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Antidepressants and Morphological Plasticity of Monoamine Neurons

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1. Introduction

In the 1950s, the monoamines 5-hydroxytryptamine (5-HT) (Woolley & Shaw, 1954), noradrenaline (NA) (Vogt, 1954), and dopamine (DA) (Carlsson, 1958) were identified in the brain. After this discovery, it was identified that the tricyclic compound imipramine and the antituberculosis drug iproniazid were effective in the treatment of clinical depression, and that these drugs can increase the extracellular concentration of monoamines by inhibiting the re-uptake of 5-HT and NA and by blocking monoamine oxidase (MAO) respectively. These findings have led to the catecholamine hypothesis of depression (Schildkraut, 1965), followed by the monoamine hypothesis (Coppin, 1967), which propose that depression is caused by deficiencies within the central catecholaminergic or monoaminergic systems respectively. At present, it is understood that all antidepressants increase monoamine levels in the brain. Other evidence supporting the monoamine hypothesis has also been put forward: reserpine, which depletes monoamines in the synaptic cleft, caused depressive symptoms in some patients taking it for the treatment of hypertension. 5-HIAA, the primary metabolite of 5-HT, was seen as reduced in the cerebrospinal fluid of clinically depressed patients. All these findings suggest that monoamine concentrations in the brain are reduced in depressive patients.

Despite compelling evidence supporting the monoamine hypothesis, there is an enigma which must be resolved. Although antidepressants raise monoamine concentrations immediately after their administration, it takes several weeks or more for their clinical efficacy to become apparent. The delayed onset of action of antidepressants suggests that they induce slowly occurring changes in the monoaminergic systems, rather than simply increasing the monoamine concentrations. It has been reported that chronic (but not acute) treatments with antidepressants cause the down-regulation of postsynaptic β -adrenergic receptors (Banerjee et al., 1977; Vetulani & Sulser, 1975). This finding presumably explained the delayed onset of antidepressant action. However, the down-regulation of β -adrenergic receptors appeared to contradict the monoamine hypothesis of depression, which proposes hypofunction in the monoaminergic systems during depression. The decreased β -adrenergic receptor sensitivity observed following treatments suggests that antidepressants exert clinical effects by attenuating *hyper*function of the noradrenergic system.

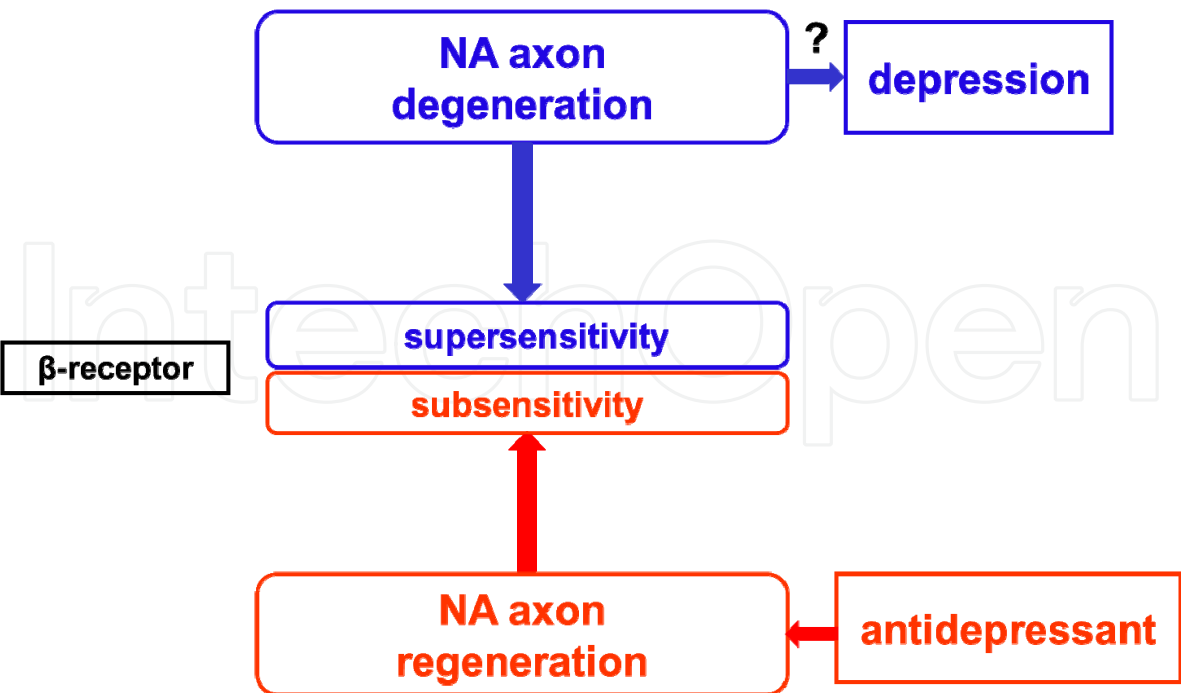


Fig. 1. A link between postsynaptic receptors (β -receptors) and presynaptic axons (NA axons). The degeneration of presynaptic NA axons induced by an NA-specific neurotoxin causes supersensitivity of postsynaptic β -receptors, while repeated administration of noradrenergic antidepressants causes subsensitivity. Based on these findings, the antidepressants have been shown to have the ability to induce NA axon regeneration (Nakamura, 1990,1991). This has led to the view that the degeneration of NA axons is involved in the pathophysiology of depression.

This discrepancy is resolved by considering an association of the receptor sensitivity with morphological changes (Fig. 1). Denervated skeletal muscle becomes supersensitive to acetylcholine due to an increase in the number of acetylcholine receptors on the muscle membrane (denervation supersensitivity). Denervation supersensitivity similar to this occurs in the central noradrenergic system: denervation of cortical NA axons with 6-hydroxydopamine (6-OHDA), a neurotoxin to catecholaminergic neurons, causes supersensitivity (up-regulation) in cortical β -adrenergic receptors (Sporn et al., 1976). As up-regulation of β -adrenergic receptors is associated with denervation of NA axons, it is possible that the converse is also true: down-regulation of β -adrenergic receptors results from an increase in the density of NA axons, i.e., regeneration or sprouting of NA axons. This idea has led to the monoamine axon hypothesis of depression, which proposes the involvement of degeneration or retraction of monoaminergic axons in the pathophysiology of depression (Nakamura, 1990; Harley, 2003). According to the monoamine axon hypothesis, antidepressant drugs exert their effects by inducing regeneration or sprouting of monoaminergic axons.

This review focuses on the effects of antidepressants on the morphological plasticity of monoaminergic axons (mainly 5-HT- and NA-axons) in the adult and developing brain. There is no report showing a link between morphological plasticity and antidepressants in DA axons, although DA neurons have been reported as having the ability to induce axonal sprouting (Hansen et al., 1995; Blanchard et al., 1996; Finkelstein et al., 2000; Stanic et al.,

2003). Therefore, this review is limited to links between antidepressants and the morphological plasticity of 5-HT and NA neurons. In addition, other factors including stress, retinoic acid, and interferon- α that affect morphological plasticity of monoamine neurons are described in relation to clinical depression. This review also discusses slow-acting (monoaminergic) and fast-acting (glutamatergic) antidepressants in relation to a possible link between the monoaminergic and glutamatergic systems.

2. Effects of antidepressants on the density of monoaminergic axons

There is evidence to support the monoamine axon hypothesis of depression. It has been shown that antidepressants that increase extracellular NA concentrations also enhance the regeneration of damaged NA axons (Nakamura, 1990, 1991), and that antidepressants that modulate 5-HT release from 5-HT axon terminals also induce axonal sprouting of 5-HT neurons (Zhou et al., 2006). Focusing on the noradrenergic system, we developed a rat model by which we can assess the ability of antidepressant drugs to induce the regeneration of NA axons (Nakamura, 1990, 1991, 1994). First, to denervate NA axons locally, 6-OHDA (2 $\mu\text{g}/0.5 \mu\text{l}$) was injected bilaterally in the frontal cortex. 6-OHDA was delivered from the tip of a 30-gauge metallic cannula, which was connected to an infusion pump with polyethylene tubing. Two weeks after the toxin infusion, one hemisphere was infused with an antidepressant at the same cortical site, and the other was infused with saline. These drugs were delivered continuously from the tip of an infusion cannula connected to osmotic minipumps (Alzet, model 2002) for more than two weeks (Kasamatsu et al., 1979). To visualize NA axons, we used either fluorescence histochemistry or immunohistochemistry. The size of NA (and DA) axon denervation was then compared between the antidepressant- and saline-infused hemispheres. We showed that antidepressants that increase the extracellular concentration of NA, such as desipramine, maprotiline, and mianserin, have the ability to induce regeneration of NA axons, but fluoxetine, a potent reuptake inhibitor of 5-HT, does not (Nakamura, 1990, 1991). Desipramine and maprotiline are potent reuptake inhibitors of NA, while mianserin has little or no effect on NA reuptake inhibition but enhances NA release by blocking presynaptic α_2 -adrenergic receptors. Zhou et al. (2006) have demonstrated the ability of antidepressants to induce axonal sprouting of 5-HT neurons by systemic injections of antidepressants in rats without damaging the 5-HT axons. In this study, they tested three types of antidepressants: the 5-HT reuptake inhibitor fluoxetine, the 5-HT reuptake enhancer tianeptine, and the NA reuptake inhibitor desipramine. These antidepressant drugs were administered intraperitoneally for four weeks. The density of 5-HT axons was examined by visualizing 5-HT axons using antibody immunohistochemistry on 5-HT or 5-HT transporters. They found that fluoxetine and tianeptine, but not desipramine, increased the density of 5-HT axons in the cerebral cortex and some limbic forebrain areas. Using an anterograde labeling technique, they also showed that branching increased in terminal axons from the dorsal raphe. These findings all strongly indicate that antidepressants that modulate 5-HT reuptake also induce axonal sprouting of 5-HT neurons.

These findings appear to suggest that an increased extracellular NA concentration in the synaptic cleft is required to induce axonal regeneration in NA neurons. Regarding 5-HT neurons, however, it is unlikely that an increase in extracellular 5-HT concentration causes axonal sprouting of 5-HT neurons, because the antidepressant-induced sprouting of 5-HT

axons occurs after treatments with both 5-HT reuptake inhibitors and facilitators (Zhou et al., 2006). It is worth noting that axonal regeneration in NA neurons is induced by NA antidepressants but not by 5-HT antidepressants (fluoxetine), while 5-HT but not NA antidepressants are able to induce axonal sprouting in 5-HT neurons. This finding suggests the possibility that terminal axons of the monoamine neurons form, at least in part, in relation to changes in the release of their own neurotransmitter.

3. Effects of stress on the morphology of monoaminergic axons

Many studies have demonstrated that 5-HT and NA axons have a great capacity to regenerate in response to brain damage (Nygren et al., 1971; Bjorklund et al., 1973; Nygren et al., 1974; Bjorklund & Lindvall, 1979; Wiklund & Bjorklund, 1980; Fritschy & Grzanna, 1992; Liu et al., 2003). It has been noted that the regeneration of 5-HT axons occurred as early as 28 days after damage from 5-HT neurotoxin injection, while the regeneration of NA axons was not evident 60 days after NA neurotoxin injection (Liu et al., 2003). Furthermore, repeated stress, which is a major cause of depression, has been shown to cause degeneration (or retraction) or regeneration (or sprouting) of monoaminergic axons (Nakamura et al., 1989; Sakaguchi & Nakamura, 1990; Kitayama et al., 1994, 1997; Liu et al., 2004, 2006; Kuramochi et al., 2009). Of interest is that the effects of repeated stress on the morphology of 5-HT and NA axons are not the same. For example, in cortices partially denervated by either 5-HT or NA neurotoxin, repeated stress causes 5-HT axon sprouting and NA axon retraction in cortical regions outside the denervation site (Liu et al., 2004). Moreover, the expression of brain-derived neurotrophic factor (BDNF), reportedly a neurotrophic factor for 5-HT axons (Eaton et al., 1995; Mamounas et al., 1995, 2000), was found to increase in cortical regions where 5-HT axon sprouting had occurred in response to stress. These findings suggest that the molecular mechanism of axonal regeneration or sprouting is different between 5-HT and NA axons. As mentioned earlier, this possibility is also supported by the finding that sprouting of 5-HT and regeneration of NA axons are induced by 5-HT and NA antidepressants, respectively.

4. Link between morphology of monoaminergic axons and depressive behavior

There are reports showing a link between morphological changes in monoaminergic axons and depressive symptoms in animal models of depression. Kitayama et al. (1994, 1997) have demonstrated that an animal model of depression resulted in the degeneration of cortical NA axon terminals. Model animals were subjected to long-term walking stress for two weeks, and showed depressive behaviors including prolonged inactivity, seclusion, aggression, motor retardation, lack of coupling behavior, fitful sleep, weight loss, and hypersensitivity to light and sound (Hatotani et al., 1977, 1979; Kitayama et al., 1994, 1997). In this model, the density of NA axons in the frontal cortex projecting from the locus coeruleus (LC) was examined using retrograde labeling of LC neurons with horseradish peroxidase injected into the cortex and immunohistochemical staining of cortical axons with dopamine- β -hydroxylase antibody. The NA axon density was significantly reduced in the depressed rats, and when subjects were allowed to engage in spontaneous running activity, their recovery rates were positively correlated with the density of NA axons (Kitayama et al., 1997). The density of cortical NA axons in depressed rats was restored by chronic

treatment with imipramine (Kitayama et al., 1994, 1997) producing a reversal of depressive behaviors (Kitayama et al., 1987). These findings all support the possibility that degeneration of NA axons is involved in the pathophysiology of depression, and that antidepressants exert their clinical efficacy by inducing the regeneration of NA axons. It is notable that some of the animals subjected to long-term forced walking stress did not demonstrate persistent inactivity but gradually recovered to control levels after the end of the stress treatments (spontaneous recovery rats). The spontaneous recovery rats showed an increase, rather than a decrease, in the density of NA axons as compared to unstressed control rats (Kitayama et al., 1997). This finding suggests that adaptation to stress produces regeneration or sprouting of NA axons. This is consistent with the observation that sprouting of NA axons occurs following chronic mild stress (Nakamura et al., 1989; Sakaguchi & Nakamura, 1990; Nakamura, 1991). It remains to be determined whether morphological plasticity of 5-HT axons is involved in the depression model of long-term forced walking stress.

A recent study has presented a possible link between the density of 5-HT axons and depressive behavior in rats (Kuramochi & Nakamura, 2009). This study examined the effects of postweaning social isolation stress on the density of 5-HT and NA axons and the presence of depressive behavior as assessed by immobility in the forced swim test. Social isolation rearing, which started at postnatal day (PD) 28 and continued until eight to nine weeks later, reduced the density of 5-HT but not NA axons in the central nucleus and basolateral nucleus of the amygdala and CA3 of the hippocampus. Moreover, increased immobility was observed in the forced swim test, suggesting that postweaning social isolation is a possible model of depression containing 5-HT axon deficits. In addition to postweaning social isolation rearing, this study examined the effects of postnatal treatment with the antidepressant clomipramine on the density of 5-HT and NA axons and the presence of depressive behavior. Paradoxically, it has been reported that neonatal treatment with clomipramine induced a rat model of depression as measured by increased immobility in the forced swim test (Velazquez-Moctezuma & Diaz Ruiz, 1992; Bonilla-Jaime et al., 2003). Furthermore, Vijayakumar and Meti (1999) have reported that neonatal treatment with clomipramine caused a decrease in levels of 5-HT and NA in several brain regions, including the frontal cortex and hippocampus. However, following the same treatment protocols, Kuramochi and Nakamura failed to find any changes in either the density of 5-HT and NA axons or the immobility observed in the forced swim test following neonatal treatment with clomipramine. This result is consistent with the finding that neonatal clomipramine treatment had little effect on tryptophan hydroxylase in the dorsal raphe or 5-HT transporter expression in the cerebral cortex (Maciag et al., 2006), and no effect on forced swim immobility (Yoo et al., 2000). The contradictory results may be due to differences in rat strains used for each experiment. The experiments in which neonatal clomipramine induced depression used Wistar rats, whereas the experiments that failed to induce depression used Sprague-Dawley rats or Long-Evans rats. Therefore, it is possible that the Wistar strain is more susceptible to neonatal treatment with clomipramine than other strains (Kuramochi & Nakamura, 2009).

Gonzalez and Aston-Jones (2006, 2008) have reported that light deprivation or long-term exposure to constant darkness in rats (DD) increased apoptosis in LC neurons and decreased the number of NA boutons in the cerebral cortex. The DD rats also demonstrated increased immobility in the forced swim test. The results suggest that the DD rats displaying

depressive behaviors could be an appropriate model for seasonal affective disorders (SAD) associated with limited light exposure, and that the pathophysiology of SAD may also involve degeneration or retraction of NA axons. Regarding the molecular mechanism of DD-induced depressive behaviors, Monje et al. (2011) have reported that activation of the proinflammatory cytokine interleukin-6 (IL-6) through the NF- κ B signaling pathway plays a pivotal role in causing such behaviors, although it remains unclear whether elevated IL-6 levels are associated with the DD-induced degeneration or retraction of NA axons.

It remains to be determined that the major symptoms of depression, i.e., depressed mood and anhedonia, are induced by changes in the morphology of 5-HT and/or NA axons. It is likely that the degeneration of 5-HT and/or NA axons causes depressed mood rather than anhedonia, because anhedonia is thought to be associated with dysfunction of the dopaminergic reward system.

5. Effects of chemical factors on morphology of monoaminergic axons

To understand the molecular mechanisms of the morphological alterations of monoaminergic axons observed in depression models or induced by antidepressants, it is important to identify the endogenous chemical factors that affect these observed changes. The following are chemicals which have been reported to induce morphological changes of monoaminergic neurons (or axons) in relation to depressive behaviors (Interferon- α , retinoic acids) or effects of antidepressants (phospholipase A2). However, it remains unclear what roles these chemicals play in the molecular mechanisms of stress-related depression.

5.1 Interferon- α

Interferon- α (IFN- α), a proinflammatory cytokine widely used for the treatment of cancers and viral illnesses, is well-known to induce depressive symptoms in 30-50% of patients (Schiepers et al., 2005; Raison et al., 2006). Based on this fact, Ishikawa et al. (2007) have shown that chronic treatments with IFN- α in rats caused significant decreases in the densities of NA axons in the dorsal medial prefrontal cortex, ventral medial prefrontal cortex, and dentate gyrus of the hippocampus and of 5-HT axons in the ventral medial prefrontal cortex and amygdala. The changes in the density of NA axons became apparent after treatments with IFN- α after nine weeks, but not at four weeks. It is not clear why such a long-term administration of IFN- α was necessary to cause the degeneration of the monoaminergic axons. One possibility is that since IFN- α has little ability to cross the blood-brain barrier (BBB) (Collins et al., 1985; Wiranowska et al., 1989), long-term administration of IFN- α may disrupt the BBB so that IFN- α becomes able to enter the brain. Moreover, it is possible that the changes in the densities of the monoaminergic axons induced by chronic administration of IFN- α are not due to IFN- α directly. As IFN- α increases other cytokines such as IL-6 and IL-8, which are also associated with depression (Bonaccorso et al., 2001), the cytokines induced by IFN- α might be responsible for the observed changes in densities (Ishikawa et al., 2007). Taken together with a possible involvement of IL-6 in DD-induced depressive behavior (Monje et al., 2011), proinflammatory cytokines may play a critical role in the pathophysiology of depression because of their association with the degeneration or retraction of monoaminergic axons.

5.2 Phospholipase A2

As mentioned in the Introduction, down-regulation of β -adrenergic receptors induced by chronic administration of antidepressants may be associated with the antidepressant-induced regeneration of NA axons. It has been reported that down-regulation of β -adrenergic receptors following repeated application of β -adrenergic agonists or chronic stress treatment is blocked by phospholipase A2 (PLA2) inhibitors, while this down-regulation can be induced by the activation of PLA2 (Limbird & Lefkowitz, 1976; Mallorga et al., 1980; Hirata & Axelrod, 1980; Torda et al., 1981; Cohen et al., 1985). Manji et al. (1991) demonstrated that PLA2 activation is involved in the down-regulation of β -adrenergic receptors induced by chronic desipramine treatment. Moreover, they suggested that in addition to elevated intrasynaptic levels of NA, desipramine acts directly on the postsynaptic membrane to contribute to the down-regulation. A possible link between down-regulation of β -adrenergic receptors and the regeneration of NA axons raised the possibility that PLA2 is involved in the molecular mechanisms of the antidepressant-induced regeneration of NA axons. Nakamura (1993, 1994) demonstrated that mepacrine or 4-bromphenacyl bromide, which are PLA2 inhibitors, attenuates the regeneration of NA axons induced by desipramine, while the PLA2 activator mellitin induces NA axon regeneration. These findings support the notion that the antidepressant-induced regeneration of NA axons is mediated, at least in part, through PLA2.

PLA2 is an enzyme that generates free fatty acids, such as arachidonic acid (AA), eicosapentenoic acid (EPA) and docosahexaenoic acid (DHA), by acting on membrane phospholipids. AA produces a variety of bioactive substances, such as prostaglandins and leukotrienes, via cyclooxygenase or lipoxygenase. Since aspirin, a cyclooxygenase inhibitor, had no apparent effect on the desipramine-induced regeneration of NA axons (unpublished data, Nakamura), it seems unlikely that the cyclooxygenase system would play a critical role in the desipramine-induced regeneration of NA axons. Many reports have shown lower levels of EPA and/or DHA being associated with clinical depression (Peet et al., 1998; De Vriese et al., 2003; Frasure-Smith et al., 2004; McNamara et al., 2007; Lin et al., 2010; Su et al., 2010). Animal studies demonstrated that administration of EPA and DHA had an antidepressant-like effect, reducing immobility in the forced swim test (Carlezon et al., 2005; Huang et al., 2008). Moreover, a recent study reported that the action of maprotiline, an NA reuptake inhibitor with the same effect, is mediated by EPA or DHA released by activation of calcium-independent PLA2 in the prefrontal cortex (Lee et al., 2011), although it remains unclear whether the EPA or DHA releases are associated with regeneration or sprouting of NA axons. Notably, there is one report which has shown the association between PLA2 genes and the risk of IFN- α -induced depression (Su et al., 2010). All these findings suggest that the PLA2-AA/EPA/DHA signaling pathway plays a crucial role in the occurrence of depressive symptoms, possibly by affecting the morphology of monoaminergic axons.

5.3 Retinoic acids

It has been reported that the acne drug Accutane (isotretinoin), the active component of which is 13-cis-retinoic acid (13-cis-RA), occasionally induces severe depression with suicidal ideation (Wysowski et al., 2001; Hull & D'Arcy, 2003; O'Donnell, 2003). There are conflicting studies to this effect: O'Reilly et al. (2006) demonstrated that chronic administration of 13-cis-RA increased depression-related behavior in adult mice, although

Ferguson et al. (2005) reported that 13-cis-RA or all-trans-RA had no such effect in rats. Based on findings that 13-cis-RA reduced neurogenesis and cell survival in the hippocampi of adult mice (Crandall et al., 2004; Sakai et al., 2004), McCaffery and coworkers have suggested that hippocampal cell loss is a major contributor to the pathophysiology of depression associated with 13-cis-RA use. Regarding the relationship between 13-cis-RA and the morphology of monoamine neurons, Ishikawa et al. (2008) demonstrated that the negative effects on the dendritic morphology of slice-cultured 5-HT neurons created by high doses of 13-cis-RA is mediated via retinoic acid receptor (RAR) and retinoid X receptor (RXR), which are nuclear receptors acting as ligand-inducible transcription factors (Chambon, 1996). It remains unclear whether 13-cis-RA induces the degeneration/retraction of monoaminergic axons through RAR and/or through RXR in the adult animal brain. It is notable that RA stimulates PLA2 activation via RA receptors, suggesting that the morphological effects of RAs such as 13-cis-RA are mediated along the PLA2 signaling pathway (Farooqui et al., 2004).

5.4 1-Bromopropane

1-Bromopropane (1-BP), a commonly used solvent in the dry cleaning industry (CDC, 2008; Blando et al., 2010), is used as an alternative to ozone layer depleting solvents as a cleaning agent for metal parts in electronics factories (Ichihara, 2005). Exposure to 1-BP has been reported to cause various neurological and neurobehavioral symptoms in humans, including numbness in the legs, ataxic gait and memory disturbances (Ichihara, 2005). In addition, workers exposed to 1-BP often display depressive symptoms (Ichihara et al., 2002; Majersik et al., 2007). To see if exposure to 1-BP causes degeneration of monoaminergic axons, Mohideen et al. (2011) examined the effects of repeated exposure to 1-BP on the density of 5-HT and NA axons in the rat brain. Exposure to 1-BP induced dose-dependent reductions in the density of NA axons in the prefrontal cortex and the basolateral nucleus of the amygdala, but no apparent change in the density of 5-HT axons. The results suggest that depressive symptoms in workers exposed to 1-BP may be associated with degeneration of NA axons in the brain, although the link between 1-BP and endogenous chemical factors involved in the degeneration of NA axons is unclear. The findings also suggest that there are exogenous chemical agents, as well as exogenous stressors, which can induce depressive symptoms, possibly by negatively affecting the morphology of monoaminergic axons.

6. Slow-acting and fast-acting antidepressants

In contrast to the delayed onset of the clinical efficacy of classical antidepressants, recent studies have reported that ketamine, an NMDA antagonist, exerts rapid antidepressant effects in humans (Berman et al., 2000; Zarate et al., 2006; Price et al., 2009). In animals, other NMDA antagonists such as MK-801 and CPP as well as ketamine have been reported to cause rapid antidepressant action in animals, though the effects are short-lasting compared to ketamine (Maeng et al., 2008; Autry et al., 2011). Many studies have corroborated the fact that the antidepressant effects of a single injection of ketamine persist up to 1-2 weeks in humans (Berman et al., 2000; Zarate et al., 2006; Price et al., 2009; Phelps et al., 2009; van het Rot et al., 2010) and animals (Maeng et al., 2008; Li et al., 2010; Autry et al., 2011), while other studies failed to confirm the persistent effects of such an injection in rodents (Popik et al., 2008; Lindholm et al., 2011). Since the fast-acting, sustained antidepressant effects of

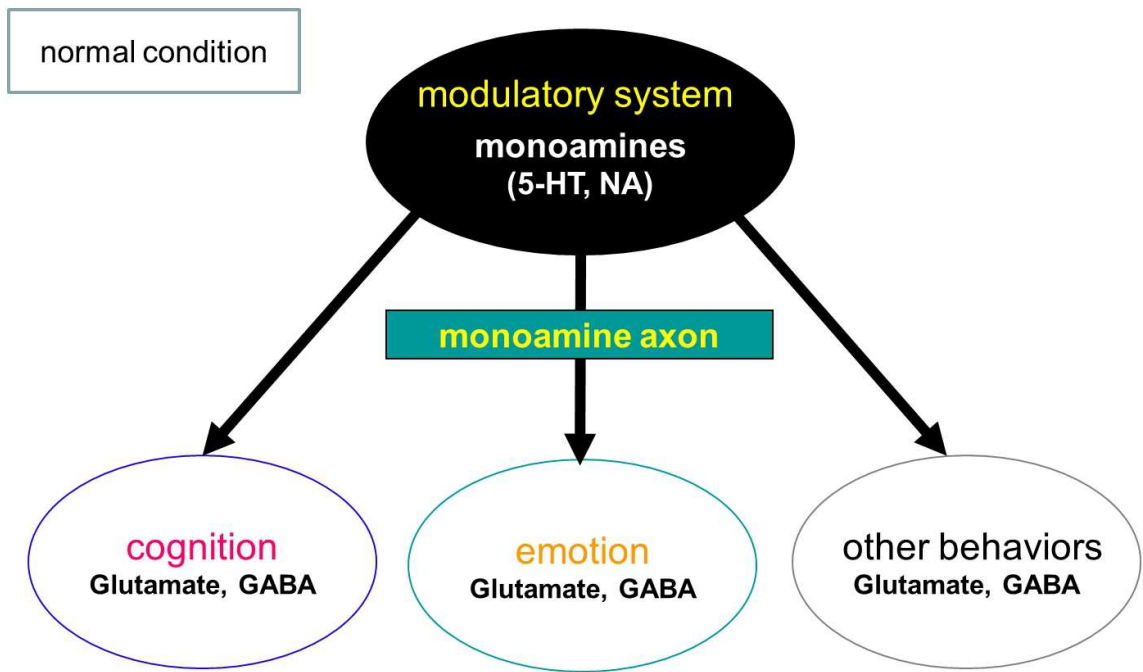


Fig. 2A. All behaviors, including cognition and emotion, are processed by neural circuits mediated by the neurotransmitters glutamate and GABA. The operations of these functional neural circuits are modified by the modulatory systems, which exert their effects by releasing monoamines.

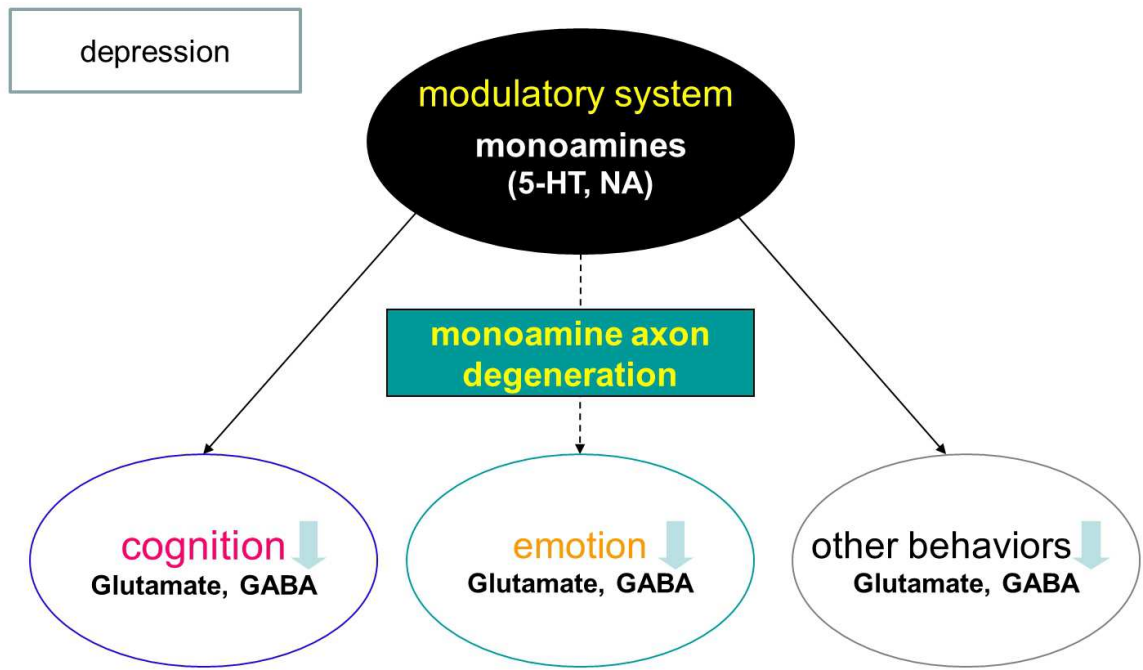


Fig. 2B. In depression, the degeneration of monoaminergic axons containing 5-HT and/or NA may occur, resulting in the disorder of neural circuits that process behaviors such as emotion.

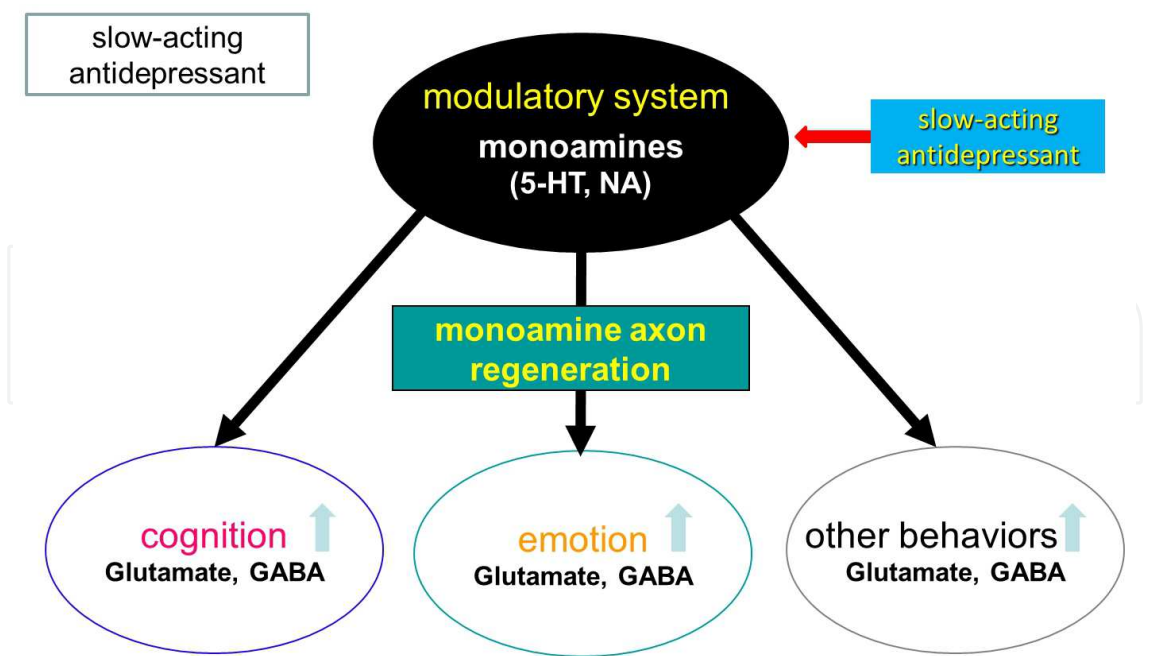


Fig. 2C. Slow-acting antidepressants affecting monoamine activity may exert their effects by inducing the regeneration of monoaminergic axons containing 5-HT and/or NA, thereby taking a few weeks or more to restore the normal conditions and operations of functional neural circuits.

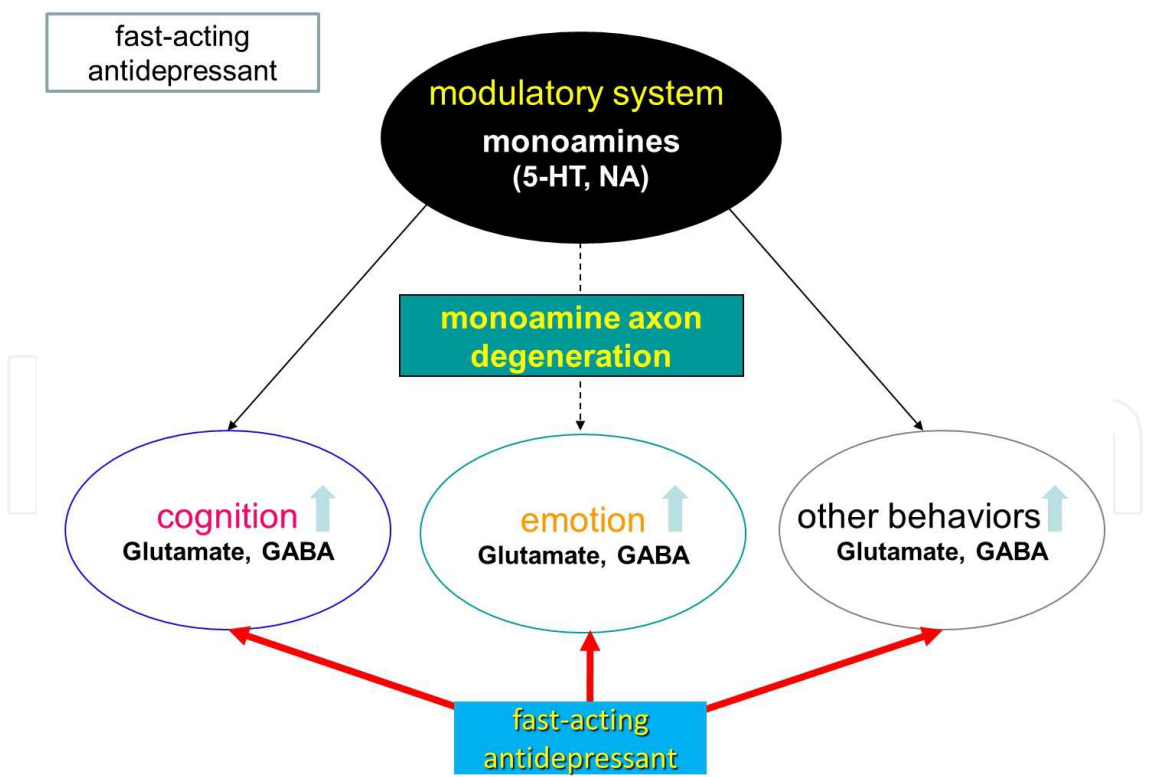


Fig. 2D. Fast-acting antidepressants may restore the normal conditions of functional neural circuits by directly affecting the glutamatergic system. However, the dysregulation of the monoamine system may continue.

ketamine are blocked by AMPA receptor antagonists, activation of AMPA receptors is presumably involved in the cellular mechanism of ketamine’s action (Maeng et al., 2008; Autry et al., 2011; Koike et al., 2011). These findings indicate that the rapid antidepressant response of ketamine is associated with the glutamatergic systems, including NMDA and AMPA receptors.

Glutamate and GABA are the major excitatory and inhibitory neurotransmitters in the brain, respectively. The information processing of functional neural circuits is mediated by glutamate and GABA. All behaviors, including cognition and emotion, are performed by the glutamatergic/GABAergic neural circuits. The neurotransmitters of monoaminergic systems influence the activity of glutamate and GABA in these functional neural circuits (Fig. 2A). Thus, glutamate and GABA play a direct role in the expression of behaviors, while the monoaminergic systems, although not directly responsible, play a role in attenuating or strengthening it by modulating the activity of glutamatergic/GABAergic neural circuits. In depression, the degeneration of monoaminergic axons containing 5-HT and/or NA may occur, causing the influence of the monoaminergic systems on the functional neural circuits to continuously decline. Consequently, this may blunt the activity of functional neural circuits that process behaviors, including emotion (Fig. 2B), leading to depression and depressive states. Antidepressants affecting the activity of 5-HT and/or NA neurons induce the regeneration of previously degenerated monoaminergic axons and restore the normal conditions of functional neural circuits (Fig. 2C). The antidepressant effects of these antidepressants occur slowly due to the time required for morphological changes to take

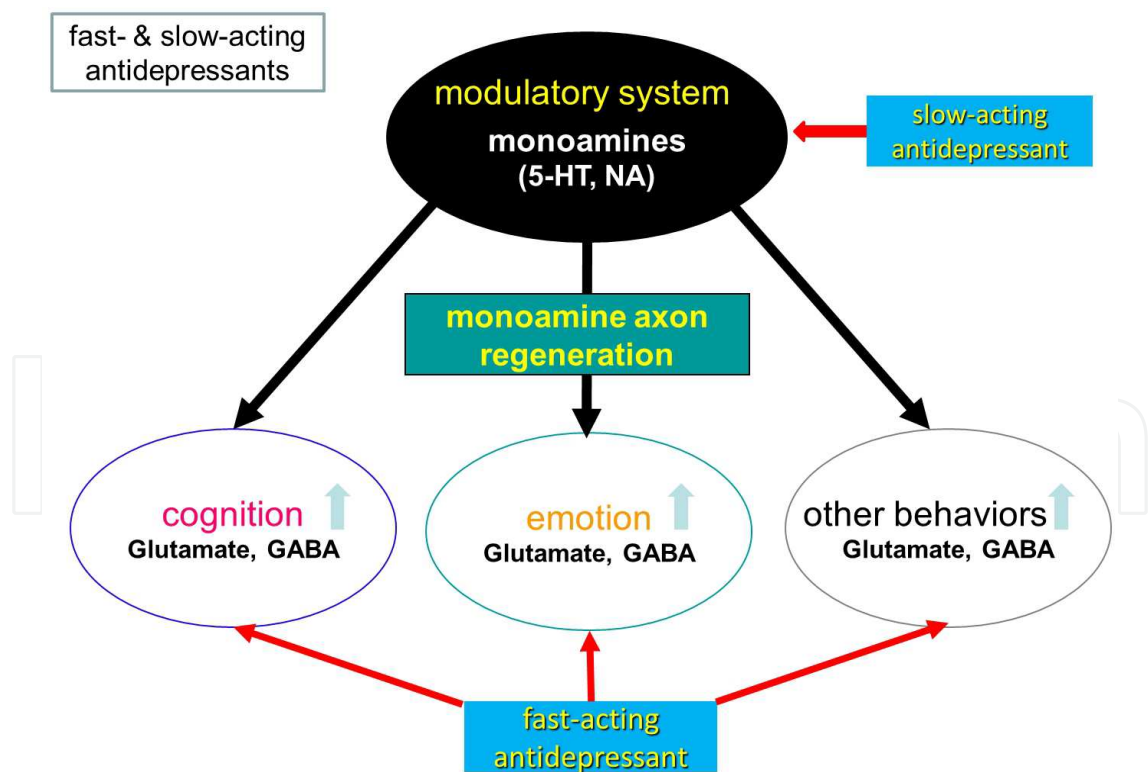


Fig. 2E. Administration of both fast- and slow-acting antidepressants may restore the normal conditions and operations of functional neural circuits within both the glutamatergic and monoaminergic systems.

place, and become manifest over several weeks. In contrast, fast-acting antidepressants such as ketamine, which affect the activity of the glutamatergic system, act directly on functional neural circuits to restore the normal healthy condition, while the monoamine systems remain dysregulated (Fig. 2D). To completely restore functionality of neural circuits, both the glutamatergic and monoaminergic systems must be restored to full capacity through administration of both fast- and slow-acting antidepressants (Fig. 2E).

7. Concluding remarks

The delayed onset of clinical efficacy of classical antidepressants may be explained, at least in part, by the fact that degeneration of 5-HT and/or NA axons is heavily involved in the pathophysiology of depression, and that such antidepressants exert their clinical efficacy by inducing a relatively slow regeneration of these monoaminergic axons. Although newer antidepressants that directly affect the glutamatergic system produce a rapid and sustained antidepressant response, the monoaminergic systems may remain suboptimal and in need of restoration. New antidepressant development should focus on maintaining these immediate effects of action on the glutamatergic system, but also restoring the modulatory activity of the monoaminergic systems in the long-term, possibly by inducing the regeneration of monoaminergic axons.

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9. References

- Aan het Rot, M., Collins, K.A., Murrough, J.W., Perez, A.M., Reich, D.L., Charney, D.S. & Mathew, S.J. (2010) Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry*, 67, 139-145.
- Autry, A.E., Adachi, M., Nosyreva, E., Na, E.S., Los, M.F., Cheng, P., Kavalali, E.T. & Monteggia, L.M. (2011) NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*, 475, 91-95.
- Banerjee, S.P., Kung, L.S., Riggi, S.J. & Chanda, S.K. (1977) Development of β -adrenergic receptor subsensitivity by antidepressants. *Nature*, 268, 455-456.
- Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S. & Krystal, J.H. (2000) Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*, 47, 351-354.
- Bjorklund, A. & Lindvall, O. (1979) Regeneration of normal terminal innervation patterns by central noradrenergic neurons after 5,7-dihydroxytryptamine-induced axotomy in the adult rat. *Brain Res*, 171, 271–293.
- Bjorklund, A., Nobin, U. & Stenevi, U. (1973) Regeneration of central 5-HT neurons after axonal degeneration induced by 5,6-dihydroxytryptamine. *Brain Res*, 50, 214-220.
- Blanchard, V., Anglade, P., Dziewczapolski, G., Savasta, M., Agid, Y. & Raisman-Vozari, R. (1996) Dopaminergic sprouting in the rat striatum after partial lesion of the substantia nigra. *Brain Res*, 709, 319-325.

- Blando, J.D., Schill, D.P., De La Cruz, M.P., Zhang, L. & Zhang, J. (2010) Preliminary study of propyl bromide exposure among New Jersey dry cleaners as a result of a pending ban on perchloroethylene. *J Air Waste Manage Assoc*, 60, 1049–1056.
- Bonaccorso, S., Puzella, A., Marino, V., Pasquini, M., Biondi, M., Artini, M. Almerighi, C., Levvero, M., Egyed, B., Bosmans, E., Meltzer, H.Y. & Maes, M. (2001) Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Res*, 105, 45–55.
- Bonilla-Jaime, H., Retana-Marquez, S., Vazquez-Palacios, G. & Moctezuma, J. (2003) Corticosterone and testosterone levels after chronic stress in an animal model of depression. *Neuropsychobiology*, 48, 55–58.
- Carlezon, W.A.Jr., Mague, S.D., Parow, A.M., Stoll, A.L., Cohen, B.M. & Renshaw, P.F. (2005) Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. *Biol Psychiatry*, 57, 343–350.
- Carlsson, A. (1958) A fluorimetric method for the determination of dopamine (3-hydroxytyramine). *Acta Physiol Scand*, 44, 293–298.
- CDC. (2008) Neurologic illness associated with occupational exposure to the solvent 1-bromopropane – New Jersey and Pennsylvania, 2007–2008.
- Chambon, P. (1996) A decade of molecular biology of retinoic acid receptors. *FASEB J*, 10, 940–954.
- Cohen, R.M., McLellan, C., Dauphin, M. & Hirata, F. (1985) Glutaraldehyde pretreatment blocks phospholipase A2 modulation of adrenergic receptors. *Life Sci*, 36, 25–32.
- Collins, J.M., Riccardi, R., Trown, P., O'Neil, D. & Poplack, D.G.. (1985) Plasma and cerebrospinal fluid pharmacokinetics of recombinant interferon alpha A in monkeys: comparison of intravenous, intramuscular, and intraventricular delivery. *Cancer Drug Deliv*, 2, 247–253.
- Coppen, A. (1967) The biochemistry of affective disorders. *Brit J Psychiat*, 113, 1237–1264.
- Crandall, J., Sakai, Y., Zhang, J., Koul, O., Mineur, Y., Crusio, W. E. & McCaffery, P. (2004) 13-cis-Retinoic acid suppresses hippocampal cell division and hippocampal-dependent learning in mice. *Proc Natl Acad Sci USA*. 101, 5111–5116.
- De Vriese, S.R., Christophe, A.B. & Maes, M. (2003) Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: Further evidence that lowered n-PUFAs are related to major depression. *Life Sci*, 73, 3181–3187.
- Eaton, M.J., Staley, J.K., Globus, M.Y. & Whittemore, S.R. (1995) Developmental regulation of early serotonergic neuronal differentiation: the role of brain-derived neurotrophic factor and membrane depolarization. *Dev Biol*, 170, 169–182.
- Ferguson, S., Cisneros, F., Gough, B., Hanig, J. & Berry, K. (2005) Chronic oral treatment with 13-cis-retinoic acid (isotretinoin) or all-trans-retinoic acid does not alter depression-like behaviors in rats. *Toxicol. Sci*, 87, 451–459.
- Finkelstein, D.I., Stanic, D., Parish, C.L., Thomas, D., Dickson, K. & Horne, M.K. (2000) Axonal sprouting following lesions of the rat substantia nigra. *Neuroscience*, 97, 99–112.
- Frasure-Smith, N., Lesperance, F. & Julien, P. (2004) Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol Psychiatry*, 55, 891– 896.

- Fritschy, J.M. & Grzanna, R. (1992) Restoration of ascending noradrenergic projections by residual locus coeruleus neurons: compensatory response to neurotoxin-induced cell death in the adult rat brain. *J Comp Neurol*, 321, 421-441.
- González, M.M. & Aston-Jones, G. (2006) Circadian regulation of arousal: role of the noradrenergic locus coeruleus system and light exposure. *Sleep*, 29, 1327-1336.
- González, M.M. & Aston-Jones, G. (2008) Light deprivation damages monoamine neurons and produces a depressive behavioral phenotype in rats. *Proc Natl Acad Sci USA*, 105, 4898-4903.
- Hansen, J.T., Sakai, K., Greenamyre, J.T. & Moran, S. (1995) Sprouting of dopaminergic fibers from spared mesencephalic dopamine neurons in the unilateral partial lesioned rat. *Brain Res*, 670, 197-204.
- Harley, C.W. (2003) Norepinephrine and serotonin axonal dynamics and clinical depression: A commentary on the interaction between serotonergic and noradrenergic axons during axonal regeneration. *Exp Neurol*, 184, 24-26.
- Hatotani, N., Nomura, J., Inoue, K. & Kitayama, I. (1979) Psychoendocrine model of depression. *Psychoneuroendocrinology*, 4, 155-172.
- Hatotani, N., Nomura, J., Yamaguchi, T. & Kitayama, I. (1977) Clinical and experimental studies on the pathogenesis of depression. *Psychoneuroendocrinology*, 2, 115-130.
- Hirata, F. & Axelrod, J. (1980) Phospholipid methylation and biological signal transmission. *Science*, 209, 1082-1090.
- Huang, S.Y., Yang, H.T., Chiu, C.C., Pariante, C.M. & Su, K.P. (2008) Omega-3 fatty acids on the forced-swimming test. *J Psychiatr Res*, 42, 58-63.
- Hull, P.R. & D'Arcy, C. (2003) Isotretinoin use and subsequent depression and suicide: presenting the evidence. *Am J Clin Dermatol*, 4, 493-505.
- Ichihara, G., Miller, J., Ziolkowska, A., Itohara, S. & Takeuchi, Y. (2002) Neurological disorders in three workers exposed to 1-bromopropane. *J Occup Health*, 44, 1-7.
- Ichihara, G. (2005) Neuro-reproductive toxicities of 1-bromopropane and 2-bromopropane. *Int Arch Occup Environ Health*, 78, 79-96.
- Ishikawa, J., Ishikawa, A. & Nakamura, S. (2007) Interferon- α reduces the density of monoaminergic axons in the rat brain. *NeuroReport*, 18, 137-140.
- Ishikawa, J., Sutoh, C., Ishikawa, A., Kagechika, H., Hirano, H. & Nakamura, S. (2008) 13-cis-retinoic acid alters the cellular morphology of slice-cultured serotonergic neurons in the rat. *Eur J Neurosci*, 27, 2363-2372.
- Kasamatsu, T., Pettigrew, J.D. & Ary, M. (1979) Restoration of visual cortical plasticity by local microperfusion of norepinephrine. *J Comp Neurol*, 185, 163-181.
- Kitayama, I., Murase, S., Koishizawa, M., Kawaguchi, S. & Nomura, J. (1987) Effect of antidepressant on behavior and central catecholamine of depression-model rats. *Jpn J Psychopharmacol*, 7, 433-436.
- Kitayama, I., Nakamura, S., Yaga, T., Murase, S., Nomura, J., Kayahara, T. & Nakano, K. (1994) Degeneration of locus coeruleus axons in stress-induced depression model. *Brain Res Bull*, 35, 573-580.
- Kitayama I., Yaga, T., Kayahara, T., Nakano, K., Murase, S., Otani, M. & Nomura, J. (1997) Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. *Biol Psychiatry*, 42, 687-696.
- Koike, H., Iijima, M. & Chaki, S. (2011) Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. *Behav Brain Res*, 224, 107-111.

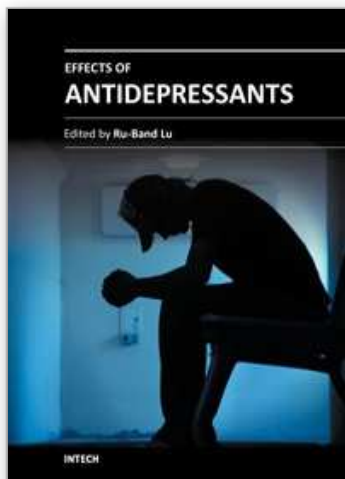
- Kuramochi, M. & Nakamura, S. (2009) Effects of postnatal isolation rearing and antidepressant treatment on the density of serotonergic and noradrenergic axons and depressive behavior in rats. *Neuroscience*, 163, 448-455.
- Lee, L.H., Tan, C.H., Shui, G., Wenk, M.R. & Ong, W.Y. (2011) Role of prefrontal cortical calcium independent phospholipase A2 in antidepressant-like effect of maprotiline. *Int J Neuropsychopharmacol*, 11, 1-12.
- Li, N., Lee, B., Liu, R., Banasr, M., Dwyer, J.M., Iwata, M., Li, X., Aghajanian, G. & Duman, R.S. (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*, 329, 959-964.
- Limbird, L.E. & Lefkowitz, R.J. (1976) Adenylate cyclase-coupled beta adrenergic receptors: Effect of membrane lipid-perturbing agents on receptor binding and enzyme stimulation by catecholamines. *Mol Pharmacol*, 12, 559-567.
- Lin, P.Y., Huang, S.Y. & Su, K.P. (2010) A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatry*, 68, 140-147.
- Lindholm, J.S., Autio, H., Vesa, L., Antila, H., Lindemann, L., Hoener, M.C., Skolnick, P., Rantamäki, T. & Castrén, E. (2012) The antidepressant-like effects of glutamatergic drugs ketamine and AMPA receptor potentiator LY 451646 are preserved in *bdnf*(+/-) heterozygous null mice. *Neuropharmacology*, 62, 391-397.
- Liu, Y., Ishida, Y., Shinoda, K., Furukawa, S. & Nakamura, S. (2004) Opposite morphological responses of partially denervated cortical serotonergic and noradrenergic axons to repeated stress in adult rats. *Brain Res Bull*, 64, 67-74.
- Liu, Y., Ishida, Y., Shinoda, K. & Nakamura, S. (2003) Interaction between serotonergic and noradrenergic axons during axonal regeneration. *Exp Neurol*, 184, 169-178.
- Liu, Y. & Nakamura, S. (2006) Stress-induced plasticity of monoamine axons. *Front Biosci*, 11, 1794-1801.
- Maciag, D., Simpson, K.L., Coppinger, D., Lu, Y., Wang, Y., Lin, R.C. & Paul, I.A. (2006) Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. *Neuropsychopharmacology*, 31, 47-57.
- Maeng, S., Zarate, C.A. Jr., Du, J., Schloesser, R.J., McCammon, J., Chen, G. & Manji, H.K. (2008) Cellular mechanisms underlying the antidepressant effects of ketamine: role of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry*, 63, 349-52.
- Majersik, J.J., Caravati, E.M. & Steffens, J.D. (2007) Severe neurotoxicity associated with exposure to the solvent 1-bromopropane (n-propyl bromide). *Clin Toxicol (Phila)*, 45, 270-276.
- Mallorga, P., Tallman, J.F., Henneberry, R.C., Hirata, F., Strittmatter, W.T., Axelrod, J. (1980) Mepacrine blocks beta-adrenergic agonist-induced desensitization in astrocytoma cells. *Proc Natl Acad Sci USA*, 77, 1341-1345.
- Mamounas, L.A., Altar, C.A., Blue, M.E., Kaplan, D.R., Tessarollo, L. & Lyons, W.E. (2000) BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. *J Neurosci*, 20, 771-782.
- Mamounas, L.A., Blue, M.E., Siuciak, J.A. & Altar, C.A. (1995) Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *J Neurosci*, 15, 7929-7939.
- Manji, H.K., Chen, G.A., Bitran, J.A. & Potter, W.Z. (1991) Down-regulation of beta receptors by desipramine in vitro involves PKC/phospholipase A2. *Psychopharmacol Bull*, 27, 247-253.

- McNamara, R.K., Hahn, C.G., Jandacek, R., Rider, T., Tso, P., Stanford, K.E. & Richtand N.M. (2007) Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. *Biol Psychiatry*, 62, 17-24.
- Mitsumoto, Y., Watanabe, A., Mori, A. & Koga, N. (1988) Spontaneous regeneration of nigrostriatal dopaminergic neurons in MPTP-treated C57BL/6 mice. *Biochem Biophys Res Commun*, 248, 660-663.
- Mohideen, S.S., Ichihara, G., Ichihara, S. & Nakamura, S. (2011) Exposure to 1-bromopropane causes degeneration of noradrenergic axons in the rat brain. *Toxicology*, 285, 67-71.
- Monje, F.J., Cabatic, M., Divisch, I., Kim, E., Herkner, K.R., Binder, B.R. & Daniela D. Pollak, D.D. (2011) Constant Darkness induces IL-6-dependent depression-like behavior through the NF- κ B signaling pathway. *J Neurosci*, 31, 9075-9083.
- Nakamura, S., Sakaguchi, T. & Aoki, F. (1989) Electrophysiological evidence for terminal sprouting of locus coeruleus neurons following repeated mild stress. *Neurosci Lett*, 100, 147-152.
- Nakamura, S. (1990) Antidepressants induce regeneration of catecholaminergic axon terminals in the rat cerebral cortex. *Neurosci Lett*, 111, 64-68.
- Nakamura, S. (1991) Axonal sprouting of noradrenergic locus coeruleus neurons following repeated stress and antidepressant treatment. *Prog Brain Res*, 88, 587-598.
- Nakamura, S. (1991) Effects of mianserin and fluoxetine on axonal regeneration of brain catecholamine neurons. *NeuroReport*, 2, 525-528.
- Nakamura, S. (1993) Involvement of phospholipase A2 in axonal regeneration of brain noradrenergic neurones. *NeuroReport*, 4, 371-374.
- Nakamura, S. (1994) Effects of phospholipase A2 inhibitors on the antidepressant-induced axonal regeneration of noradrenergic locus coeruleus neurons. *Microsc Res Tech*, 29, 204-210.
- Nygren, L.G., Olson, L. & Seiger, A. (1971) Regeneration of monoamine-containing axons in the developing and adult spinal cord of the rat following intraspinal 6-OH-dopamine injections or transections. *Histochemie*, 28, 1-15.
- Nygren, L.G., Fuxe, K., Jonsson, G. & Olson, L. (1974) Functional regeneration of 5-hydroxytryptamine nerve terminals in the rat spinal cord following 5,6-dihydroxytryptamine induced degeneration. *Brain Res*, 78, 377-394.
- O'Donnell, J. (2003) Overview of existing research and information linking isotretinoin (accutane), depression, psychosis, and suicide. *Am J Ther*, 10, 148-159.
- O'Reilly, K.C., Shumake, J., Gonzalez-Lima, F., Lane, M.A. & Bailey, S.J. (2006) Chronic administration of 13-cis-retinoic acid increases depression-related behavior in mice. *Neuropsychopharmacology*, 31, 1919-1927.
- Peet, M., Murphy, B., Shay, J. & Horrobin, D. (1998) Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry*, 43, 315-319.
- Phelps, L.E., Brutsche, N., Moral, J.R., Luckenbaugh, D.A., Manji, H. & Zarate Jr., C.A. (2009) Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. *Biol Psychiatry*, 65, 181-184.
- Popik, P., Kos, T., Sowa-Kucma, M. & Nowak, G. (2008) Lack of persistent effects of ketamine in rodent models of depression. *Psychopharmacology* 198, 421-430.

- Price, R.B., Nock, M.K., Charney, D.S. & Mathew, S.J. (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry*, 66, 522–526.
- Raison, C.L., Capuron, L. & Miller, A.H. (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*, 27, 24–31.
- Sakaguchi, T. & Nakamura, S. (1990) Duration-dependent effects of repeated restraint stress on cortical projections of locus coeruleus neurons. *Neurosci Lett*, 118, 193–196.
- Sakai, Y., Crandall, J.E., Brodsky, J. & McCaffery, P. (2004) 13-cis Retinoic acid (accutane) suppresses hippocampal cell survival in mice. *Ann NY Acad Sci.*, 1021, 436–440.
- Schiepers, O.J., Wichers, M.C. & Maes, M. (2005) Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry*, 29, 201–217.
- Schildkraut, J. J. (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiat*, 122, 509–522.
- Sporn, J.R., Harden, T.K., Wolfe, B.B. & Molinoff, P.B. (1976) β -Adrenergic receptor involvement in 6-hydroxydopamine-induced supersensitivity in rat cerebral cortex. *Science*, 194, 624–626.
- Stanic, D., Finkelstein, D.I., Bourke, D.W., Drago, J. & Horne, M.K. (2003) Timecourse of striatal re-innervation following lesions of dopaminergic SNpc neurons of the rat. *Eur J Neurosci*, 18, 1175–1188.
- Su, K., Huang, S., Peng, C., Lai, H., Huang, C., Chen, Y., Aitchison, K.J. & Pariente, C.M. (2010) Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon- α -induced depression by regulating polyunsaturated fatty acids levels. *Biol Psychiatry*, 67, 550–557.
- Torda, T., Yamaguchi, I., Hirata, F., Kopin, I.J. & Axelrod, J. (1981) Quinacrine-blocked desensitization of adrenoceptors after immobilization stress or repeated injection of isoproterenol in rats. *J Pharmacol Exp Ther*, 216, 334–338.
- Velazquez-Moctezuma, J. & Diaz Ruiz, O. (1992) Neonatal treatment with clomipramine increased immobility in the forced swim test: an attribute of animal models of depression. *Pharmacol Biochem Behav*, 42, 737–739.
- Vetulani, J. & Sulser, F. (1975) Action of various antidepressant treatment reduced reactivity of noradrenergic cyclic AMP-generating system in limbic forebrain. *Nature*, 257, 495–496.
- Vijayakumar, M. & Meti, B. L. (1999) Alterations in the levels of monoamines in discrete brain regions of clomipramine-induced animal model of endogenous depression. *Neurochem Res*, 24, 345–349.
- Vogt, M. (1954) Norepinephrine and epinephrine in the central nervous system. *Pharmacol Rev*, 6, 31–32.
- Wiklund, L. & Bjorklund, A. (1980) Mechanisms of regrowth in the bulbospinal 5-HT system following 5,6-dihydroxytryptamine induced axotomy. II. Fluorescence histochemical observations. *Brain Res*, 191, 109–127.
- Wiranowska, M., Wilson, T.C., Thompson, K. & Prockop, L.D. (1989) Cerebral interferon entry in mice after osmotic alteration of blood-brain barrier. *J Interferon Res*, 9, 353–362.
- Woolley, D.W. & Shaw, E. (1954) A Biochemical and pharmacological suggestion about certain mental disorders. *Science*, 119, 587–588.

- Wysowski, D.K., Pitts, M. & Beitz, J. (2001) An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol*, 45, 515-519.
- Yoo, H.S., Bunnell, B.N., Crabe, J.B., Kalish, L.R. & Dishman, R.K. (2000) Failure of neonatal clomipramine treatment to alter forced swim immobility: chronic treadmill or activity-wheel running and imipramine. *Physiol Behav*, 70, 407-411.
- Zarate, C.A., Jr, Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S. & Manji, H.K. (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*, 63, 856-864.
- Zhou, L., Huang, K.X., Kecojevic, A., Welsh, A.M. & Koliatsos, V.E. (2006) Evidence that serotonin reuptake modulators increase the density of serotonin innervation in the forebrain. *J Neurochem*, 96, 396-406.

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Over the last fifty years, many studies of psychiatric medication have been carried out on the basis of psychopharmacology. At the beginning, researchers and clinicians found the unexpected effectiveness of some medications with therapeutic effects in anti-mood without knowing the reason. Next, researchers and clinicians started to explore the mechanism of neurotransmitters and started to gain an understanding of how mental illness can be. Antidepressants are one of the most investigated medications. Having greater knowledge of psychopharmacology could help us to gain more understanding of treatments. In total ten chapters on various aspects of antidepressants were integrated into this book to help beginners interested in this field to understand depression.

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