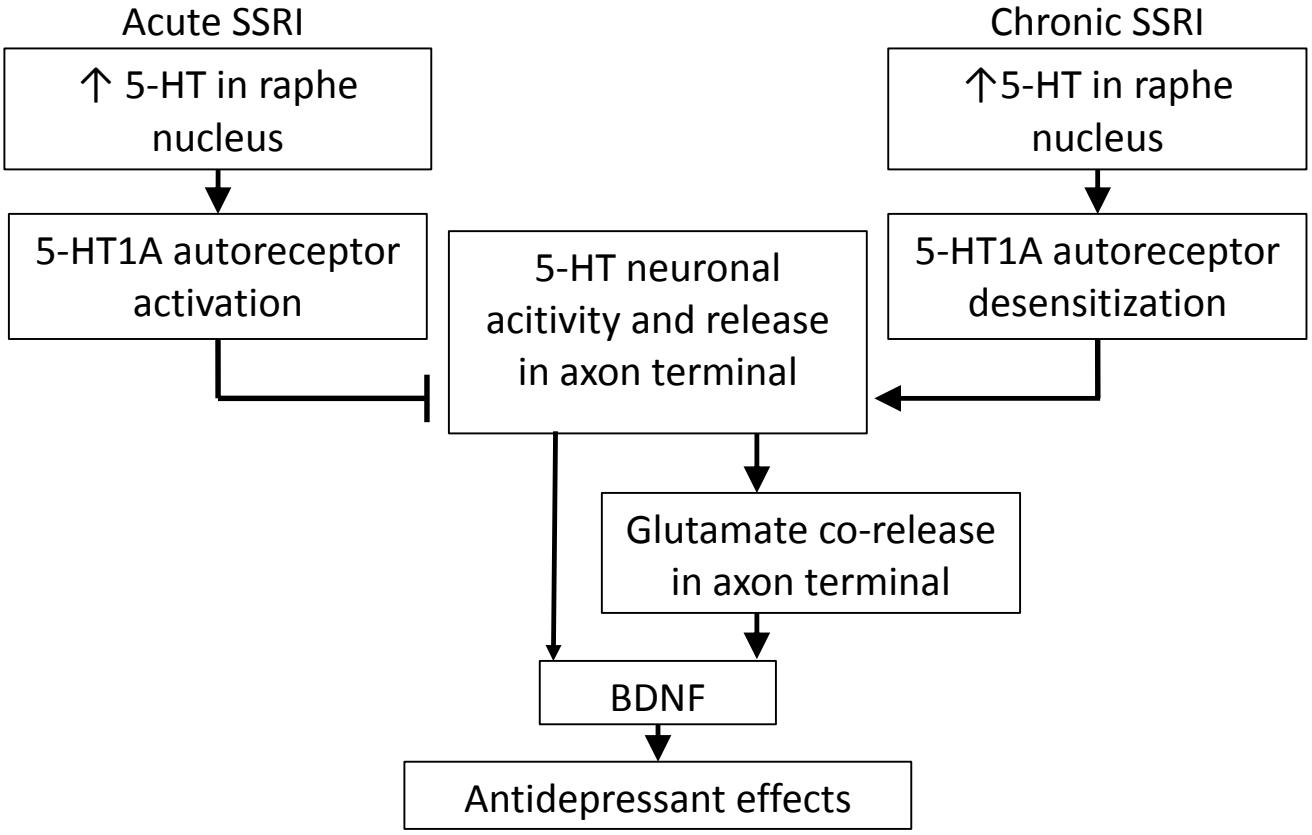

Figure 9 Hypothetical model of antidepressant effects of SSRIs involving serotonin, glutamate and BDNF, mainly focusing on the neuroplastic processes that may underlie the antidepressant effects of SSRIs. Acute SSRI use increases serotonin levels in raphe neurons. By activating 5-HT1A autoreceptors, co-release of serotonin and glutamate is inhibited at axon terminals resulting in less BDNF expression and causing no antidepressant effects, or even pro-depressive effects. Chronic SSRIs administration causes 5-HT1A autoreceptor desensitization and then serotonin-glutamate co-release is restored back to normal. Glutamate, and in a lesser extent serotonin directly, increase BDNF transcription which may underlie the antidepressant effects of SSRIs.

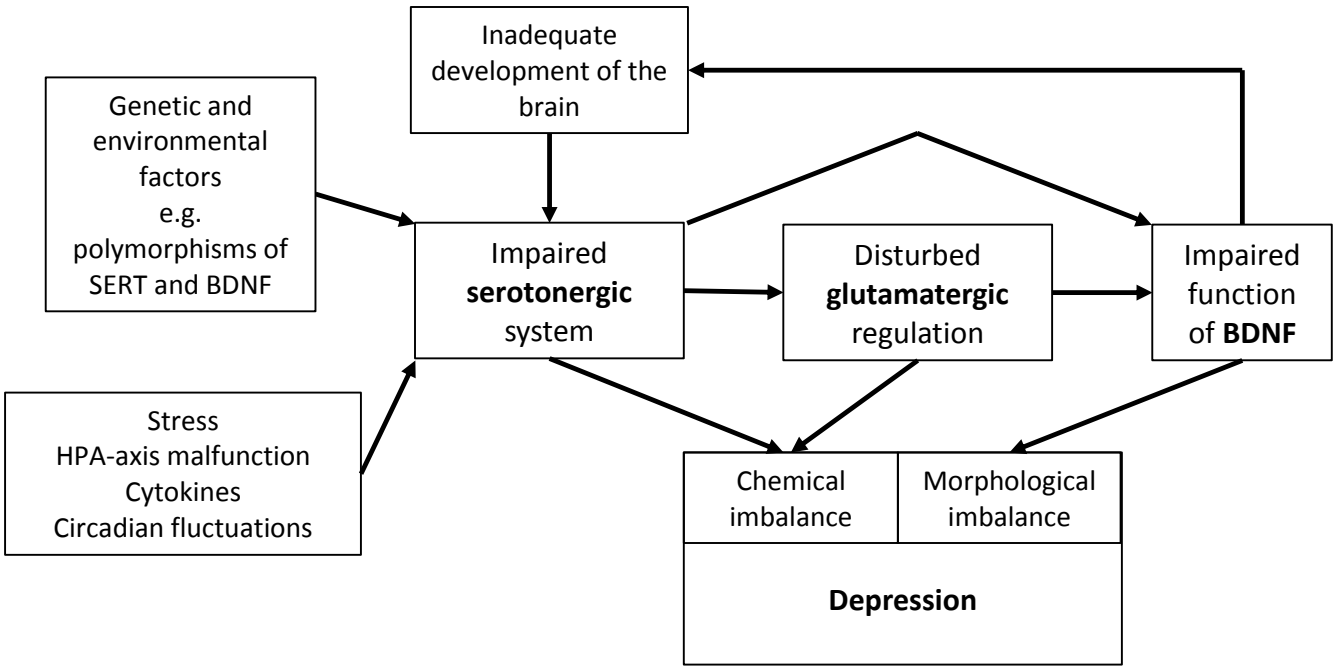

Figure 10 Hypothetical model of depression involving serotonin, glutamate and BDNF causing chemical and morphological imbalances which may underlie depression. Several factors, such as stress, HPA-axis malfunction, cytokines and circadian fluctuation, genetic-environment interactions and impaired brain development, can cause an impaired serotonergic system. Serotonergic dysfunction can lead to a disturbed regulation of glutamate and eventually to BDNF malfunction. Serotonin and glutamatergic impairments can contribute to chemical imbalances underlying depression, whereas an ill-functioning BDNF system can cause morphological abnormalities associated with depression.

Returning to the main questions posed in the introduction, it can be concluded that serotonin does play a major role in depression and the effect of antidepressant action. Deduced from the literature described above, it may be an indirect regulatory role, rather than a directly causal relationship. Neuroplastic changes are a good candidate in regarding antidepressant actions, and may also be involved in causing depression. While the neuroplastic hypothesis of depression mainly focused on BDNF or glutamate, serotonin appears to be able to regulate neuroplastic changes indirectly, and to a lesser extent, directly.

By following glutamate and BDNF levels after acute and chronic antidepressants treatment, future research can confirm this hypothetical model and verify whether serotonin-regulated, glutamate-mediated, BDNF-induced neuroplastic changes can contribute to depression and the effects of antidepressant drugs. As Sanacora and colleagues said, 'The brain is in good part a glutamatergic/GABAergic machine' (Sanacora et al., 2012). Therefore, it would be likely that such a powerful system as the glutamatergic system can heavily influence processes in the brain which may underlie depression. Nevertheless, the contribution of co-released glutamate in depression and antidepressant effects, described in the models above, is not yet fully understood and further research needs to be done to determine the role of this co-released glutamate. Furthermore, a better understanding of the interactions between serotonin, glutamate and BDNF can also improve antidepressant drug use by combining or alternating drugs acting on different systems. For example, combining glutamate increasing drugs and SSRI to achieve both fast and robust antidepressant effects.

In this review, more pieces of the puzzling, paradoxical role of serotonin in depression and antidepressant research have been put together. Nevertheless, the entire picture is not fully elucidated and more work has to be done to unravel the intracellular, transcriptional world behind the neurotransmitters and neurotrophic factors involved in depression.

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