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Chapter

Perspective Chapter: Depression as a Disorder of Monoamine Axon Degeneration May Hold an Answer to Two Antidepressant Questions - Delayed Clinical Efficacy and Treatment-Resistant Depression

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Abstract

It has long been known that the pathophysiology of depression is associated with a reduction in the brain concentrations of monoamines, that is, serotonin, noradrenaline, and dopamine. Although conventional antidepressant drugs increase monoamine contents immediately after their administration, it takes several weeks or more before their clinical efficacy becomes evident. The mechanism of the delayed onset of antidepressant effects remains elusive. Furthermore, over 30–50% of patients with depression show resistance to antidepressant drug treatment. Thus, two major questions remain to be resolved—(1) delayed clinical efficacy of antidepressant drugs, and (2) a large percentage of treatment-resistant depression. First, this review describes the evidence, obtained from animal and human studies, that similar to early-stage Parkinson's disease, depression is a neurodegenerative disease characterized by the degeneration of monoamine axons and the delayed clinical efficacy of antidepressants is due to their regenerative action on damaged monoamine axons. Moreover, the causes of treatment-resistant depression are discussed in relation to inflammation as a cause of neurodegeneration. This review provides new insights into not only the pathophysiology of depression but also the diagnosis and therapy of early stages of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease.

Keywords: depression, parkinson's disease, antidepressant, treatment-resistant, omega-3 fatty acid, neurodegeneration, regeneration

1. Introduction

It has long been known that the pathophysiology of depression is associated with a reduction in the concentration of monoamines, that is, serotonin (5-HT), noradrenaline (NA), and dopamine (DA), in the brain [1, 2]. Conventional antidepressant drugs

for clinical use increase monoamine contents immediately after their administration, whereas it takes several weeks or more before their clinical efficacy becomes evident. The delayed onset of action of antidepressants suggests that antidepressants exert their effects by inducing slowly occurring changes in the brain. Furthermore, over 30–50% of patients with depression show resistance to antidepressant drug treatment [3–5]. Thus, two major questions remain to be resolved—(1) How do the delayed clinical effects of antidepressant drugs occur, and (2) why does a large percentage of patients with depression show resistance to antidepressant treatment. This review article focuses on addressing these questions based on the evidence that depression is not a disease caused simply by the deficiency of neurotransmitters, but a neurodegenerative disease characterized by axonal degeneration of monoamine neurons without cell death [6–11].

2. Delayed onset of antidepressant effects

2.1 Antidepressants and monoamine axon regeneration/sprouting

Recent animal and human studies have demonstrated that depression is a neurodegenerative disease characterized by the degeneration of monoamine axons without cell death, and the delayed clinical efficacy of antidepressants is due to their regenerative action on damaged monoamine axons. In 1990, it was reported for the first time 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 selective serotonin reuptake inhibitor (SSRI), does not [6, 7]. The regenerative effects of antidepressants on NA axons lesioned by 6-hydroxydopamine (6-OHDA) could be induced by antidepressant infusions in the rat cerebral cortex for more than 2 weeks but not for less than 1 week. Furthermore, the ability of antidepressants to induce axonal sprouting of 5-HT neurons has been demonstrated by systemic injections of antidepressants for 4 weeks daily in rats without damaging 5-HT axons [9]. In this study, fluoxetine and the 5-HT reuptake enhancer tianeptine, but not the NA reuptake inhibitor desipramine, increased the density of 5-HT axons in the cerebral cortex and some limbic forebrain areas. These findings indicate that antidepressants associated with 5-HT reuptake, but not NA reuptake, induce axonal sprouting of 5-HT neurons. Based on the sprouting or regenerative effects of antidepressants on NA and 5-HT axons, the axonal degeneration of monoamine neurons has been suggested to be involved in the pathophysiology of depression and antidepressants exert their action by inducing the regeneration of monoamine axons. In addition, it is suggested that the pathophysiology of depression includes NA-axon and/or 5-HT-axon degeneration, and NA- and 5-HT-specific antidepressants are effective in inducing NA and 5-HT axon regeneration, respectively.

2.2 Depression and monoamine axon degeneration

Further evidence has been provided using animal models of depression to show that axonal degeneration of monoamine neurons is involved in the pathophysiology of depression. The rat model of depression, which was developed by repeated exposure to forced walking stress for 2 weeks, showed depressive behaviors including prolonged inactivity, seclusion, aggression, motor retardation, lack of coupling behavior, fitful sleep, weight loss, and hypersensitivity to light and sound [12]. Subsequent

studies have demonstrated that this stress-induced depression model reveals the degeneration of NA axons in the cerebral cortex [8]. In this depression model with NA axon degeneration, imipramine (intraperitoneal injections for 20 days) could induce regeneration of cortical NA axons and ameliorate the depression-like behaviors [8]. A most recent study showed that in a mouse model of poststroke depression with degeneration of NA- and 5-HT axons, chronic treatment with fluoxetine reversed depression-like behaviors and a loss of 5-HT axons, but not NA axons [11]. Furthermore, light deprivation was found to induce a loss of NA axons, but not 5-HT axons, in the frontal cortex and depression-like behaviors in rats, while desipramine improved the NA axon loss and depressive behaviors [10]. Postnatal isolation rearing, which induced depressive behavior in adolescent/young adult rats, reduced the density of 5-HT axons, but not NA axons, in the hippocampus and amygdala [13]. A recent study has shown that exposure to 1-bromopropane, an alternative to ozone-depleting solvents, which is known to induce depressive symptoms in a subset of people exposed to this chemical, induced the degeneration of NA axons, but not 5-HT axons, in the adult rat [14]. It has also been presented that repeated electroconvulsive shock that is most effective in the treatment of clinical depression promotes the regeneration of 5-HT axons of the rat hippocampus damaged by the 5-HT specific neurotoxin [15]. In the chronic social defeat stress model of depression with reduced 5-HT innervation in the hippocampal dentate gyrus (DG) and ventromedial prefrontal cortex (vmPFC) of mice, chronic deep brain stimulation of vmPFC reversed depression-like behavior and restored 5-HT innervation in the DG and vmPFC [16]. Further evidence for the involvement of the degeneration of monoamine axons in the pathophysiology of depression has been reported: Interferon- α , which is widely used for the treatment of cancers and viral illnesses, is known to frequently induce depressive symptoms [17], reduces the density of NA and 5-HT axons in the frontal cortex, hippocampus, and amygdala of rats [18]. Finally, human brain imaging studies have shown evidence that the degeneration of monoamine axons is associated with depressive symptoms [19–21]. In these studies, the density of axon terminals of monoamine neurons was measured by positron emission tomography using radiotracers of presynaptic monoamine transporters. Although scant in number and limited to Parkinson's diseases with depressive symptoms, the imaging studies have provided evidence to support the involvement of loss of monoamine axons in the occurrence of depressive symptoms. Importantly, a recent imaging study reported that depressed patients showing the improvement of depressive symptoms after cognitive behavioral therapy revealed an overall increase in cerebral 5-HT transporter availability, suggesting the occurrence of 5-HT axon regeneration/sprouting after depression treatment [22]. Furthermore, in depressed suicide victims, immunohistochemistry using an antibody to serotonin transporters showed a localized decrease in the density of 5-HT axons in the PFC [23].

All these studies support the view that depressive symptoms are caused by the loss of monoamine axons and antidepressants exert their effects by inducing the regeneration of monoamine axons. Thus, the delayed onset of antidepressant efficacy can be explained by the time required for the regeneration of monoamine axons.

3. Plausible causes of treatment-resistant depression

Based on the view that depression is a neurodegenerative disease, the possible causes of treatment-resistant depression are considered due to (1) mismatch of impaired

monoamines and prescribed antidepressant drugs, (2) severe degeneration or cell death, (3) persistent inflammation, and (4) omega-3 fatty acid deficiency. Obviously, we cannot exclude other causes of treatment-resistant depression (**Figure 1**).

3.1 Mismatch of impaired monoamines and prescribed antidepressant drugs

One of the causes of treatment-resistant depression could be explained by the possibility that there are different types of depression whose pathophysiology differs in which monoamine is involved (5-HT, NA, DA, or two or more monoamines). The problem is that there are no objective diagnostic tools to differentiate which monoamine is involved in the pathophysiology of depressive symptoms of individual patients. In fact, as mentioned before, animal studies have suggested that there are various types of depression that differ in the monoamine(s) involved [10, 11, 13, 14, 18]. In clinical practice, SSRIs are most commonly prescribed as first-line antidepressant drugs without any distinct evidence that the depressive symptoms of patients are due to 5-HT deficiency. At present, it is difficult for clinicians to correctly administer antidepressant drugs to individual patients with depression. If patients with depression are not administered antidepressant drugs that are able to regenerate the particular monoamine axons that are damaged in their case, they may suffer from treatment-resistant depression.

3.2 Severe degeneration or cell death

Another likely cause of treatment-resistant depression may be attributable to the possibility that the degeneration of monoamine axons is not localized at axon terminals, but extends further from the terminals. In the most severe case, retrograde axonal degeneration may result in the degeneration of the neuron soma (cell death).

Figure 1. Plausible causes of treatment-resistant depression. The causes of resistance to antidepressant drugs may be due to (1) mismatch of impaired monoamines and prescribed antidepressant drugs, (2) severe degeneration or cell death, (3) persistent inflammation, and (4) omega-3 fatty acid deficiency. Others may include deficiency of signaling pathways or molecules related to regeneration of monoamine axons.

In fact, a great loss of NA neurons in the locus coeruleus has been reported to be associated with depressive symptoms in patients without dementia as well as those with Alzheimer's disease or Parkinson's disease [24, 25]. A loss of 5-HT neurons in the raphe nucleus is also reported to be associated with depressive symptoms of patients with Parkinson's disease [26]. Depressive symptoms due to the loss of monoamine neurons can hardly be treated with the administration of conventional antidepressant drugs as well as electroconvulsive shock therapy. It is noted that at the early stages of Parkinson's disease and Alzheimer's disease the degeneration of the distal axons occurs first, and in the late stages, persistent axonal degeneration finally results in the degeneration of the neuron soma [27–29]. This implies that in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, possibly including depression, the degeneration of the distal axons precedes the loss of the neuron soma. Postmortem and imaging studies have shown that in Parkinson's disease about 30% of DA neurons of the substantia nigra compacta (SNc) and about 50–70% of striatal DA axon terminals are lost by the time of motor symptom onset [30, 31]. The reason for making the distal axons more vulnerable to insults than the neuron soma can be explained by the fact that the distal portions of axons are most remote from the cell body that supplies proteins and chemicals required for the survival and growth of axons.

Whether distal axon degeneration is prone to cell death or not could be dependent on the length of axons from the neuron soma to the distal axon terminal and the morphological features of axon terminals (**Figure 2**). In Parkinson's disease, motor symptoms occur due to the degeneration of SNc DA neurons projecting to the dorsal striatum. Since the distance between the two brain regions is relatively short, retrograde axon degeneration of SNc DA neurons is considered to result in cell death more easily. In contrast, NA neurons of the locus coeruleus and 5-HT neurons of the raphe nucleus send their axons to long distances from the brainstem to the cerebral cortex [32], thus taking a long time to cause soma degeneration. On the other hand, it has been reported that DA neurons of the ventral tegmental area (VTA), which project their axons to the ventral striatum (nucleus accumbens) and are responsible for reward-related behavior, are involved in the pathophysiology of depression [33, 34]. Similar to SNc DA neurons, VTA DA neurons project relatively short axons to the nucleus accumbens. Although the axon length of both DA neurons is almost the same, however, DA neurons of the SNc are more prone to cell death in Parkinson's disease, compared to DA neurons of the VTA [35, 36]. A single-neuron tracing study demonstrated that a single DA neuron of the SNc forms highly overlapping innervation with extremely dense axonal arborizations in the dorsal striatum [37], while that of the VTA has much smaller axonal arbors in the ventral striatum (**Figure 2**) [27, 36]. A large and dense axonal arborization in the terminal field is considered to contribute to cell death of DA neurons of the SNc in Parkinson's disease [36]. Thus, in addition to axonal length, the spread and size of terminal axon arbors may play a pivotal role in vulnerability to neuronal cell death. It is also noted that because 5-HT, NA, and DA axons all have a great capacity to spontaneously regenerate or sprout in response to damage in the adult brain [38–41], the competition between degenerative and regenerative mechanisms may occur after axonal damage, finally resulting in either axonal regeneration or cell death.

3.3 Persistent inflammation

In recent years much evidence has been accumulating that inflammation is a key player in the pathogenesis of neurodegenerative diseases, such as Parkinson's disease

Figure 2. Retrograde axonal degeneration and cell death of monoamine neurons depend on axonal length and morphological features of axon terminals. NA neurons of the locus coeruleus and 5-HT neurons of the raphe nucleus have long axons, rarely causing cell death, and depressive symptoms can occur predominantly due to axonal degeneration without cell death. In contrast, DA neurons of the VTA and SNc have relatively short axons. Although the axon length of both DA neurons is almost the same, DA neurons of the SNc are more prone to cell death in Parkinson's disease, compared to DA neurons of the VTA. A single DA neuron of the SNc forms highly overlapping innervation with extremely dense axonal arborizations, while that of the VTA has much smaller axonal arbors. A large and dense axonal arborization in the terminal field is considered to contribute to cell death of DA neurons of the SNc in Parkinson's disease. NA: Noradrenaline, 5-HT: Serotonin, DA: Dopamine, VTA: Ventral tegmental area, and SNc: Substantia nigra compacta.

and Alzheimer's disease [42, 43]. Many researchers also reported that inflammation plays an important role in the occurrence of depressive symptoms and is associated with treatment-resistant depression [4, 5, 44, 45]. A subset of patients with depression and animal models of depression revealed increased levels of pro-inflammatory cytokines in the periphery and brain, including IL-1 β , IL-6, and TNF- α , and a variety of stresses including psychosocial stress could induce activation of key inflammatory pathways to elevate the serum levels of pro-inflammatory cytokines such as IL-6 [44–48]. Based on these findings, as mentioned previously, long-term repeated intraperitoneal injection of the pro-inflammatory cytokine interferon- α induces the degeneration of 5-HT and NA axons in the rat brain, though there is no apparent change in the number and shape of 5-HT and NA neuronal somata [18]. Accordingly, it is reasonable to assume that prolonged inflammation and persistent release of pro-inflammatory cytokines produce the degeneration of 5-HT and/or NA axons without cell death, resulting in the occurrence of depressive symptoms. If inflammation as a cause of the axonal degeneration of monoamine neurons persists without anti-inflammatory treatment during repeated administration of antidepressants, patients are likely to suffer from treatment-resistant depression.

3.4 Omega-3 fatty acid deficiency

Chronic treatment with antidepressants is reported to cause the downregulation of β -adrenergic receptors [49]. On the other hand, the denervation of cortical NA axons with the neurotoxin 6-OHDA causes upregulation (supersensitivity) in cortical

β -adrenergic receptors [50]. As upregulation of β -adrenergic receptors is associated with NA axon degeneration, it is possible that downregulation of β -adrenergic receptors results from regeneration or sprouting of NA axons. If upregulation of β -adrenergic receptors occurs due to the degeneration of NA axons in the brains of patients with depression, antidepressants could normalize the sensitivity of β -adrenergic receptors by the downregulation following the regeneration of NA axons. Further studies have shown that downregulation of β -adrenergic receptors following repeated application of β -adrenergic agonists or chronic stress treatment is blocked by phospholipase A2 (PLA2) inhibitors, while this downregulation can be induced by the activation of PLA2 [51, 52]. Moreover, it has been demonstrated that PLA2 activation is involved in the downregulation of β -adrenergic receptors induced by chronic desipramine treatment [53]. A possible link between the downregulation 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. Based on these findings, the PLA2 inhibitor mepacrine or 4-bromophenacyl bromide could attenuate the regeneration of NA axons induced by desipramine, while the PLA2 activator melittin induced NA axon regeneration [54]. These findings suggested that the PLA2 signaling pathway is involved in the pathophysiology of depression.

PLA2 generates the omega-6 polyunsaturated fatty acid arachidonic acid (AA) and omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by acting on membrane phospholipids. PLA2 enzymes are subdivided into several groups and among them, two groups of PLA2, cytosolic PLA2 (cPLA2) and calcium-independent PLA2 (iPLA2), play a major role in the release of AA, EPA, and DHA from the cell membrane [42, 55]. PLA2 and its products, omega-3 and omega-6 fatty acids, reveal the capacity to produce axon outgrowth of adult mouse sensory neurons *in vitro*, aged rat sensory neurons in culture, and cultured hippocampal and PC12 cells [56–58]. Importantly, acute administration of DHA is reported to induce sprouting of 5-HT axons as well as corticospinal axons in an adult rat model of spinal cord injury [59]. A recent study also reported that in the damaged cornea of the adult mouse, DHA induces axonal regeneration of trigeminal sensory nerves via the iPLA2 activity of the receptors of the neuroprotective molecule pigment epithelium-derived factor [60]. Furthermore, using iPLA2 β -knockout mice, the impairment of iPLA2 β was found to cause widespread degeneration of axons in the central and peripheral nervous systems, including nigrostriatal DA axons, although the changes were not observed in developing and young mice, but became evident in older mice [61, 62]. All these findings suggest that PLA2 and its products play a key role in the degeneration and regeneration of axons in the periphery and brain, including monoamine axons in the adult brain.

Recently, many reports have shown lower levels of EPA and/or DHA being associated with depression [63–66]. Animal studies demonstrated that administration of EPA and DHA had an antidepressant-like effect, reducing immobility in the forced swim test [67, 68]. Moreover, it has been reported that the antidepressant effect of maprotiline, an NA reuptake inhibitor, is mediated by DHA released by activation of iPLA2 in the mouse prefrontal cortex [69]. Notably important is that EPA and DHA are essential fatty acids and must be obtained from the diet. Consequently, if patients with depression do not get enough of these fatty acids from their diet during the administration of antidepressant drugs, they may suffer from treatment-resistant depression. Notably, in adolescents with SSRI-resistant depression who exhibited robust DHA deficits, DHA supplementation with fish oil increased DHA status and enhanced the antidepressant effects of SSRI [70].

4. Depression and neurodegenerative diseases

Depression is considered a neurodegenerative disease, such as Parkinson's disease and Alzheimer's disease. Parkinson's disease with the degeneration of DA neurons of the SNc related to motor function produces motor symptoms, while the degeneration of 5-HT and NA neurons related to mood regulation results in depressed mood and anxiety of patients with depression. In addition, the degeneration of DA neurons of the VTA may be associated with anhedonia in patients with depression. Nonspecific symptoms of depression, such as sleep problems, tiredness, and changes in appetite, may be attributable to the degeneration of 5-HT and NA axons, because loss of these monoamine axons, which are distributed to almost the entire brain, could likely produce a variety of symptoms. A major difference between depression and Parkinson's disease as well as Alzheimer's disease is that the neuropathology of depression is characterized predominantly by the degeneration of axons, while the neurodegenerative changes of Parkinson's disease and Alzheimer's disease include a great loss of the neuron cell somata. The depressive symptoms of patients with depression can occur due to axonal degeneration of monoamine neurons even without soma degeneration, whereas the motor symptoms of Parkinson's disease and cognitive impairment of Alzheimer's disease become evident after the occurrence of soma degeneration. This is well consistent with the fact that depression often precedes symptoms of neurodegenerative diseases, typically including Parkinson's disease and Alzheimer's disease [71, 72]. Thus, depression may be useful as a predictor of the future occurrence of neurodegenerative diseases characterized by cell death. In any case, detection of axonal degeneration before cell death is important for the treatment of Parkinson's disease and Alzheimer's disease. It is noted that DHA supplementation before the onset of dementia results in beneficial outcomes in patients with Alzheimer's disease [55, 73, 74]. Omega-3 supplementation, as a primary intervention, also reduces cognitive decline in patients with mild to moderate Alzheimer's disease [75]. These results suggest that in Alzheimer's disease omega-3 fatty acids reduce mild cognitive impairment by producing axonal regeneration before the occurrence of cell death.

5. Involvement of PLA2 signaling in antidepressants effects

As mentioned earlier, neuroinflammation is reported to play a key role in neurodegenerative changes of neurological diseases, such as Parkinson's disease and Alzheimer's disease. In addition, the possibility is also discussed that the degeneration of monoamine axons, which is considered to occur in patients with depression, may be due in part to neuroinflammation. In recent years much attention has been paid to the roles of the PLA2 signaling pathway in neuroinflammation in relation to neurodegenerative diseases. It has been reported that cPLA2 releases AA and EPA, while iPLA2 preferentially releases DHA. In addition, AA and its products, such as prostaglandins and leukotrienes, play a major role in pro-inflammatory responses, whereas DHA and EPA and their products, such as resolvins and protectins, are involved in anti-inflammatory responses [55, 76, 77]. Omega-3 fatty acids and their metabolites play a regulatory role in the transition from pro-inflammatory to anti-inflammatory phases by inhibiting pro-inflammatory signaling pathways [55]. Thus, the release of AA and its products in the brain induces inflammatory neuronal damage such as axonal degeneration, whereas omega-3 fatty acids and their metabolites exert anti-inflammatory actions to induce the resolution of inflammation and recovery, including the process of axonal regeneration (**Figure 3**).

Figure 3.
 A possible mechanism of degeneration and regeneration of monoamine axons related to pro-inflammatory and anti-inflammatory actions of PLA2. In the pro-inflammatory phase, cPLA2 and its pro-inflammatory metabolites cause the degeneration of monoamine axons, whereas iPLA2 and its anti-inflammatory metabolites (omega-3 fatty acids) play pivotal roles in inflammation-resolution and recovery by exerting anti-inflammatory and regenerative actions. There are distinct interactions between pro-inflammatory and anti-inflammatory signaling pathways. Antidepressants are considered to activate iPLA2 signaling pathway and induce anti-inflammatory response and the regeneration of monoamine axons through omega-3 fatty acids and their metabolites. PLA2: Phospholipase A2, cPLA2: Cytosolic phospholipase A2, iPLA2: Calcium-independent phospholipase A2.

Therefore, it is possible, at least in part, that antidepressants, which can activate iPLA2 signaling pathways, induce the axonal regeneration of monoamine neurons by anti-inflammatory and regenerative actions of omega-3 fatty acids and their metabolites.

6. Biomarkers for axonal degeneration

As noted in this review, many recent studies have clearly demonstrated that depression is a neurodegenerative disease and shares many similarities with well-known neurodegenerative diseases such as Parkinson’s disease and Alzheimer’s disease. Particularly, axonal degeneration is a common phenomenon that occurs at the early stages of Parkinson’s disease and Alzheimer’s disease, and possibly in depression. It is thus essential to devise new tools for the detection of axonal degeneration of affected neurons. If this is realized, Parkinson’s disease and Alzheimer’s disease at early stages, characterized by axonal degeneration without cell death, will be treatable with drugs with the ability to induce axonal regeneration. In depression, one of the promising and powerful tools for detecting monoamine axon degeneration is neuroimaging of monoamine axon terminals using radiotracers of transporters of each monoamine axon. Interestingly, a more recent study reported that plasma phosphoethanolamine is a reliable biomarker of depression because it was significantly decreased in patients with depression and inversely correlated with the severity of depressive symptoms, including depressed mood, loss of interest, and psychomotor retardation [78]. Similarly, plasma levels of ethanolamine and phosphatidylethanolamine were found to

be reduced in early-stage Parkinson’s disease [79], while ethanolamine and phosphoethanolamine were also decreased in cerebrospinal fluid [80] and postmortem brains [81, 82] of Alzheimer’s disease patients. Because ethanolamine and phosphoethanolamine are the precursors of the phospholipid phosphatidylethanolamine that plays a role in the incorporation of omega-3 fatty acids in the cell membrane, it is possible that phosphatidylethanolamine and its precursors are one of the reliable biomarkers of axonal degeneration of at least a subset of patients with depression as well as neurodegenerative diseases such as Parkinson’s disease and Alzheimer’s disease.

7. Conclusion

Recent animal and human studies have demonstrated that similar to early-stage Parkinson’s disease, depression is a neurodegenerative disease characterized by the degeneration of monoamine axons without cell death. This review may contribute not only to understanding the pathophysiology of depression but also to new approaches to the diagnosis and therapy of neurodegenerative diseases such as Parkinson’s disease and Alzheimer’s disease.

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Conflict of interest

The author declares no conflict of interest.

Abbreviations

AA	arachidonic acid
cPLA2	cytosolic phospholipase A2
DA	dopamine
DG	dentate gyrus
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
5-HT	serotonin
iPLA2	calcium-independent phospholipase A2
NA	noradrenaline
6-OHDA	6-hydroxydopamine
PFC	prefrontal cortex
PLA2	phospholipase A2
SNc	substantia nigra compacta
SSRI	selective serotonin reuptake inhibitor
vmPFC	ventromedial prefrontal cortex
VTA	ventral tegmental area

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