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Role of Intracranial Self-Stimulation and BDNF in Reversal of Stress Induced Deficits

B.S. Shankaranarayana Rao

Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Hosur Road, Bangalore - 560 029.

Intracranial electrical self-stimulation (ICSS) has been considered as one of the intensely rewarding behavioural experiences, perhaps more influential than feeding or sexual behaviour. We have demonstrated that the electrical self-stimulation of lateral hypothalamus (LH) and substantia nigra ventral tegmental area (SN-VTA) for 10 days results in a significant increase in dendritic branching points, intersections, dendritic length, excrescences and spine densities in CA3 hippocampal and motor cortical pyramidal neurons (Shankaranarayana Rao et al. 1993; 1998c; 1999a-b). Such alterations in the dendritic morphology induced by ICSS experience are found to be long lasting (Shankaranarayana Rao et al. 1998b). These structural changes were associated with an increase in the levels of noradrenaline (NA), dopamine (DA), glutamate and AChE activity in the hippocampus (Shankaranarayana Rao et al. 1998a). It has also been shown that prior exposure to ICSS experience can induce facilitation of acquisition and better performance of operant and spatial learning tasks (Yoganarasimha et al. 1998).

On the contrary, repeated stress or an excess of glucocorticoids can exacerbate neuronal damage in response to insults and in severe cases, can lead to neuronal atrophy and death, which results in cognitive impairments. These effects are related to the actions of stress and glucocorticoids (Sunanda et al. 1998), and glutamate function (Sunanda et al. 2000b), neuronal metabolism and the generation of cytotoxic free radicals. Recent studies demonstrate that the regulation of neurotrophic factors may contribute to the actions of stress on neuronal function. Acute or chronic stress decreases the expression of brain derived neurotrophic factor (BDNF), the most abundant neurotrophin in the brain, in specific regions of the hippocampus and forebrain regions.

Expression of neurotrophins contributes to the survival and growth of neurons. The potential role of neurotrophins in the actions of the stress has been examined. Acute or chronic stress decrease the levels of BDNF mRNA in the CA3 pyramidal neurons of the hippocampus (Duman et al. 1995, Mitra et al. 1999), which are highly susceptible for stress induced dendritic atrophy or death of neurons (McEwen 1999, Shankaranarayana Rao et al. 2001). However, the role of BDNF in the atrophy and resistance of CA3 pyramidal neurons remains to be determined.

The genetic approach in mice offers the opportunity for a combined molecular, anatomical, physiological and behavioral analysis of the role of BDNF in neuronal plasticity. Unfortunately, mice deficient in BDNF are grossly abnormal in the development of the peripheral nervous system and usually die within the first 2 weeks after birth. Therefore, to address the role of BDNF in hippocampal plasticity, Tonegawa and colleagues at MIT (Huang et al. 1999) took a different approach by generating transgenic mice in which postnatal rise of BDNF level in hippocampus was genetically accelerated, using the promoter of α

Ca^{++}/CaMKII. The total level of BDNF mRNA in hippocampus was approximately 5-fold higher than those in the wild-type mice. RNA in situ hybridization showed that BDNF over expression was mostly restricted to CA1, CA3 and dentate gyrus of the hippocampus. We have demonstrated that postnatal increase in BDNF enhanced dendritic arborization and spine densities in CA3 neurons of the hippocampus (Shankaranarayana Rao et al. 2000). Accordingly, we have evaluated the role of enhanced levels of BDNF in chronically stressed rats.

ICSS experience ameliorates the lesion induced behavioral deficits

ICSS rewarding experience seems to be a consistent way to facilitate the learning and memory functions and has been shown to improve a wide variety of learned responses. Several studies indicate that ICSS can modulate different types of learning and memory consolidation processes. Our recent studies have revealed that the ICSS experience for 10 days from SN-VTA caused facilitation of acquisition of operant and spatial learning tasks and also ameliorated fornix and entorhinal cortex lesion induced learning deficits in rats (Yoganarasimha and Meti 1999). The observed facilitation of cognitive functions and amelioration of lesion-induced deficits are mediated through the mesohippocampal dopaminergic system.

Our studies also showed that the ICSS-experience from VTA dopaminergic neurons ameliorates the lesion induced behavioural deficits by promoting synergistic interaction between different neurotransmitters and reorganization of hippocampal neuronal circuitry, thus re-establishing the hippocampal function. Further, ICSS-experience may induce transformation of certain synaptic subtypes into more efficacious ones, which include conversion of silent synapses into functional synapses and by synaptogenesis and synaptic remodeling, ultimately enhancing the synaptic transmission in the hippocampus. The future work will be directed at elucidating other mechanisms, which could be influenced by ICSS-experience in the hippocampus such as enhanced synthesis of neurotrophic factors. Neurotrophic factors can counteract the insults arising out of lesions in neural pathways. Studies must be also extended to unravel the role of ICSS-experience in modulating gene expression in the hippocampus.

Reversal of stress induced cognitive deficits and cholinergic dysfunction by ICSS

Chronic restraint stress causes spatial learning and memory deficits (Sunanda et al 2000a), cholinergic dysfunction (Sunanda et al. 2000b) and dendritic atrophy in the hippocampal pyramidal neurons (Shankaranarayana Rao et al. 2001, Sunanda et al. 1995, Vyas et al. 2002). By contrast, intracranial self-stimulation (ICSS) rewarding behavioral experience is known to increase dendritic arborization, spine and synaptic density, accompanied by an increase in the levels of noradrenaline, dopamine, glutamate and acetyl cholinesterase (AChE) activity in the hippocampus. In addition, self-stimulation rewarding experience facilitates the acquisition and performance in operant and spatial learning tasks and ameliorates the lesion induced behavioral deficits. Accordingly, we have studied the role of ICSS rewarding experience on chronic stress induced memory deficits and cholinergic dysfunction.

Our results revealed that chronic restraint stress impairs the acquisition and performance of rewarded alternation task in T-maze and decreases the levels of AChE activity in the hippocampus. ICSS experience from VTA facilitated the acquisition and performance of rewarded alternation task and resulted in an increase in the levels of AChE activity in the hippocampus. Interestingly, stress-

induced behavioral deficits and cholinergic dysfunction were completely reversed by 10 days of self-stimulation experience (Ramkumar et al. 2002). We propose that self-stimulation rewarding behavioral experience can ameliorate the stress induced behavioral deficits and cholinergic dysfunction by inducing the neuronal plasticity.

Stress decreases the expression of BDNF mRNA levels in the hippocampal neurons

Exposure to stressful events is associated with increased levels of excitatory amino acids, which produces structural changes and neuronal damage especially in the hippocampus resulting an impaired spatial learning and memory. Because excitatory aminoacids, mainly glutamate and neurotrophic factors affect neuronal survival, we questioned whether they might be relevant to the heightened vulnerability of hippocampal neurons following stress. To begin investigating this possibility, we examined the effects of immobilization stress on the expression of mRNA for BDNF, Kainate and mGLUR receptors in adult rat brains using in situ hybridization. We found that immobilization stress markedly reduced BDNF mRNA levels in the hippocampus. This demonstrates that BDNF is a stress-responsive gene and raise the possibility that alteration in the expression of this or other growth factors might be important in producing some of the physiological and pathophysiological effects of stress in the hippocampus. Where as, the expression of kainate and mGLUR receptor mRNA was increased in different subdivisions of hippocampus in stressed rats (Mitra et al. 1999). These changes may underlie an increased synaptic efficiency or alternatively an increased vulnerability of hippocampal neurons to glutamate neurotoxicity leading to learning and memory impairments.

BDNF prevents stress-induced degeneration of hippocampal neurons

Chronic stress induces changes in hippocampal CA3 pyramidal neuron arborization (Shankaranarayana Rao et al. 2000). Since the neurotrophin, BDNF is neuroprotective, and has been shown in previous studies to play a role in hippocampal dendritic morphology, we hypothesized that BDNF would protect neurons from dendritic morphology changes induced by chronic stress. To investigate this hypothesis, we used transgenic mice over-expressing BDNF in the hippocampus, and subjected them to chronic immobilization stress. Golgi staining showed that, when compared to wild-type littermates, the transgenic mice showed much less changes in stress induced dendritic morphology. These results suggest that BDNF can protect neurons from stress induced morphological changes.

Summary

It is well documented that enriched environment and behavioral training can lead to improved learning and memory capabilities, accompanied by morphological changes in the hippocampal neurons. It has been hypothesized that such experience-dependent cognitive improvement results from these structural modifications. ICSS, a rewarding behavioral experience, which brings about changes in the hippocampal neurons, may ameliorate the spatial learning impairments in the stressed rats by accelerating the recovery process. Our previous study has demonstrated that stress-induced hippocampal dendritic atrophy could be reversed after 45 days of rehabilitation (Shankaranarayana Rao et al. 2001). Whereas, the behavioral recovery observed in the present study could be achieved within 10 days due to SS experience. Interestingly, the stress-induced dendritic atrophy of CA3 pyramidal neurons can be completely protected

by BDNF. This shows that the neuroptrophins exerts neuroprotective role in the adult hippocampus against the severe form of physical stress, which is known to cause cognitive deficits. Thus, stress-induced neuronal atrophy, biochemical and behavioral deficits may manifest in the form of different neuropsychiatric disorders and any means to reverse the stress-induced deficits could be of clinical importance.

Although a complete understanding of the mechanisms of reversal of stress-induced deficits will require extensive studies, there are several points worthy of comment. First, stress can lead to cell death and atrophy of certain populations of sensitive neurons, whereas other neurons are more resistant. Characterization of the cellular and molecular determinants that make a neuron more sensitive or resistant will enable attempts to prevent or reverse the deleterious effects of the stress. Second, the effects of the stress can lead to enhanced toxicity to other types of neuronal insult. Such interactions may explain why stress leads to psychiatric illnesses in some individuals who have been exposed to prior insult, where as others, without prior insult, are more resistant. Third, expressions of neurotrophins, like BDNF, are rapidly regulated by stress and may thereby contribute to stress-induced cell atrophy and survival. Such acute regulation suggests that neurotrophins may act as modulators of neuronal activity and function and not just as trophic factors. Finally, these effects of stress could underlie, in part, stress-related psychiatric disorders and may be involved in their reversal during treatment. A potential role for cell atrophy and death in certain stress-related psychiatric disorders means that these illnesses are not simply a result of neurochemical imbalances of neurotransmitters and their metabolites. Rather, studies of the etiology and treatment of these illnesses must be based on novel hypotheses that involve the cellular and molecular determinants that control the health and survival of neurons. Our current research is focused on addressing some of these questions by evaluating comprehensively the stress-induced deficits and possible cellular and molecular mechanisms of reversal or prevention/protection of neurons.

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