Dynamic changes of TrkB gene expression in *Streptococcus pneumoniae* meningitis after treatment with antibiotics and dexamethasone

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Original article

Background: **Although more and more new potent antibiotics have been used, the incidence of neurological sequelae of *Streptococcus pneumoniae* meningitis has not improved in children over the last decade. The expression of TrkB mRNA, a receptor of brain-derived neurotrophic factor, is associated with the incidence of neurological sequelae of *Streptococcus pneumoniae* meningitis.**

Methods: **Rats of 3 weeks old were used to construct a model of *Streptococcus pneumoniae* meningitis and served as normal controls. They were administered with antibiotics or antibiotics plus dexamethasone, respectively. The expression of the TrkB gene was detected in the brain by *in situ* hybridization.**

Results: **In the brains of *Streptococcus pneumoniae* inoculated rats, TrkB mRNA was significantly up-regulated after inoculation for 24 hours, and then down-regulated in a dose-dependent manner after treatment with antibiotics. This up-regulation was seen after treatment with antibiotics plus dexamethasone. TrkB mRNA expression was also observed in some infiltrating inflammatory cells.**

Conclusions: **The results of the study support the hypothesis that TrkB signal transduction pathways might play an important role in *Streptococcus pneumoniae* meningitis, probably by protecting the brain from damage. The role of TrkB might be weakened after the treatment with antibiotics. Our findings suggest that targeting TrkB receptors might be a rational strategy for prevention of neurological sequelae caused by *Streptococcus pneumoniae* meningitis.**

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Introduction

Bacterial meningitis is the most common serious infection of the central nervous system. Its death rate varies from 5% to 40%, and transient or permanent neurological sequelae include deafness, epilepsy, mental retardation and impairment of motorsensory function arising in up to a third of survivors.[1,2] In particular, the incidence of neurologic sequelae in *Streptococcus pneumoniae* meningitis is very high. Though advanced antimicrobial agents have a profound effect on the clinical course and prognosis of bacterial meningitis, outcome has only been modestly improved by intensive medical care technology as well as new, effective antibiotics. Further improvements in treatment are dependent on better understanding of the pathophysiological events that occur after activation of host's inflammatory responses by either bacteria or their products, and of the molecular mechanisms underlying the genesis of brain damage during bacterial meningitis and after initial treatment with antibiotics.[3,4]

TrkB belongs to the Trk family of tyrosine kinase receptors and mediates the response to brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 (NT-4/5).[5] Neurotrophin signaling through this receptor regulates cell survival, proliferation, the fate of neural precursors, growth and patterning of axons and dendrites, and the expression and activity of other functionally important proteins such as ion channels and neurotransmitter receptors.[6] A recent study[7] has also shown that activation of Trk receptor tyrosine kinases may occur via a G-protein-coupled receptor

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mechanism without involvement of neurotrophins. Two G-protein-coupled receptor ligands, adenosine and pituitary adenylate cyclase-activating polypeptide, can activate Trk receptor activity to increase the survival of neural cells.[7]

In a previous study,[8] we found that the expression of BDNF mRNA and its production in the brain are down-regulated after administration of antibiotics in *Streptococcus pneumoniae* meningitis, and that there is a dose-dependent down-regulation of BDNF after treatment with antibiotics. After the administration of antibiotics plus dexamethasone, however, the expression of BDNF mRNA and its production were increased, and then adjuvant administration of exogenous BDNF could rescue neurons from *Streptococcus pneumoniae* meningitis.[8,9] BDNF activates various signal transduction pathways in cells and exerts its biological function by binding with the high-affinity TrkB receptor to activate protein tyrosine kinase.[10] However, the role of TrkB receptor in *Streptococcus pneumoniae* meningitis remains unknown. In this study, the animal model of *Streptococcus pneumoniae* meningitis was used to further investigate the expression of TrkB receptor mRNA in the brain after occurrence of *Streptococcus pneumoniae* meningitis and treatment.

Methods

Animals and experimental design

In a total of 90 three-week-old Sprague-Dawley rats obtained from the Medical Experimental Animal Center of Zhejiang University, 9 were enrolled in a model group injected with *Streptococcus pneumoniae* or normal saline. The development of bacterial meningitis was confirmed histologically. Other rats were randomly divided into four groups: (1) infected groups (n=10 in each), which were inoculated with *Streptococcus pneumoniae* and sacrificed at 24 hours and 5 days after inoculation, respectively; (2) groups treated with antibiotics (n=38), which were assigned into four subgroups: the rats in subgroup I (n=12), II (n=10) and III (n=10) inoculated with *Streptococcus pneumoniae* were treated with ceftriaxone (100 mg/kg, 75 mg/kg and 50 mg/kg subcutaneously, respectively) once daily starting at 24 hours after inoculation for 3 days and then sacrificed; those in subgroup IV (n=6) injected with normal saline were treated with ceftriaxone (100 mg/kg subcutaneously) once daily starting at 24 hours after injection for 3 days and then sacrificed; (3) group treated with antibiotics plus dexamethasone (n=11), which were treated with ceftriaxone (100 mg/kg subcutaneously) and dexamethasone (3 mg/kg intraperitoneally) once daily starting at 24 hours after inoculation for 3 days and then sacrificed; (4) normal control groups (n=6 in each), which were injected with normal saline and decapitated at 24 hours and 5 days after injection.

Infection of the organism

The strain of serotype 3 *Streptococcus pneumoniae* was obtained from the National Leechdom and Bioprodutes Appraisal Institute in Beijing. In order to infect the infant rats, the organism was cultured on blood-agar plates, then inoculated into vital Aer broth and incubated overnight at 37ºC in air with 5% CO_2 to the growing logarithmic phase. The organism was then centrifuged and washed with normal saline, and finally resuspended in normal saline with concentration close to 10^7 colony-forming units.

Induction of bacterial meningitis

The rats were anesthetized by intraperitoneal injection of 0.15-0.3 mL/100 g 10% chloral hydrate. The induction of bacterial meningitis was described previously.[11] About 50 μL of cerebrospinal fluid was removed via intracisternal puncture. After removal of the cerebrospinal fluid, 50 μL volume containing *Streptococcus pneumoniae* (10^7 colony-forming units or normal saline) was injected intracisternally into each of the 90 rats. The animals were housed under 12-hour light/12-hour dark conditions. Their cerebrospinal fluid was re-sampled after inoculation at 24 hours. To confirm the development of bacterial meningitis, the cerebrospinal fluid was cultured and the brain of rats in the model group was examined histologically by hematoxylin eosin and cresyl violet staining. The number of cells in the cerebrospinal fluid was counted before and after inoculation. Fifteen of the animals died during the development of meningitis and treatment (8 rats belonged to the infection group sacrificed on the 5th day; 2, 2 and 2 rats belonged to sub-group I, II and III of the group treated with antibiotics respectively; and 1 rat belonged to the group treated with antibiotics plus dexamithasone).

Brain tissue preparation

The animals were anesthetized with 0.15-0.3 mL/100 g of 10% chloral hydrate, perfused through the heart with 50 mL phosphate buffer saline, and then with 200 mL of ice-cold 4% paraformaldehyde in phosphate buffer saline. The brains of the animals were removed and post-fixed in the same fixative solution for 4 hours at 4ºC, then put into 30% sucrose in phosphate buffer. Cryostat coronary sections of the brain through the hippocampus were cut into 15 μm thick sections for *in situ* hybridization.

In situ hybridization

In situ hybridization analysis for TrkB mRNA utilized the oligonucleotide probes. Synthetic oligonucleotide probes (Boster Bioengineering, Inc, China) were labeled by digoxin, using long terminal labeled methods. To increase the sensitivity of the method, multiphase (three different = 30 bp long) oligonucleotide probes, which were complementary to human TrkB cDNA and whose sequence were 5'-TCCAA TCTCG GAAAT GCCAC GATGC CAGGA-3'; 5'-AAATG GAGTG TTACT CCCAT TGGAG ATGTG-3'; 5'-GGAGG GTATG GATGC CCTTG ATGTT CTTCC-3 respectively, were used. Briefly, mount sections were hybridized with labeled oligonucleotide probes in 50% deionized formamide, 4×SSC, 1×Denhart's solution, 0.01 mol dithiothreitol, 0.5 mg/mL yeast tRNA, 0.1 mg/mL polyvinyrrolidone and 10% dextran sulphate overnight at 40ºC, and washed for 15 minutes in 2×SSC at 37ºC. The sections were incubated with antidigoxin antibody for 60 minutes at 37ºC, and then processed for biotinylated immunohistochemistry. Hybridized signal was shown with diaminobezidin. In control procedures, hybridization treatment of tissue without probes resulted in no specific hybridization signal.

Image analysis

Hybridization signals were quantified by computerized image analysis. One coronary section through the hippocampus and dentate gyrus were blindly analyzed from each animal, and 10 measurements were made on the corresponding areas of the brain cortex and hippocampus from each animal. Mean values obtained from the section of each animal were used for statistical analysis.

Differences in mRNA levels between the infected group, treated group and uninfected control group were determined by one-way ANOVA and the post hoc test. $P<0.05$ was considered statistically significant.

Results

Histopathology of meningitis

After inoculation with *Streptococcus pneumoniae* for 24 hours, the infected rats developed meningitis. (1) The total number of leukocytes in the cerebrospinal fluid obtained after infection increased more markedly than that in the cerebrospinal fluid obtained before infection ($P<0.01$), in which granulocytes were predominant. But there was no significant change in leukocyte number in cerebrospinal fluid (CSF) of the rats injected with normal saline. (2) Bacterial culture of the homogenized cerebrospinal fluid from the infected rats was positive for the same *Streptococcus pneumoniae* strain, but negative before inoculation and in the control group. (3) The brain histopathology of the infected group was characterized by subarachnoid cavity, ventricular and leptomeninges inflammational exudate, spot-like hemorrhage in the parenchyma, and neuronal injury of the cerebral cortex and hippocampus, but neither inflammation nor neuronal injury was found in the brain of the rats injected with normal saline.

Expression of TrkB mRNA

The increase of TrkB mRNA in hybridization in the brain neurons at 24 hours after infection with *Streptococcus pneumoniae* was more evident than that of the normal control group (Fig. 1; Fig. 3A *vs.* Fig. 3C) ($P<0.01$). Up to the 5th day after infection, the expression of TrkB mRNA returned to the level of the control group ($P<0.05$) (Fig. 1; Fig. 3B *vs.* Fig. 3C). The expression of TrkB mRNA returned to the level of the control group on the 5th day after infection ($P>0.05$). After the infected rats were administered with antibiotics (ceftriaxone, 100 mg/kg), however, the expression of TrkB mRNA in the brain neurons was much lower than that of the normal control group, the infected group sacrificed on the 5th day (Fig. 1, Fig. 3B-3D), and the normal group treated with antibiotics (Fig. 2, Fig. 3E) ($P<0.01$). In the brain neurons of the rats in the infected group treated by 100 mg/kg ceftriaxone, the down-regulation of TrkB mRNA expression was greater than that of the infected group treated with 50 mg/kg ceftriaxone (Fig. 2; Fig. 3D *vs.* Fig. 3F) ($P<0.05$), but there was no significant difference between the infected group treated with 100 mg/kg and 75 mg/kg ceftriaxone or between the infected group treated with 75 mg/kg and 50 mg/kg ceftriaxone ($P>0.05$). There was no significant difference between the normal group treated with antibiotics and the normal control group (Fig. 2). In the brain neurons of the rats administrated with antibiotics

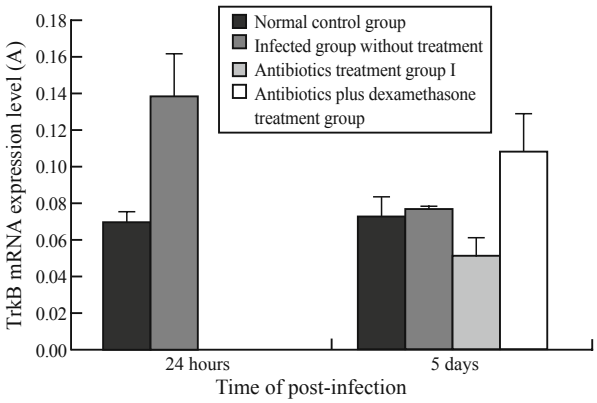

Fig. 1. The change of TrkB mRNA expression in the brain neurons from various groups.

plus dexamethasone, however, the expression of TrkB mRNA was higher than that of rats treated with antibiotics only (Fig. 1, Fig. 3G) ($P<0.01$).

Meanwhile, in the brains of the infected rats, strong hybridized signal was observed in some infiltrating inflammatory cells in the leptomeninges, subarachnoid cavity and ventricles (Fig. 3H).

Discussion

We have the following major findings in our study. First, TrkB mRNA level was increased in the brain neuron after inoculation of *Streptococcus pneumoniae* for 24 hours. Second, after antibiotics treatment of *Streptococcus pneumoniae* meningitis, TrkB mRNA levels were lowered and almost undetectable in the brain neurons, and this down-regulation of TrkB mRNA by antibiotics was dose-dependent. Third, the expression of TrkB mRNA was up-regulated in the brain neurons treated with antibiotics plus dexamethasone. Fourth, TrkB mRNA was observed in some infiltrated inflammatory cells after development of bacterial meningitis. These findings suggest that TrkB might be correlated with the pathophysiology of *Streptococcus pneumoniae* meningitis.

It is still unclear why TrkB mRNA expression is elevated during the acute phase of *Streptococcus pneumoniae* meningitis, but possibilities are consistent with our results. First, studies[12,13] have shown that the biosynthesis of TrkB mRNA may be modulated by Ca^{2+} cellular inflow, depolarization, and excitatory amino acids. The activity-dependent enhancement of TrkB internalization and its tyrosine kinase requires Ca^{2+} influx through N-methyl-D-aspartate receptors and Ca^{2+} channels.[14] Bacterial meningitis is often followed by the depolarization of membrane, release of excitatory amino acids and inflow of Ca^{+2}.[15] The neurons in response to the factors can promptly promote the expression of TrkB receptor. Next, TrkB expression is dependent on the endogenous BDNF.[16] TrkB elevation may be a result of up-regulation of the BDNF in response to bacterial invasion. During bacterial meningitis, many brain cells express cytokines and other proinflammatory molecules in response to stimuli generated by bacterial lysis.[1] Our studies showed that not only neurons but also a continued influx of infiltrated inflammatory

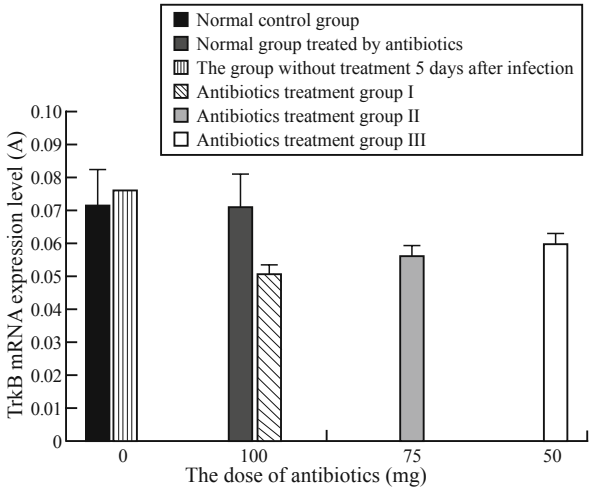

Fig. 2. The change of TrkB mRNA expression in the brain neurons from the group treated by various antibiotics dose.

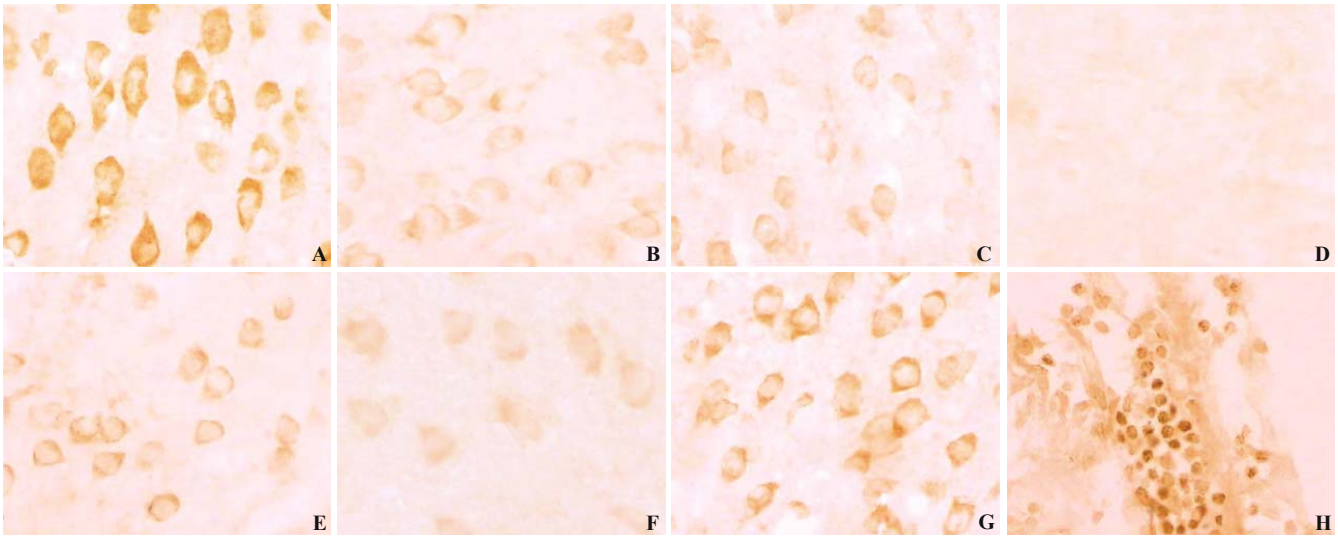

Fig. 3. TrkB mRNA expression in the neurons of the cerebral cortex and inflammatory cells in the ventricle. **A:** 24 hours after infection (infection group without treatment); **B:** 5 days after infection (infection group without treatment); **C:** Normal control group; **D:** Infected group after administration of ceftriaxone 100 mg/kg; **E:** Normal group treated with ceftriaxone 100 mg/kg; **F:** Infected group after administration of ceftriaxone 50 mg/kg; **G:** Infected group after administration of antibiotics plus dexamethasone; **H:** Inflammatory cells in the ventricle 24 hours after infection.

cells express TrkB mRNA, which may be part of the inflammatory response. The results are consistent with other investigations demonstrating that immune cells express TrkB *in vitro* and *in vivo*.[17,18]

The potential role of increased expression of TrkB mRNA after development of *Streptococcus pneumoniae* meningitis is not yet clear. Many studies have demonstrated that TrkB receptor can be activated by BDNF and neurotrophin-4 (NT-4), thereby affecting both development and function of the nervous system. BDNF/TrkB interaction regulates migration of subventricular zone (SVZ) precursor cells.[19] Memory acquisition and consolidation are associated with an increased BDNF mRNA expression and the activation of its receptor TrkB. Genetic and pharmacologic deprivation of BDNF or TrkB impairs learning and memory. In a positively motivated radial arm maze test, activation of the TrkB/phosphatidylinositol-3 kinase (PI3-K) signaling pathway in the hippocampus is associated with consolidation of spatial memory through an activation of translational processes. In a negatively motivated passive avoidance test, mitogen-activated protein kinase is activated during acquisition of fear memory. Furthermore, a recent study[20] has suggested the importance of interaction between BDNF/TrkB signaling and NMDA receptors for spatial memory. As a Src-family tyrosine kinase, Fyn plays a role in this interaction by linking TrkB with NR2B. These findings suggest that BDNF/TrkB signaling in the hippocampus plays a crucial role in learning and memory. TrkB ligands BDNF and NT-4 can directly influence human dendritic cells during their maturation.[21] NT-4 mediates cell survival through TrkB thus preventing neural cells from death in various pathological conditions. NT-4, in combination with other trophic factors, is involved in the postnatal survival of retinal neurons during development and degeneration.[22] Previously, we found that adjuvant administration of exogenous BDNF can patently increase the population of survival neurons in the brain after occurrence of *Streptococcus pneumoniae* meningitis. In addition, our studies have shown that the BDNF and TrkB mRNA were all observed in some infiltrated inflammatory cells after occurrence of *Streptococcus pneumoniae* meningitis. These findings support the hypothesis that the BDNF activates various signal transduction pathways in cells and might not play neuroprotective role but also modulate immune function in the brain damage process of rats with *Streptococcus pneumoniae* meningitis by binding the high-affinity TrkB receptor. Recently, it has been shown that activation of Trk receptor tyrosine kinases can be activated by a G protein-coupled receptor mechanism, without involvement of neurotrophins. Adenosine and adenosine agonists can activate Trk receptor phosphorylation specifically through the seven transmembrane spanning adenosine 2A (A2A) receptor. Several features of Trk receptor transactivation are noteworthy and differ significantly from other transactivation events. Slower Trk receptor transactivation can result in a selective increase in activated serine/threonine protein kinase B (Akt). Unlike the biological actions of other tyrosine kinase receptors, increased Trk receptor activity by adenosine may lead to increased cell survival.[23] TrkB in hippocampal neurons can be observed after treatment with adenosine, a neuromodulator that acts through G protein-coupled receptors. Adenosine activates phosphatidylinositol 3-kinase/Akt through a Trk-dependent mechanism that results in an increased cell survival after withdrawal of nerve growth factor or BDNF.[24] Other studies have shown that TrkB is required for the development and/or maintenance of normal synaptic connectivity of granule cells, indicating an important role of TrkB in the granule cells and hippocampal circuitry.[25] TrkB receptor is necessary for the maintenance of hippocampal spines during postnatal life.[26] TrkB signaling regulates the developmental maturation of the somatosensory cortex and the neural precursor cell proliferation and differentiation during cortical development.[27,28] Therefore, our studies support the hypothesis that targeting TrkB receptors might be a rational strategy for the development of novel and effective methods for preventing neurologic sequelae after development of *Streptococcus pneumoniae* meningitis.

Despite the use of new and effective antibiotics, the reason *Streptococcus pneumoniae* meningitis is still associated with high rates of mortality and permanent sequelae in children should be elucidated. Experimental *Streptococcus pneumoniae* meningitis in the present study showed that the expression of TrkB mRNA after administration of antibiotics was much lower than that of the normal control group, the normal group treated with antibiotics, and the infected group without treatment. There was a dose-dependent down-regulation of TrkB after administration of antibiotics in the infected group, but there was no effect on the expression of TrkB in the normal group treated with antibiotics. The changes of TrkB mRNA expression were concurrent with the expression of BDNF following antibiotic treatment of *Streptococcus pneumoniae* meningitis. This finding suggests that the concomitance between TrkB and intrinsic BDNF was reduced in *Streptococcus pneumoniae* meningitis after treatment with antibiotics. Our results support the hypothesis that the expression of TrkB receptor might be inhibited, and endogenous neuroprotection might be

weakened after antibiotic treatment by inhibiting signal transduction pathways via TrkB intervention. It might be one of the mechanisms that neurologic deficits occur with high frequency after occurrence of *Streptococcus pneumoniae* meningitis. Since *Streptococcus pneumoniae* meningitis is caused by bacteria. Therefore, its treatent should include eradication of bacterial pathogens by antibiotics and administration of activating TrkB receptors, which are helpful to prevent the brain from damage.

Glucocorticoids are advocated to be used as an adjuvant treatment in childhood *Streptococcus pneumoniae* meningitis to attenuate host inflammatory responses for improved neurologic defects. Although whether glucocorticoids can decrease brain damage in patients with bacterial meningitis is still controversial, some clinical and animal experiments have shown that adjuvant treatment of dexamethasone attenuates the mortality rate and incidence of neurologic defects such as sensorineural hearing loss. Our study showed that the administration of antibiotics plus dexamethasone could increase the expression of TrkB mRNA in experimental *Streptococcus pneumoniae* meningitis. The physiological relevance of TrkB up-regulation by dexamethasone in *Streptococcus pneumoniae* meningitis is not clear. Recent studies have shown that TrkB receptors are normally activated by neurotrophins such as BDNF. But the activation of Trk receptors by glucocorticoids does not depend on increased production of neurotrophins. The ability of glucocorticoids to increase Trk receptor activity results in the protection of neurons deprived of trophic support and could be modulated by steroid-converting enzymes. Pharmacological study and short hairpin RNA experiments indicate that Trk receptor activation by glucocorticoids depends on a genomic action of the glucocorticoid receptor. The ability of glucocorticoids to promote Trk receptor activity represents a molecular mechanism that integrates the actions of glucocorticoids and neurotrophins.[29]

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