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PLASTICITY IN THE VISUAL SYSTEM: ROLE OF NEUROTROPHINS AND ELECTRICAL ACTIVITY

L. MAFFEI*

Istituto di Neuroscienze del CNR, Area della Ricerca, Via G. Moruzzi 1, 56100 Pisa and Scuola Normale Superiore, Piazza dei Cavalieri, 7, 56126 Pisa, Italy

At the beginning of this paper, I like to pay a tribute to the memory of Carlo Terzuolo as a man and as a scientist. I have learnt immensely from him, from his enthusiastic attitude to science, from his genuine interest in the progress of knowledge. The previous conference in Brainerd that he organized so many years ago was an open window to what appeared to be new and important in neuroscience research in that period. I saw Carlo a few weeks before his death. Even if he had problems with his health, he was discussing science and scientists with the freshness of a student. He was a man without compromises, a difficult man, as often is the case for persons, who have great beliefs and goals. My remembrance of him is full of admiration.

INTRODUCTION

Neurotrophins have usually been considered for their involvement in the development of the nervous system and for differentiation and maintenance of specific functions of certain classes of neurons in adult life. In recent years evidence has emerged that neurotrophins might have other functions related to neural activity-dependent development and more generally to the plasticity of the brain and in particular of the neocortex. The first evidences in this sense came from studies in visual cortical plasticity in rats (10). The functional properties of mammalian visual cortical neurons are immature at eye opening, and develop gradually during the first months of postnatal life. As shown by Wiesel and Hubel (15) for the cat and monkey, the development of the rat visual system is strongly influenced by manipulation of visual experience such as monocular deprivation or dark rearing. For instance, one week of monocular deprivation (MD) during the critical period is sufficient to shift the ocular dominance distribution of visual cortical cells so that 80% of the cells are driven exclusively or predominantly by the non deprived eye. We showed that administration of NGF in the ventricles or in the visual cortex prevents the amblyopic effects of monocular deprivation, the most striking results being that the visual binocular cells remain binocular and visual acuity, tested electrophysiologically and behaviourally, remains normal. In addition, we demonstrated that the classical effects of dark rearing, namely habituation of cortical responses to visual stim-

*Address for correspondence: Prof. L. Maffei, Istituto di Neuroscienze del CNR, Area della Ricerca, Via G. Moruzzi 1, 56100 Pisa, Italy. Tel. 050 3153179, Fax 050 3153220, E-mail: maffei@in.pi.cnr.it

ulation, increased receptive field size, decreased orientation selectivity of cortical cells, increased binocularity, decreased visual acuity are also prevented by administration of NGF.

To further investigate the role of NGF in the development and plasticity of the visual system, we blocked endogenous NGF by means of antibodies against NGF and we found that this block interferes dramatically with the development of the visual system and prolongs the critical period (2).

Subsequently, a large number of investigations tackled the problem of the role of neurotrophins on the plasticity of the visual system, employing different species and different experimental protocols. The results obtained are not always in accordance and there is still controversy on the identity of the active neurotrophin. It is still unclear, in particular, whether different neurotrophins play similar or different roles and what are their effects on the electrical activity of cortical neurons *in vivo*. We therefore compared the effects of all neurotrophins, NGF, BDNF, NT-4 and NT-3 on visual cortical plasticity and on cell spontaneous and visually evoked activity (9). Rats were monocularly deprived for one week at the peak of the critical period and neurotrophins infused intracortically. Assessment of the outcome of MD was done electrophysiologically, by *in vivo* recordings from the striate cortex contralateral to the deprived eye. We found that different neurotrophins play their roles in visual cortical plasticity through different mechanisms and in particular through a different interplay with electrical activity. NGF and NT-4 are both able to counteract the effects of monocular deprivation without causing any detectable alteration in cell responsiveness or selectivity. BDNF is less effective on ocular dominance plasticity. BDNF has a peculiar characteristic: it is the only neurotrophin which alters visual cortical cell electrical activity, both spontaneous and evoked. Particularly interesting seems the similarity between the effects of NGF and NT-4, which bind to different receptors, expecially if compared with the difference in action between the two TrkB ligands, BDNF and NT-4. This difference becomes striking at close distance from the infusion site, where BDNF induces a paradoxical dominance of the deprived eye on visual cortical cells while NT-4 does not.

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NEUROTROPHINS AND THE MODULATION OF SYNAPTIC TRANSMISSION IN THE VISUAL CORTEX

A possible mechanism of action of neurotrophins on neural plasticity is the modulation of synaptic efficacy: we have investigated whether neurotrophins can modulate synaptic transmission in the visual cortex using an *in vitro* preparation, synaptosomes prepared from the visual cortex of rats at the peak of the critical period (P23). For the moment, we have limited our study to NGF and BDNF (14). Both NGF and BDNF potentiate glutamate and acetylcholine release, while only BDNF does so for GABA release. The effects on Glu are not secondary to ACh release, sug-

gesting a direct effect of NGF on glutamatergic synaptosomes (14). As for the *in vivo* effects of NGF, TrkA plays the major role in mediating NGF effects also in the case of NGF potentiation of Glu release and p75 plays a small facilitatory role. For BDNF, its effects on release seem to be mediated exclusively by TrkB (14).

We are left with the hypothesis that different neurotrophins have different roles in rat visual cortical plasticity and probably act on different targets. Indeed, both our data and evidences from the literature indicate that the different neurotrophins might play their role on the stage of visual cortical plasticity through different mechanisms. We shall discuss these possible mechanisms separately for NGF, BDNF and NT-4.

NGF

Two likely sites of actions can be taken into consideration in the light of the available experimental evidence. These are the visual cortex and the basal forebrain cholinergic neurons with their projections to the cortex. These two sites could well offer synergistic contributions for the action of NGF. Receptors TrkA and p75 are present in the basal forebrain cholinergic nuclei and in their cortical terminations. NGF injected into the cortex is promptly transported to the basal forebrain nuclei (6) while NGF infused into the ventricles induces TrkA phosphorylation of their neurons. It is already known from previous experiences that cholinergic projections to the visual cortex play a permissive role in gating ocular dominance plasticity (1). NGF might modulate the level of activity in the cholinergic system and indirectly modulate synapse modification of cortical neurons. On the other hand, NGF increases release not only of Ach, but also of Glu from visual cortical synaptosomes; this suggests that NGF, in addition to its action on cholinergic afferents could also exert a direct effect on intracortical excitatory circuitry (2, 14).

BDNF

It is possible to hypothesize an action of BDNF on the cholinergic afferents from the basal forebrain and on the excitatory cortical circuitry, similar to that of NGF; in addition, a direct action of BDNF on thalamic afferents is also possible. Indeed, TrkB is present on basal forebrain afferents, on pyramidal neurons and on geniculate neurons. Furthermore, BDNF increases both ACh and glutamate release from cortical synaptosomes (14).

Peculiar of BDNF action is the modulation of intracortical inhibitory circuitry. Indeed, TrkB is present on intracortical inhibitory interneurons and BDNF, but not NGF, promotes GABA release from cortical synaptosomes (14); in addition, BDNF regulates the expression of neuropeptides characteristics of intracortical inhibitory interneurones, such as NPY (11 and our unpublished experiments) and regulates the electrical activity of cultured intracortical interneurons (13). More recently, evidence for an accelerated development of intracortical inhibition has been reported by our group in transgenic mice overexpressing BDNF (8). BDNF modulation of intracortical inhibition could explain some of its effects, such as the paradoxical shift of ocular dominance distribution and the loss of orientation

selectivity close to the infusion cannula found by Galuske et al. (7) in MD cats. None of these "pathological" effects has been reported for NGF, thus reinforcing the hypothesis of different mechanisms of action for the two neurotrophins. Also the disruption of ocular dominance columns organization found by Cabelli et al. (3, 4) in kittens after BDNF infusion could be attributed to an alteration of the balance between excitation and inhibition.

NT4

To our knowledge, our results are the first demonstration that NT-4 is able to prevent almost completely the functional effects of monocular deprivation, namely the shift of ocular dominance distribution.

The mechanisms of action of NT-4 have been less investigated than those of BDNF and the literature on this problem is very scanty. Potentially, since BDNF and NT-4 share the same receptor, TrkB, NT-4 action on visual cortical plasticity could be analogous to those for BDNF. However, experimental findings indicate that this cannot be the whole story. We found that NT-4 does not change the activity of visual cortical neurons, while BDNF does. In addition, NT-4, locally delivered to thalamic afferents by means of microbeads, is the only neurotrophin effective in preventing the shrinkage of LGN neurons in monocularly deprived ferrets (12). This observation suggests that, at the level of thalamic afferents, NT-4 is clearly more active than the other neurotrophins.

MAPK ACTIVATION AND VISUAL CORTICAL PLASTICITY

We have recently investigated the molecular chains underlying visual cortical plasticity (5). Mitogen activated protein Kinase (MAPK also called ERG), has been shown to be an important component of activity dependent signaling cascades within neurons and its activation seems to be required for both synaptic plasticity, learning and memory. One of the known factors able to modulate MAPK activity are neurotrophins. Neurotrophins and electrical activity are potent regulators of visual cortical plasticity in mammals, but whether MAPK cascade activation plays a role in visual cortical plasticity is however unknown. We have investigated the role of MAPK activation in visual cortical plasticity using two approaches, *in vitro* and *in vivo*. *In vitro* we have used the classical approach of LTP in cortical slices and *in vivo* the paradigm of MD. We have shown that two different inhibitors of the MAPK pathway suppress LTP in cortical slices and that their intracortical administration to monocularly deprived rats prevents the shift in ocular dominance. MAPK pathway results therefore to be necessary for experience dependent plasticity and for LTP in the developing visual cortex.

SUMMARY

We report recent results concerning the action of neurotrophins on the development and plasticity of the visual system of mammals and in particular of their visual cortex. It has been demonstrated that NGF prevents all the effects of monocular deprivation during the critical period. BDNF, that in part also prevents the effects of monocular deprivation, has the interesting additional property of accelerating the development of inhibitory processes.

In transgenic mice overexpressing BDNF only in the cortex, the critical period for plasticity initiates a week earlier and presents a precocious closure. Visual acuity also develops much before than in normal animals. These phenomenological observations are paralleled by a precocious increase of inhibitory synapses and inhibitory currents in pyramidal neurons. LTP, tested by stimulation of the white matter, recording in layers 2 and 3 of the visual cortex, presents modifications correlated with the alterations observed in the critical period. Last we report the finding from *in vitro* and *in vivo* experiments that MAPkase (Erg 1 and 2) is the molecular chain of events driven both by light and neurotrophins, likely at the bases of the phenomena of plasticity observed during the critical period.

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