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Stress-induced plasticity of monoamine axons

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TABLE OF CONTENTS

1. ABSTRACT

Central serotonergic (5-HT) and noradrenergic (NA) neurons, which innervate the same regions of the brain, are known to play a crucial role in emotion and mood. These monoamine neurons have a great capacity to alter axonal morphology in response to repeated stress. The morphological responses of 5-HT and NA axons to repeated stress are different, and they sometimes even demonstrate opposite responses (namely, either sprouting or degeneration). Moreover, a morphological interaction also occurs between 5-HT and NA axons during axonal regeneration. This review describes the differential features of axonal plasticity of 5-HT and NA neurons in relation to stress, and discusses the possible roles that the morphological plasticity of 5-HT and NA axons may play in the pathophysiology of depression.

2. INTRODUCTION

Central serotonergic (5-HT) and noradrenergic (NA) neurons have been demonstrated to participate in a variety of physiological functions, including the waking-sleeping cycle, mood and emotion (15, 47, 51). These monoamine neurons innervate the same regions of the brain (12, 49, 50), and are linked to each other in such a way that changes in one are reflected in the other (40). 5-HT and NA axons possess the capacity to dynamically change the morphology of axon terminals in response to exogenous stimuli such as brain damage (5, 6, 9, 13, 14) and repeated stress (21, 38, 44). It is well known that 5-HT and NA neurons are affected by stress, and changes in the activities of these monoamine neurons are involved in stress-related behaviors such as anxiety (4, 18, 41). The impairments of the 5-HT and NA systems are thought to be associated with the pathophysiology of clinical depression (3, 21, 26, 42),

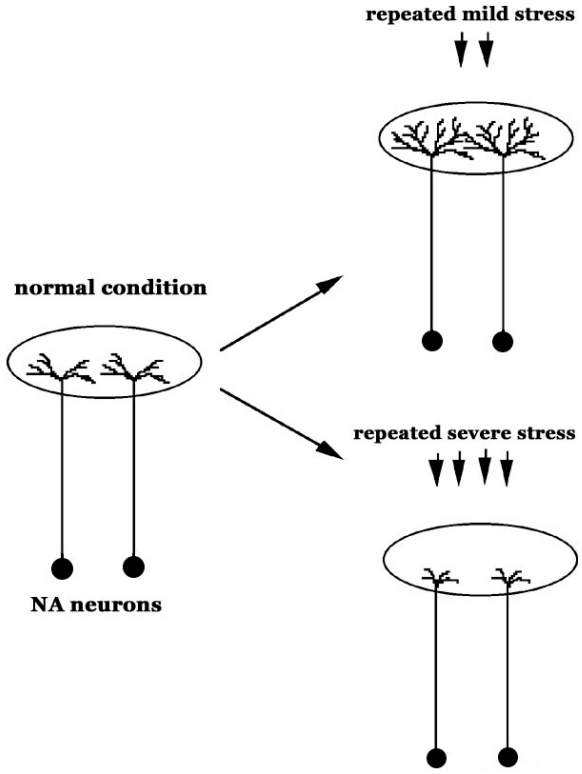

Figure 1. Effects of repeated stress on the morphology of NA axons. The morphological responses of NA axons to repeated stress depend on the severity and duration of stress treatment: Short-lasting, mild stress induces the sprouting of NA axons in the adult rat brain, while long-lasting, severe stress induces the retraction of NA axons.

although the detailed association remains unclear.

This review describes the morphological responses of central 5-HT and NA axons to repeated stress, focusing specifically on a comparison between these two monoamine axons. In addition, the possibility is discussed that stress-induced changes in monoamine axon plasticity are associated with the pathophysiology of clinical depression. Accumulating evidence suggests that impairments of neuroplasticity, including neurogenesis in the hippocampal dentate gyrus and morphological changes in the prefrontal cortex, are involved in the pathophysiology of depression (1, 10, 16, 17, 29, 39, 43). However, the subject of this review is limited solely to the morphological plasticity of monoamine axons, although there may be a causal link between each type of neuronal plasticity.

3. AXONAL PLASTICITY OF MONOAMINE NEURONS

Monoamine neurons have long been known to have a great capacity for axonal plasticity in response to brain damage (7, 14, 30, 31, 48). The regeneration of 5-HT and NA axons easily occurs in the adult brain as well as in the developing brain. However, whether or not any difference exists in the capacity and speed of axonal regeneration between 5-HT and NA neurons remains to be elucidated. Recent studies from our laboratory have demonstrated distinct differences in the capacity and speed of the regeneration of these monoamine axons (22, 23, 24). Moreover, we have previously shown that the morphological responses of 5-HT and NA axons to repeated stress sometimes demonstrate opposite responses (namely, sprouting or degeneration).

To study the axonal plasticity of 5-HT and NA neurons, specific neurotoxins to 5-HT and NA neurons, which can induce the degeneration of these neurons, are very useful for providing a model of axonal regeneration. In our recent studies, neurotoxins to 5-HT or NA axons were locally injected into the frontal cortex of adult rats to cause partial denervation. The monoaminergic axons were visualized by immunohistochemistry using antibody to 5-HT and dopamine-beta-hydroxylase. The occurrence of the regeneration of 5-HT and NA axons was assessed by measuring the denervation area of these monoamine axons. Using this method, we examined whether the speed of axonal regeneration differs between 5-HT and NA neurons (22). In this study, the animals were sacrificed at 14 days (14-day group) and 30 days (30-day group) after the local injection of neurotoxins to 5-HT or NA axons in the frontal cortex. The denervation area of 5-HT axons significantly decreased in the 30-day group compared to the 14-day group, thus indicating the occurrence of the regeneration of 5-HT axons at 30 days after axonal damage. However, since the denervation area of NA axons showed no significant change between the two groups, there was no evidence for the regeneration of NA axons at one month after axonal damage. These results suggest that the regeneration of 5-HT axons after axonal damage thus occurs more rapidly than that of NA axons. Nakai *et al.* reported that the reinnervation of NA axons in the visual cortex of adult cats continuously proceeded throughout 52 weeks after neurotoxin injection (32). As a result, the regeneration of NA axons is thought to begin late and proceed slowly after axonal damage.

4. EFFECTS OF REPEATED STRESS ON NA AXONS

The morphological changes in monoamine axons have been shown to occur not only after brain damage, but also following repeated stress. So far, more data are available for the morphological plasticity of NA axons than 5-HT axons regarding repeated stress.

Most notable is the finding that repeated stress induces the sprouting or retraction (degeneration) of NA axons in the adult rat brain, depending on the duration of stress treatment (21, 38, 44): Short-lasting stress induces the sprouting of NA axons (33, 38), while long-lasting stress induces retraction or degeneration of NA axons (20, 37) (Figure 1). For example, rats, which were restrained in a small cage and immersed in warm water for 10 min daily for 2 weeks, have been shown to reveal the sprouting of NA axons in the cerebral cortex (38). On the other hand, rats were forced to run continuously till near exhaustion and the rectal temperature dropped to 33°C or less. Next, the animals were allowed to rest for 24 hrs and this

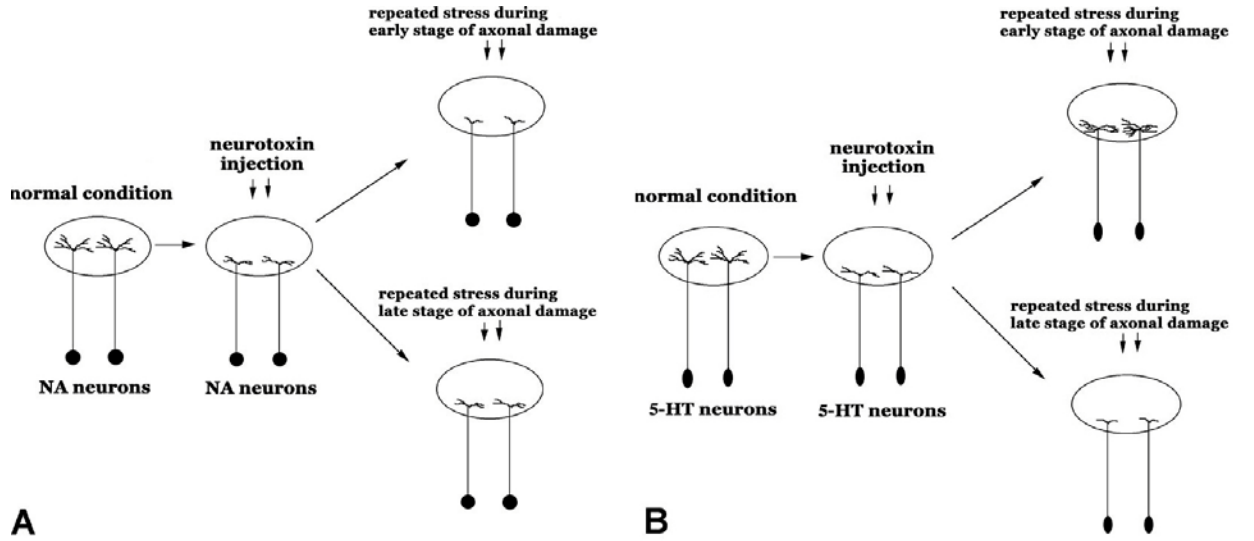

Figure 2. The differential effects of repeated stress on the morphology of NA (A) and 5-HT (B) axons. The axonal morphology of 5-HT and NA neurons is differentially modified by the timing of stress: Repeated stress during the early stages of axonal damage induces opposite changes in the morphology of cortical 5-HT (sprouting) and NA axons (degeneration), while repeated stress during the late stages of axonal damage induces no apparent changes in the morphology of NA axons, but it does suppress the regeneration of 5-HT axons.

sequence of stress and rest was repeated for 12±2 days. Such long-lasting stress resulted in a severe degeneration of cortical NA axons (20, 21, 37). These animals are thus considered to be an appropriate depression model (see Section 6).

5. EFFECTS OF REPEATED STRESS ON THE REGENERATION OF MONOAMINE AXONS

Recent studies have indicated that repeated stress can affect the regeneration of 5-HT and NA axons occurring after axonal damage (22, 24). The effects of repeated stress on the axonal regeneration of monoamine neurons are related to the timing of stress treatment: The morphological responses of 5-HT and NA axons to repeated stress are different between the early and late stages of axonal damage (Figure 2). In this series of experiments, neurotoxins to 5-HT or NA axons were locally injected into the frontal cortex to produce a partial degeneration of the monoamine axons, and thereafter mild restraint stress treatment was started at either 1 day (early stage of axonal damage) or 16 days (late stage of axonal damage) after the neurotoxin injection.

In the early-stage stress group, stress was repeated daily for 20 min during the first 2 days and for 40 min during the next 11 days (24). On the fourteenth day after neurotoxin injection, the brains were removed for immunohistochemical staining of 5-HT and NA axons. Repeated stress caused no significant effect on the denervation area of 5-HT or NA axons in the early-stage stress group. However, the morphological responses of 5-HT and NA axons to repeated stress were found to occur in regions outside the denervation site: 5-HT axons showed marked sprouting in cortical regions other than the denervation site, including the frontal, occipital, and olfactory primary cortices. No significant change in the 5-HT axons occurred in the temporal cortex. In contrast, opposite morphological responses of NA axons to repeated stress occurred outside the cortical regions with the denervation of NA axons. The density of the cortical NA axons outside the denervation site significantly decreased following repeated stress, thus indicating the occurrence of the retraction or degeneration of NA axons. Since brain-derived neurotrophic factor (BDNF) is known to be a neurotrophic factor for brain 5-HT neurons (10, 27, 28), it is possible that the stress-induced sprouting of 5-HT axons is caused by an increase in BDNF expression. In fact, the number of BDNF-immunopositive cells increased throughout the entire cerebral cortex, thus supporting the stress-induced sprouting of 5-HT axons (24), while either the denervation of 5-HT axons alone or repeated stress alone did not affect BDNF expression in the cerebral cortex. Moreover, no change in the BDNF expression in the cerebral cortex showing the stress-induced degeneration of NA axons was observed. However, it remains unclear as to whether the stress-induced sprouting of 5-HT axons is directly associated with the increased BDNF expression.

In the late-stage stress group, the stress was given daily for 40 min for 14 consecutive days (30-day stress group) (22). Non-stressed animals were divided into two groups, animals sacrificed at 14 days (14-day control group) and those sacrificed at 30 days (30-day control group) after the toxin injection. The denervation area of 5-HT, but not that of NA axons, revealed a significant decrease in the 30-day control group relative to the 14-day control group, thus indicating the occurrence of the regeneration of 5-HT axons as mentioned before (see Section 1). Since the denervation area of 5-HT axons in the 30-day stress group was not significantly different from that in the 14-day control group, repeated stress was

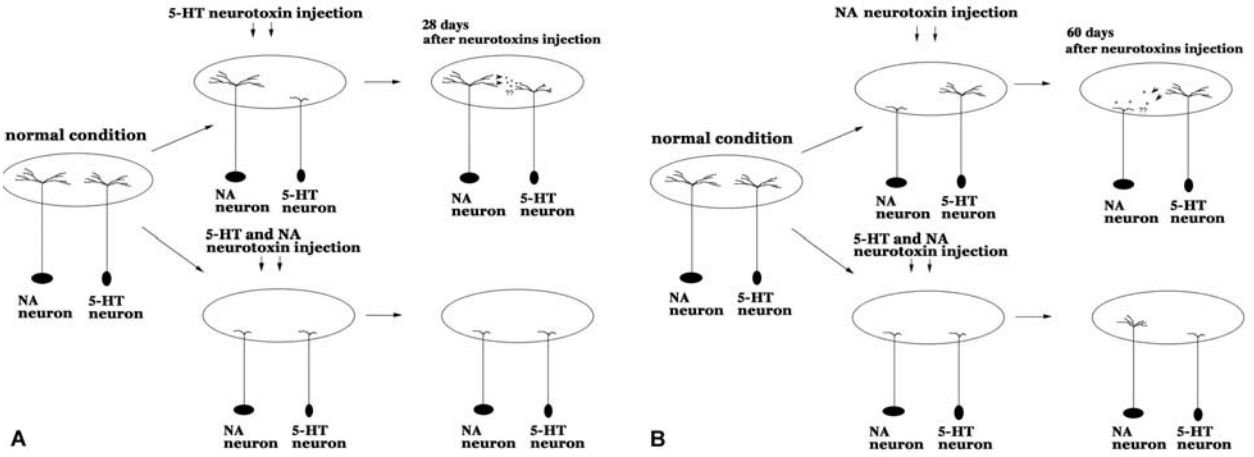

Figure 3. The morphological interaction between 5-HT and NA axons during axonal regeneration. The interaction occurs in opposite directions: NA axons exert a facilitatory effect on the regeneration of 5-HT axons (A), while 5-HT axons are inhibitory to NA axon regeneration (B).

suggested to have an inhibitory influence on the regeneration of 5-HT axons. These results suggest that repeated stress, which is given during the early stages of axonal damage, induces opposite changes in the morphology of cortical 5-HT (sprouting) and NA axons (degeneration). On the other hand, repeated stress during the late stages of axonal damage induces no apparent changes in the morphology of the NA axons, but it does suppress the regeneration of 5-HT axons. Taken altogether, 5-HT axons appear to be more dynamic in morphological plasticity than NA axons. This difference in the capacity for axonal plasticity may have some implications for the pathophysiology of clinical depression (See later section).

6. MORPHOLOGICAL INTERACTION BETWEEN 5-HT AND NA AXONS DURING AXONAL REGENERATION

Since 5-HT and NA axons innervate similar regions of the brain, these two systems may have some morphological and functional interaction in the terminal regions. The activity of NA at serotonergic terminals has been reported to possibly lead to a decreased release of 5-HT, while the activation of postsynaptic adrenoreceptors on 5-HT neurons may lead to an increase in the release of 5-HT (40). Blier proposed that since the projections of 5-HT neurons have an inhibitory effect on NA neurons, the complex behavioral patterns of depression may thus reflect functional interactions between the brain NA and 5-HT systems (8). Considering the great capacity of 5-HT and NA axons to dynamically alter their morphology at the terminal, it is likely that the functional interactions between 5-HT and NA neurons are closely associated with the morphological interactions between terminal axons of 5-HT and NA neurons. Although the interactions between 5-HT and NA axons at the terminal are thought to play a crucial role in behavior or neural disorders such as anxiety and depression (16), there has so far been no report on the morphological interactions between these two monoamine axons.

In a recent study, we showed for the first time that morphological interactions between 5-HT and NA axons in the terminal regions can apparently occur during axonal regeneration (23) (Figure 3). To investigate the morphological interactions between the two monoamine axons during axonal regeneration, two neurotoxins to 5-HT and NA axons were injected together into one cortical site, while a single neurotoxin to either 5-HT or NA axons was injected into the symmetrical site in the other hemisphere. The denervation areas were measured at 3 levels: the injection site, 0.5 mm and 1.0 mm posterior to the injection site. Axonal density was measured at 1.5 mm posterior to the injection site and then the denervation area and density of axons were compared between both hemispheres. This denervation model enabled us to assess the role of 5-HT or NA axons in the regeneration of the other monoamine axons.

To evaluate the role of 5-HT axons in the regeneration of NA axons, the denervation area and the density of NA axons in the cerebral cortex were measured at 14 days and 60 days after the toxin injections. Regarding the role of NA axons in the regeneration of 5-HT axons, the denervation area and the density of 5-HT axons in the cerebral cortex were measured at 7 days and 28 days after the toxin injections. The denervation area and density of NA axons in the 60-day group were significantly smaller and greater, respectively, in the 5-HT + NA-neurotoxin treated side than that in the NA-neurotoxin alone treated side, while no significant difference was found between the two hemispheres in the 14-day group. These findings suggest that 5-HT axons exert an inhibitory effect on the regeneration of NA axons, since NA axons revealed a marked regeneration in the absence of 5-HT axons. On the other hand, the denervation area and density of 5-HT axons in the 28-day group were significantly smaller and greater, respectively, on the 5-HT-neurotoxin alone treated side than that on the 5-HT + NA- neurotoxin treated side. There was no difference in the denervation area and density of 5-HT axons in the two hemispheres in the 7-day group. As a result, in contrast to the role of 5-HT in the regeneration of NA axons, NA axons appear to exert a facilitatory effect on the regeneration of 5-HT axons.

Considering the difference in the speed of

regeneration between 5-HT and NA axons and the differential roles of the two monoamine axons in axonal regeneration, the mechanisms of axonal regeneration are thought to differ, at least in part, between the 5-HT and NA system. As mentioned earlier, repeated stress given during the early stages of axonal damage induces opposite changes in the morphology of cortical 5-HT (sprouting) and NA axons (degeneration). The opposite morphological responses of 5-HT and NA axons to repeated stress may be associated with the interactions between the two axons. Moreover, it remains to be determined whether either the axons containing 5-HT or NA, or the contents of the monoamine axons (5-HT or NA, or other substances) play a crucial role in this interaction.

7. A SUMMARY OF THE FINDINGS OF THE STUDIES ON 5-HT AND NA AXONAL PLASTICITY

The results of our recent studies on the morphological plasticity of 5-HT and NA axons are summarized as follows:

- Short-lasting, mild stress induces the sprouting of NA axons in the adult rat brain, while long-lasting, severe stress induces the retraction of NA axons (Figure 1).

- 5-HT axons are more easily affected by stress than NA axons, and the regeneration of 5-HT axons following axonal damage occurs more rapidly than that of NA axons. As a result, 5-HT axons are thought to show a more dynamic morphological plasticity than NA axons.

- The axonal plasticity of 5-HT and NA neurons is differentially modified by the timing of stress (Figure 2). The morphological responses of 5-HT and NA axons to repeated stress are not the same, and they are sometimes opposite to one another (namely, either sprouting or degeneration), thus suggesting that the molecular mechanisms of the stress-induced axonal plasticity may be different between 5-HT and NA axons.

- The morphological interaction between 5-HT and NA axons during axonal regeneration is opposite: NA axons exert a facilitatory effect on the regeneration of 5-HT axons, while 5-HT axons exert an inhibitory effect on NA axon regeneration (Figure 3).

In association with these findings, the next section discusses the possibility that the axonal plasticity of 5-HT and NA neurons is involved in the pathophysiology of clinical depression.

8. THE POSSIBLE INVOLVEMENT OF AXONAL PLASTICITY OF 5-HT AND NA NEURONS IN THE PATHOPHYSIOLOGY OF CLINICAL DEPRESSION

The pathopysiology of depression has long been thought to be associated with low levels of 5-HT and NA in the brain (45, 46). The findings supporting this monoamine hypothesis include the following: 1) Most clinically effective antidepressants enhance the neurotransmission of 5-HT and NA neurons by increasing the synaptic concentrations of these monoamines; 2) Reserpine, which depletes 5-HT and NA stores, induces depression; 3) The cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid, the major metabolite of 5-HT, as well as the density of 5-HT transporter binding sites were found to be decreased in the postmortem brain tissue of suicide victims and depressed patients. However, there is a puzzling problem regarding the monoamine hypothesis. Although antidepressants increase the synaptic concentrations of 5-HT and NA immediately after drug administration, the clinical efficacy of antidepressants is not usually apparent for at least 2 to 3 weeks after the start of drug administration. The delayed onset of the clinical efficacy of antidepressant drugs suggests that the pathophysiology of depression is associated with slowly occurring changes in brain neurons rather than with a simple decrease in the concentrations of the monoamines.

Data are accumulating which suggest that the morphological changes of 5-HT and NA axons are involved in the pathophysiology of depression (20, 21, 33-36). There are two major findings supporting the possible involvement of axonal plasticity of monoamine neurons in the pathophysiology of depression (monoamine axon hypothesis): 1) Antidepressants such as desipramine and miaserin induced (or facilitated) the regeneration of NA axons (34, 35). 2) A rat model of depression, which was created by exposing the animals to long-term forced walking stress, revealed the degeneration of NA axons in the cerebral cortex (20, 21). This depression model showed symptoms similar to human depression, including a persistent immobility and a disruption of hormonal rhythms. The degeneration of cortical NA axons as well as behavioral deficits in the depression model could be restored by the chronic administration of imipramine. On the other hand, there are also data supporting the involvement of morphological plasticity of 5-HT axons in the pathophysiology of clinical depression. Austin *et al.* have reported the density of 5-HT transporter-immunoreactive axons to be reduced in the prefrontal cortex in depressed suicide victims (2). In animal experiments, Madhav *et al.* have demonstrated for the first time that repeated electroconvulsive treatment has the ability to promote the sprouting of 5-HT axons in the partly lesioned hippocampus (25).

If morphological changes in 5-HT and NA axons underlie the pathophysiology of clinical depression, then the results of our recent experiments on axonal plasticity suggest that 5-HT and NA axons may be differentially involved in the pathophysiology of depression (Figure 4). Since 5-HT axons show a more dynamic morphological plasticity than NA axons, the morphological impairment of 5-HT axons may be related to either mild types of depression or early states of depression. In contrast, the morphological changes in NA axons may be associated with more severe depression. This argument is consistent with the view that NA reuptake inhibitors are more

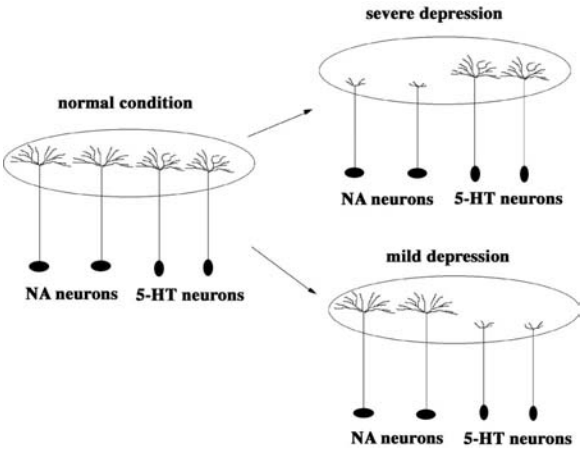

Figure 4. A proposed model of depression based on the differential features of axonal plasticity of 5-HT and NA neurons. Since 5-HT axons are more dynamic in morphological plasticity than NA axons, the degeneration (retraction) of 5-HT axons may be related to either mild types of or early states of depression. In contrast, the degeneration (retraction) of NA axons may be associated with more severe depression. It is also possible that severe types of depression include the degeneration of both 5-HT and NA axons.

effective in severe forms of major depression than selective 5-HT reuptake inhibitors (19, 40). Moreover, the inhibitory effects of repeated stress on the regeneration of 5-HT axons may also be associated with a delayed recovery from depressive symptoms under chronic stress. For the development of more effective treatments for clinical depression, special consideration should thus be given to the interaction between 5-HT and NA axons (16) as well as the differential features in the morphological plasticity of these monoamine axons.

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