Chapter 3.4

Nerve Growth Factors and Neurotrophins

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Abstract

Cell division, cell death, and cell differentiation are hallmarks of embryogenesis. Such processes are supported by neurotrophins that have the capacity of regulating not only developmental processes, but also neuronal survival, morphological adaptation, and neural plasticity.

Nerve growth factor (NGF) is a prototype of neurotrophins capable of influencing survival and differentiation of neuronal cells during development. It has been shown that the cholinergic neurons of the basal forebrain critically depend on NGF for differentiation and survival. Exogenous administrations of NGF induced up or down regulation of cholinergic enzymatic activity that in turn altered the number of muscarinic receptors. Apart from its trophic function through activation of tyrosine kinase A receptors, NGF also can be neurotoxic through activation of p75 ^{NTR} receptors.

Such dual and opposite effect suggests that exogenous NGF supplementation could alter the exact maturation of the cholinergic system either in a positive or in a negative way, depending on the period of the treatment. This was confirmed with NGF treatment during postnatal week two generating an adult-like spatial learning capacity despite animals being less than 5 weeks old. This superiority was maintained into adulthood. By contrast, NGF treatment during postnatal week one impaired spatial learning and hindered development into adult-like efficiency. These results reveal a developmentally crucial period for spatial learning mechanisms with a critical modulatory role of NGF.

Introduction

Among growth factors, neurotrophins appear to play a critical role particularly in neurite outgrowth and terminal arborization. In addition to their classical role in neuronal differentiation and survival, neurotrophins have been strongly implicated in axon pathfinding.[63] The notion that growth factors can guide growing axons to their targets was introduced more than 20 years ago.[51] This assumption was confirmed by culture experiments showing that nerve growth factor (NGF) induces a chemotactic response of sensory neurons.[31] The growing tip of the axons, the growth cones expresses growth factor receptors. The neurotrophic influence seems to depend on the receptor-mediated uptake and on the retrograde axonal transport toward the soma of the responsive neuron.[44,69] In vivo and in vitro experiments led to the hypothesis that growth factors promote the development of innervation. As will be revealed later, the effects of NGF on the development of cholinergic neurons support this idea. However, the concentration of NGF required to produce this effect appears to be higher than endogenous levels of NGF. To explain this paradox, it has been postulated that, as most of the developing neurons die during embryogenesis, because of their insufficient ability to compete for the limited amount of a trophic factor[42,45,24] and undergo synaptic plasticity.[66]

Memories Are Made of These: From Messengers to Molecules, edited by Gernot Riedel and Bettina Platt.

Neurotrophin Expression and Regulation of Neurogenesis during Development

The five closely related factors nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), -4 (NT4) and -5 (NT5) constitute the neurotrophin family. In the developing rat nervous system, the distribution of NT3, BDNF and NGF transcripts display a simultaneous increase in their expression between the 11th and 12th embryonic day and are widely distributed at embryonic days 12 and 13. This timing approximately corresponds with the developmental onset of neurogenesis (for example, see ref. 4). Despite the simultaneous gene expression of neurotrophins, the levels differ greatly at early embryonic stages . Nt-3 is the most highly expressed in the embryo while BDNF is expressed lowest. During development, NT-3 expression appears to follow proliferation, migration and differentiation of neurons and decreases within CNS regions as they mature. BDNF expression in the newborn rat is most prominent in CNS regions in which neurogenesis has already occurred and increases with maturation. Finally, NGF expression varies locally during development, but these variations do not follow a consistent pattern.[47] This absence of specificity would suggest a more general action of NGF on neurogenesis.

Embryogenesis, characterized by continuous cell division, death and differentiation is supported by neurotrophins, which regulate developmental processes, neuronal survival, morphology, and neural plasticity. The synaptic targets of the cells that enable neurotrophins neuronal survival. A partial or complete deletion of targets results in reduced innervation of neurons and reduced numbers of surviving neurons.[35] However, it seems that the target neurons may not be the only source of trophic support for neuronal survival.[58] Directional guidance of the growth cones appears to depend on second messengers, particularly cAMP, and the growth cone behavior seems to be regulated by the sum of second-messenger signals generated by several guidance cues.[50] Data have shown that an abrupt change in levels of guidance molecules are necessary for steering axons to an intermediate point or to a synaptic target.[51,72] This seems to indicate that a uniform pattern of guidance molecules prevents growth cones to extract guidance information and to enter their targets correctly. It appears that once secreted, immediate binding to cofactors could spatially restrict the actions of growth factors. For example, NGF and BDNF are immediately catanolised after secretion by the cell surface.[5] As NGF expression presents variations during development, it could also play a particularly important role in functional neuronal connections.

Neurotrophin Receptors

Actions of NGF depend on specific receptors. Their activation can lead to a wide range of responses, and these responses seem to depend on the activation of distinct second-messenger pathways. Growth factors bind to different tyrosine kinase members, NGF binds to trkA, BDNF to trkB, NT3 to trkB and trkC and NT4 to trkB, while the p75 ^{NTR} low affinity receptor binds NGF, BDNF and NT3-4 (Fig. 1).

The p75 has no catalytic intracellular tyrosine kinase domain, but it is capable of mediating the neurotrophin signals. The ligand binding of p75 increases the high-affinity trkA binding sites and enhances trkA autophosphorylation and selectivity for neurotrophin ligands. The trk-independent pathway of p75 increases intracellular ceramide levels and further NFκB transcription factor[17] and JNK kinase.[18] Conversely, trkA activation can inhibit p75-mediated signaling, but the mechanism of this inhibition remains unclear.[40]

Nerve Growth Factor and the Basal Forebrain Cholinergic System

NGF is the most widely studied and characterized polypeptide growth factor capable of influencing survival and differentiation of neural cells during development.[44,45] Although, this prototype neurotrophic factor is well known to regulate the survival of neuronal populations, its function in the control of nerve growth remains unclear. Investigations on newborn and

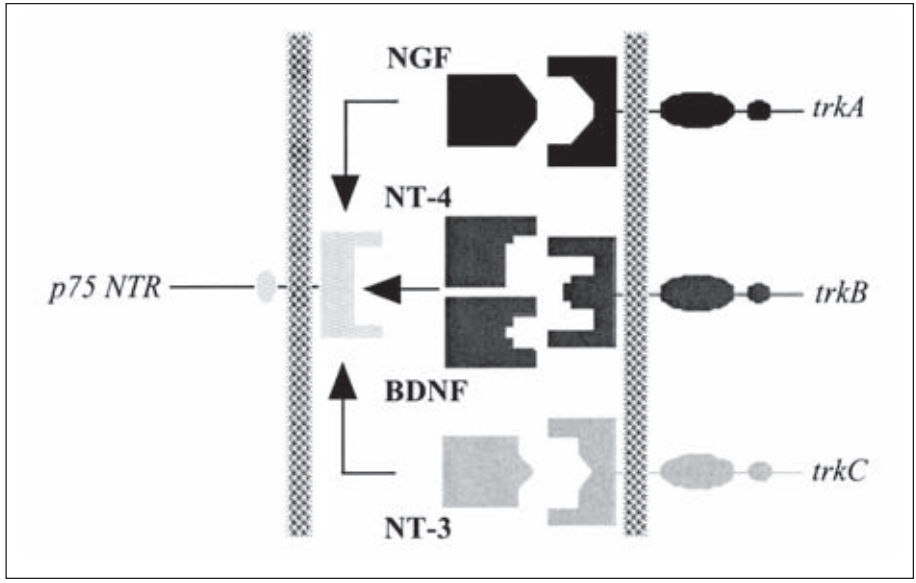

Figure 1. Schematic representation of neurotrophin binding showing that NGF binds to trkA, BDNF and NT4 to trkB, NT3 to trkC while the p75 ^{NTR} low affinity receptor can bind NGF, BDNF and NT3-4.

adult rats have shown that exogenous NGF affects at least two parameters of the basal forebrain and striatal cholinergic neurons:

- It induces a selective and prominent increase of choline acetyltransferase (ChAT) activity[29,55,56,39,25] (Kramer, 1999).
- It enlarges the size of the cholinergic neurons (Purves et al 1988).

Enzyme activity is a classical measure for evaluating the maturation of neuronal tissue. The development of enzyme activity in the terminal fields of the cholinergic forebrain system takes place during the first four postnatal weeks.[65] During ontogeny, the basal forebrain cholinergic neurons depend on NGF for their differentiation and the expression of neurotransmitter phenotype.[42,37] Fiber terminals originating in the septal complex are present within the hippocampus formation by at least fetal day 20. Septal terminals are diffusely distributed initially and segregate to their mature position during the second postnatal week.[55] Cholinergic enzyme activity increases between birth and PN 5 in the hippocampus and frontal cortex. It reaches a peak value by PN 30 except in striatum, which achieved maximal activity at PN 60. This increase in activity is transient, and a major decrease is observed between PN 30 and 60.[66]

The cholinergic neurons of the basal forebrain depend on NGF for their differentiation and survival, and the expression of neurotransmitter phenotype (Hefti et al., 1989).[77,43,37] Exogenous administration of NGF in neonatal rats produces an up and down-regulation of muscarinic cholinergic receptors in the cerebral cortex that could be correlated with concomitant changes in ChAT activity.[21] In neonatal mice, a single intracerebroventricular injection of NGF enhanced reactivity to the muscarinic blocker scopolamine suggesting an acceleration of cholinergic maturation, (Calmandrei et al., 1991).[2] This result supports the notion of the trophic action of NGF for these neurons since NGF antibody administration produced a decrease of ChAT activity in the hippocampus, septal area, cortex, and striatum of rat pups.[71] In the other hand, NGF can kill neurons during normal development by activating the p75 ^{NTR} receptor, and this apoptotic effect through p75 ^{NTR} receptor is not shared by the other neurotrophins. For example, it has been shown that p75 ^{NTR} positive, trkA-negative cholinergic neurons in the

basal forebrain of mice are normally eliminated within two weeks after birth.[68] During apoptosis, the absence of trkA expression appears to be a common denominator of NGF-induced cell death in the CNS. The expression of trkA often comes after that of p75 ^{NTR,} suggesting that in the intact organism, NGF-induced toxicity may be limited to early stages of development.[24] More generally, these effects indicate that the occurrence of endogenous NGF in the CNS is physiologically relevant for regulating the function of forebrain cholinergic neurons.

Taken together, these results suggest that exogenous NGF supplementation during development could either promote cholinergic maturation through trophic actions or damage the functionality of the system by an apoptotic effect. This dual and opposite role seems to rely on the maturation of the central cholinergic system depending on the presence of different NGF receptors. Thus, we could hypothesize that high levels of NGF in the first postnatal week are susceptible to induce behavioral disturbances through preferential activation of p75 ^{NTR,}. In the other hand, exogenous NGF given during the second postnatal week is likely to accelerate cholinergic maturation and thus enhanced cognitive abilities. Establishment of NGF actions in the developing nervous system cannot be achieved in the absence of behavioral data.

Behavioral Studies of NGF Administrations

A large body of data support the hypothesis that normal spatial learning and memory processes depend on cholinergic function in the hippocampus and cortex. Maturation of spatial behavior, like learning and memory capacities in general appear relatively late in development. Data from experimental neuropsychology, comparative anatomy and field research show that behavioral adaptation requiring accurate spatial memory are most often mediated by permanent or transitory changes in the functional configuration of the hippocampus and cortex. Functional activity of the hippocampus and cortex rely on cholinergic input from the basal forebrain . These structures require 4-8 weeks to develop and NGF appears to play an important role in their maturation. Icv NGF injections during the first postnatal week produce a reduction of both ChAT and AChE activities in hippocampus. Neurochemical changes are also detected in 120-day old rats and are accompanied by an increase in the density of muscarinic receptors in the cerebral cortex.[72] The same treatment given during the second postnatal week induced a decrease in the muscarinic receptor number that return to control values shortly after treatment has ceased. Such up and down regulation of muscarinic receptors is associated with concomitant changes in ChAT activity[72,21] and might reflect the selection of cholinergic terminals. These results suggest the presence of critical periods during postnatal development withNGF injections having opposite effects on the maturation of the central cholinergic system. This also depends on the presence of different NGF receptors. We could thus expect that exogenous NGF administrations during these critical periods could differentially affect development and maintenance of cognitive abilities like spatial learning.

Does Early Icv NFG Injections Alter the Development of Spatial Abilities in Immature Rats ?

In rats, navigation tasks like the Morris e navigation task allow the study of spatial learning and memory processes. In the classical procedure ("place only"), animals learn to find a hidden platform on the basis of distant landmarks in the environment. The relational properties of the surrounding cues, no one of which is necessary, direct the movements towards a goal. This behavior is considered as a "place response". In contrast, "cue responses" are movements guided by a specific cue. In the Morris task for example, this behavior is observed when the platform is made visible. For normal adult rats with intact spatial abilities, no single landmark is necessary for place discrimination in the Morris navigation task. The addition of a conspicuous cue signaling the presence of the hidden platform induces the development of straight swim paths and the removal of the cue does not alter the memory of the goal position. In immature rats, the goal seeking response critically depends on cue presentation.[63,64,8] This effect, corresponding to an overshadowing of the distant cues by the more proximal one, isdependent on central

cholinergic function.[9] Thus, training in the presence of a salient cue indicating a goal location is a task particularly sensitive to modifications in memory processing. In these studies, immature rats (28 control, 28 icv NGF injected: 14 in days 2 and 3 and 14 in days 12 and 13) were trained in both a 'place only' and a 'place & cue' version of the Morris navigation task starting at PD22 (see refs. 10, 11). This task was chosen owing to previous experiments[8] in which cholinergic manipulations has particularly severe behavioral consequences in rats applying a mixed learning strategy combined cue response with place response (Fig. 2A).

During the fourth postnatal week, adult-like spatial learning abilities emerge in normal rats,[62] but the full repertoire of spatial strategies is yet to develop.[8] Thus, training of immature rats showed a progressive reduction of escape latency in both place only and place & cue version with animalsexpressing a bias toward the training quadrant (Fig. 2B and C). A tendency towards better spatial performance was observed in rats injected with NGF on postnatal days 12 and 13, but this was only apparent in the place & cue condition. In rats treated on postnatal days 2 and 3, the spatial abilities were not clearly altered by the treatment. Further overtraining (stabilisation) in the "place only" condition revealed an improvement of escape efficacy in the 12/13 day NGF group (Fig. 2A) which was similarly observed in the place & cue version (Fig. 2C). It is interesting to note a decrease in efficiency of rats NGF-treated on days 2 and 3 and trained in the place & cue, but not the place only, version.

Probe trials, during which the platform and the suspended cue were removed, were used to measure spatial memory. In line with training data, NGF treatment increased the time spent in the training quadrant during probe trial 1. Data are summarized in (Fig. 3) A more restrictive measure of accuracy (annulus crossings), however, revealed that only spatial memory of rats treated with NGF on days 12 and 13 was enhanced (Fig. 3A and B).

Following "place & cue" training, the expected overshadowing of distant landmarks was observed in both control and NGF 2/3 days treated rats. However, spatial memory of rats treated on days 12 and 13 was not affected by this training procedure (Fig. 3B). We continued to train animals with the platform at a new location (Fig. 2A, phase 2). This procedure exaggerated the superior performance of the NGF 12/13-day group, especially in the place only version. Such a difference is surprising given that the cue hanging above the new position was expected to exert a powerful attraction. This effect, however, was not observed. Following learning of the new location, the improvement of the spatial accuracy observed in rats treated with NGF on days 12- and 13 was maintained during another probe trial. This was independent of the training condition. NGF rats treated on days 2 and 3 and trained in a "place only" condition displayed a decrease of spatial memory following training to the new location (Fig. 3C and D).

In the present work, immature rats showed a progressive reduction of escape time in both place only and place & cue conditions and they expressed a bias toward the training quadrant, but their efficacy was limited. If trained without the hanging cue, the immature subjects showed rapid learning of the new spatial position, as indicated by the time spent in the new training quadrant during the second probe trial. As expected also, we measured a significant overshadowing effect of the presence of the cue upon the performance of immature rats. This appeared as a lack of bias toward the most recently trained position when escape has been facilitated by the presence of a cue hanging above the platform during training. Indeed, these rats showed a rapid adaptation of escape to the new position while they were allowed vision of the cue. However, following removal of this cue, they gave no indication that they had memorized the position of the platform relative to the distant room cues. Immature subjects seem to pay less attention to distant room cues when trained with a salient cue associated with the invisible target. This effect, could be due to the relative importance of the proximal cue that prevents an allocentric use of the more distant landmarks.[8,63] In comparison, the performance of rats treated on days 12 and 13 was comparable to what can be expected from normal adult rats in these conditions (see ref. 9): rapid acquisition of escape, accurate memory of the spatial position, efficient use of the salient cue to learn about the position of the platform relative to distant environmental cues and rapid learning of a new escape position.

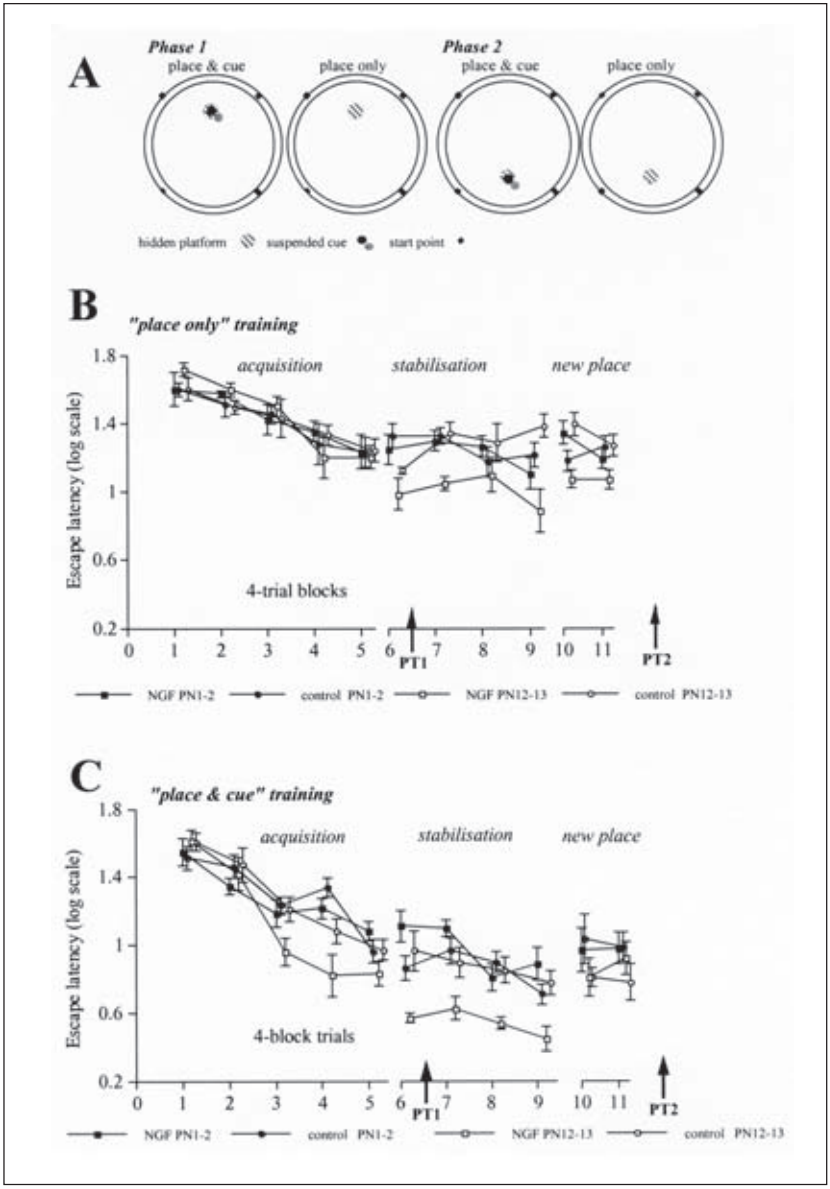

Figure 2. A) Schematic representation of the apparatus used for the Morris navigation task. Positions of the platform and, if provided, hanging cues are indicated. B) Mean (±sem) escape latencies (logarithmic scale) during training in the Morris navigation task by control (N=28) and NGF treated, 22 day-old rats trained in the absence of the suspended cue ("place only" condition). Acquisition, blocks 1-5, corresponds to the 20 first trials. Stabilization, blocks 6-9, corresponds to the asymptote of the escape latency. New place, block 10 and 11, the location of the hidden platform was changed. C) Mean (±sem) escape latencies (logarithmic scale) during training in the Morris navigation task by control and NGF treated, 22 day-old rats trained in the "place & cue" condition. Acquisition, blocks 1-5, corresponds to the 20 first trials. Stabilization, blocks 6-9, corresponds to the asymptote of the escape latency. New place, block 10 and 11, the location of the hidden platform was changed. (Explain abbreviations here.)

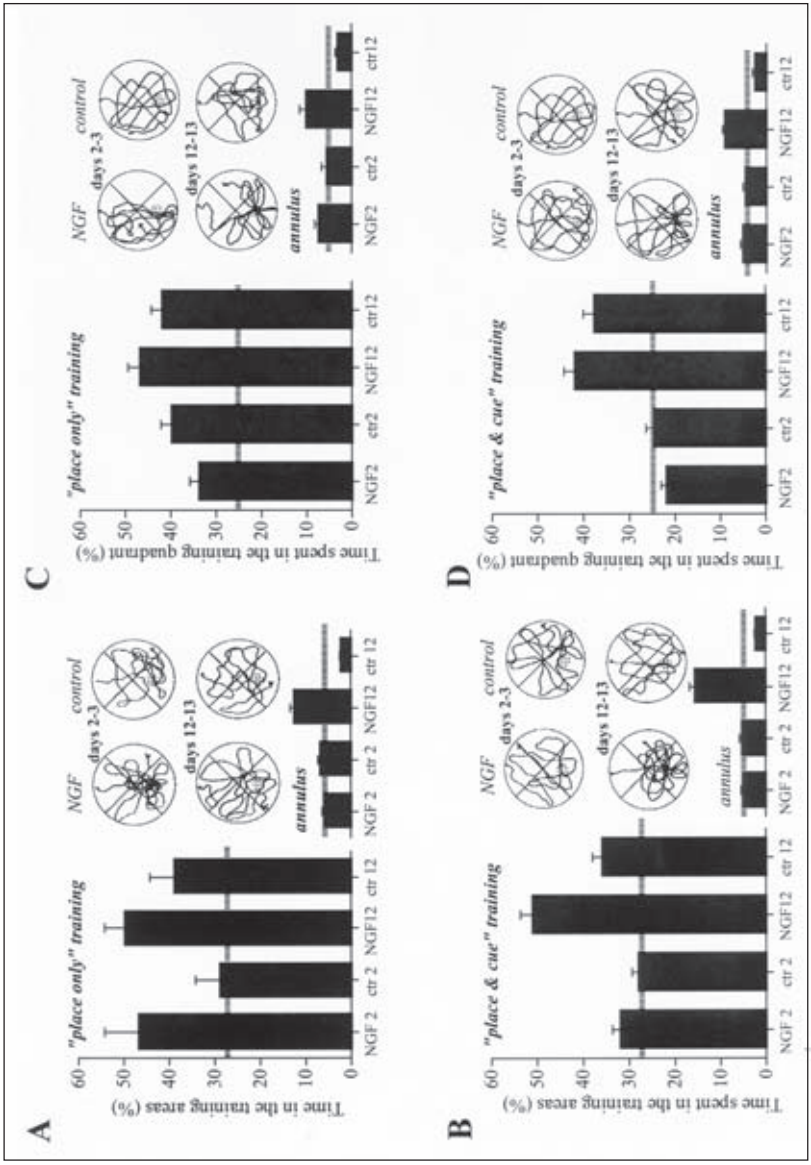

Figure 3. Following training, a probe trial (PT1) was given between block 6 and 7 of the stabilization phase, following trial 24. A) Mean (±sem) of the percentage of time spent in the training quadrant of the pool during a 60-second probe trial after training in the place only condition. Swim paths taken by representative rats are also given. Annulus crossings were measured as percentage of time spent in the platform area (Ø14-cm) of the training quadrant. B) Probe trial data for the place & cue trained groups. Mean (±sem). C) Probe trial 2 (PT2) was given after reversal training. Data from place only group. Mean (± sem). D) Probe trial 2 data of animal trained in the «place and cue» condition. Mean (± sem).

Are These Effects Maintained in Adulthood?

To assess long-term effects of NGF treatment, some of the rats treated on days 12 and 13 were tested in an 8-arm radial maze at the age of six months. All rats treated on days 2 and 3 were retrained in the Morris navigation task following the same procedure at the age of two months.

Rats Treated on Days 12 and 13

A general improvement on place learning ability that was observed in immature rats treated with NGF on days 12 and 13 was maintained in adulthood. The long-term effect of NGF treatment, assessed at six months in the radial maze task, was demonstrated by an early reduction of the errors in the NGF treated rats. A secondary effect of treatment was displayed by sex comparison. During the free choice phase, female control rats made a higher number of reentries while NGF treated female rats performed like male rats. Although the forced choice phase confirmed the efficiency of the NGF treated rats, the effects of treatment and sex were no more consistent as if such procedure elevated attentional processes in control rats (Fig. 4).

Rats Treated on Days 2 and 3

The effect of NGF injections on days 2 and 3 upon adult spatial performance was more extensive and appeared as a general impairment in spatial learning and memory abilities. Retrained at the age of two months, control rats showed equally efficient capacities in a cued and a noncued training condition. In contrast, NGF treated rats showed a decrease in escape efficacy particularly marked in a cued condition (Fig. 5A).

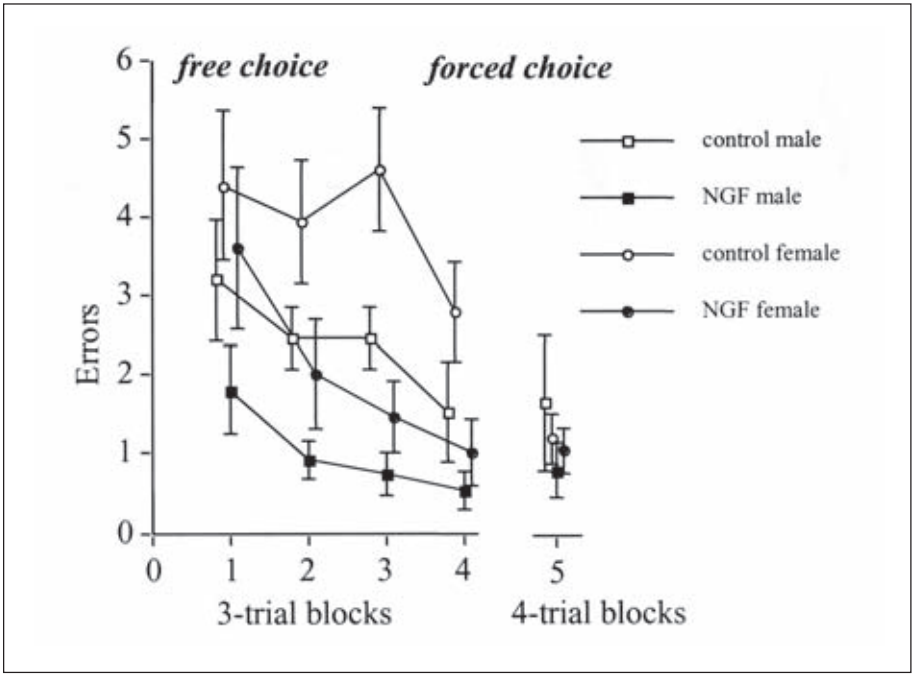

Figure 4. Mean number of errors (±sem) per block in the free choice and forced choice acquisition phases of the radial maze testing applied to 6 month-old control and NGF rats treated on days 12-13. MALE-FEMALE comparison.

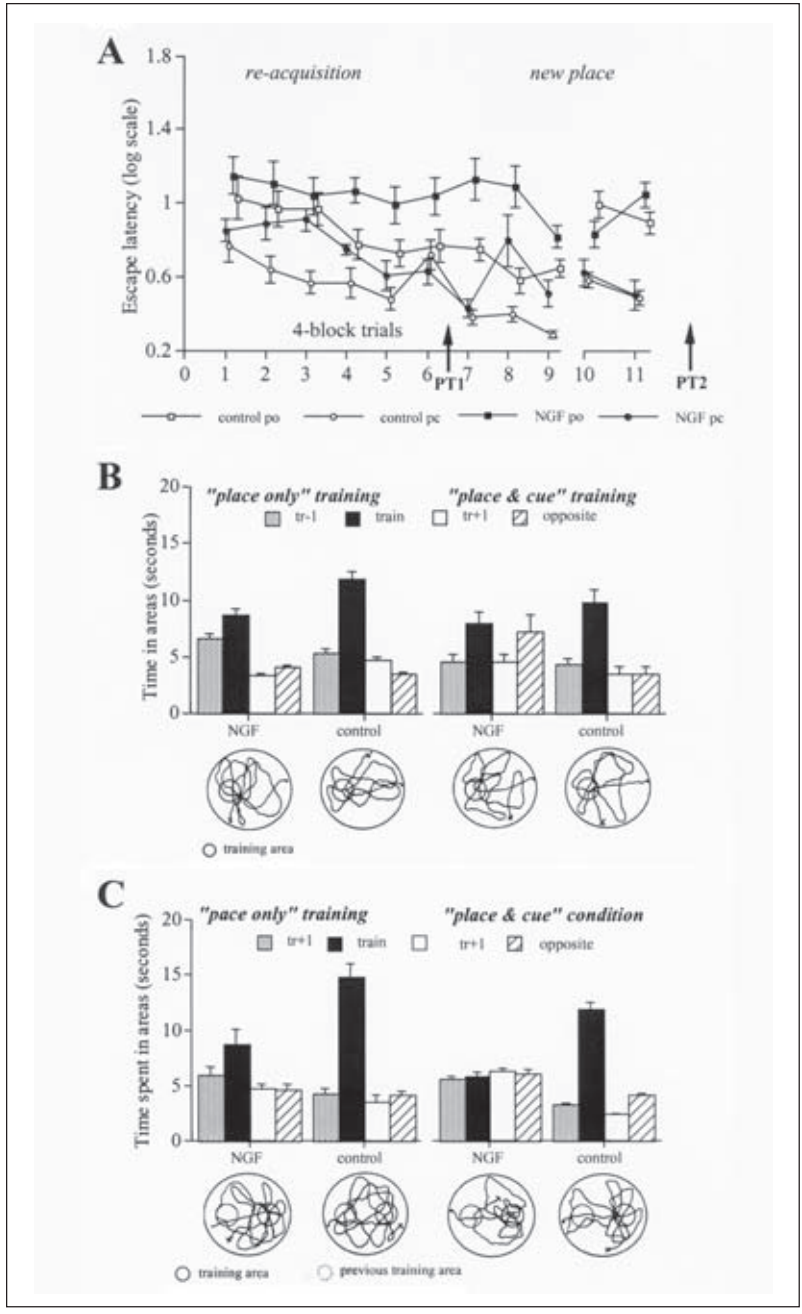

Figure 5. A) Mean (±sem) escape latencies (logarithmic scale) during retraining in the Morris navigation task in the "place & cue" and the «pla"e only» trai"ing conditions by NGF and control two month-old adult rats. (For details, see Fig. 2B). B) Mean (±sem) of probe trial 1 administered after 24 training trials. (For details, see Fig. 3). (quadrant labeling: tr+1 = adjacent right ; train = training ; tr-1 = adjacent left ; opposite = opposite). C) Mean (± sem) of probe trial 2 after reversal training. (For details, see Fig. 3).

Compared withcontrol animals, the spatial bias for the training quadrant measured during the first probe trial was consistently reduced in treated rats. This effect was independent of training condition (Fig. 5B).

Reversal learning distinguished the two learning procedures with a place & cue reversal being learnt more readily (Fig. 5A). Subsequent probe trials confirmed that NGF 2/3-day postnatally treated animals did not remember the new platform compared with controls (Fig. 5C).

In general, the treated rats appeared significantly impaired in all aspects of the place learning task when adults. They had longer escape latencies and weaker biases toward the training sector following acquisition in both training conditions. The treated rats showed reduced capacities to learn a new position. This later deficit was particularly obvious following training with a cued platform since they showed nearly no bias toward this position during the probe trial. In contrast, control rats showed flexible and accurate behavior. These results suggest that the treated rats were especially sensitive to the effect of a salient cue overshadowing the more subtle distal cues.

Discussion

NGF appears to regulate specifically the postnatal maturation of the central cholinergic nervous system (for a review, see ref. 15). Cholinergic projections to the hippocampus are essential for normal learning and memory capacities[43] (see also Jaffard and Marighetto, and Pepeu and Giovannini in this book). Neurotrophic factors contribute substantially to many of the neuronal changes in the brain (for a review, see ref. 6, Hagg et al 1993; refs. 44, 67). For example, BDNF appears to modulate transmission and plasticity in the hippocampus during development,[30] can enhance synaptic transmission in the adult hippocampus (Kang and Schuman, 1995), and increases in BDNF and NT-3 m RNA in the CA1 region of hippocampal slices have been shown following long-term potentiation (LTP).[60] In vivo, recent studies have shown that spatial and contextual learning are related to the expression of BDNF mRNA in the hippocampus.[31,34,42] The development of LTP in the hippocampus is influenced by the activity of septohippocampal cholinergic fibers[13,28] generating the theta rhythm.[3,54,70] An optimal tuning of the cholinergic system is indispensable for efficient spatial learning, but there are diverse interpretations as to the function of cholinergic activation for solving spatial tasks. Cholinergic blockade with muscarinic antagonists impairs various components of spatial abilities (see Pepeu and Giovannini in this book) such as the sensitivity to distant cues,[33,74,76] the organisation of exploratory responses[75,12] or the development of appropriate behavioural strategies necessary for the acquisition of movement sequences under distal cue guidance.[74] Since cholinergic blockade was most efficient when administered before training (see refs. 33, 1) this treatment might interfere with the initial storage of information, or with the process by which ongoing information is integrated before the selection of an appropriate behavioural strategy. Along this line, experiments have confirmed that cholinergic dysfunction does affect the attention to environmental stimuli.[58,14] This suggests an involvement of cholinergic transmission in attentional processes and in the selection of an appropriate strategy as well, which does not necessarily preclude a participation in memory processes.

Icv injections or infusion of NGF in young adult rats have been shown to prevent retrograde neuronal death, to promote recovery after damage to the septohippocampal pathway and to improve retention of a spatial memory task in impaired aged rats (Markowska et al., 1996).[36,22,61] Likewise, NGF injections appear to compensate for deficits induced by septo-hippocampal lesions or ageing.[26,27] In particular, NGF could modulate both the number and appearance of basal forebrain cholinergic neurons of cognitively impaired aged rats2[3] and increase the number and size of cholinergic synaptic elements.[19]

Trophic action of NGF is known to prevent neuronal death. This property seems to rely on trkA receptor activation that regulates neuronal function like synaptic plasticity.[38] During development, however, NGF binding to low affinity p75 receptors appears to induce neuronal

death.[24] Van der Zee and collegues (1996) have shown that p75 receptor mediates apoptosis of approximately 25% of the cholinergic basal forebrain neurons in mice between postnatal day 6 and 15, but only in cholinergic neurons that lack trkA receptors. In adulthood, by contrast, recovery after injury could be mediated by the p75 low-affinity neurotrophin receptor. Van der Zee et al (2002, in press) now provide evidence that NGF infusion after fimbria fornix transection did not induce a reversal of choline ChAT expression in adult p75 ^{LNTR} deficient mice.

Opposite to expectations derived from binding studies, postnatal NGF administration resulted in cognitive enhancement, which was particularly obvious in rats trained in the presence of a salient cue. Efficient spatial representation requires attention to each of the different cues, despite large inequalities in salience. This may be due to differences in size, contrasts with the background, or varying distances from the pool and the platform. Different treatments inducing cholinergic system modifications in rats indicate that either impairment or enhancement was more consistent when rats were trained in the presence of a salient local cue.[9,7]

It is known that a salient local cue facilitates escape. It is assumed that a cued task does not require spatial memory per se, but rather an association between the cue and the goal for the development of a guidance strategy. It has also been demonstrated that lesions of the striatum affect the cued task while lesions of the fornix reduce performance in place tasks (Mc Donald & White).[20] In most cued tasks, the platform is visible, so that a rapid escape can be based on the single rule of approaching the conspicuous platform. In our task, however, the cue does not precisely coincide with the platform and offers only a partial support to landing. When the rat is in the proximity of the target, the cue is positioned above its head and thus might appear less salient. Such a cued task requires to chain at least two different strategies , i.e., a cue guidance combined with a memory of the platform position of the relative more distant room cues. As discussed by,[39] an optimal behaviour might require an active process "that readily upsets the imbalance between competing memory systems." This suggests that the elaboration and the use of a spatial representation might require a temporary memory of the local cues' salience, and one of the main functions of the cholinergic system might be the modulation of attentional processes by the balancing of the relative importance of the various components of the environment.

Finally, NGF seems to have a dual role that consists in preventing or inducing neuronal cholinergic death during development. This early regulation of the cholinergic system appears to be critical for the development of normal spatial capacity. The effects of early exogenous NGF administrations depend on the maturational state of the neuronal tissue. Given during periods crucial for development, NGF will preferentially induce p75 receptor expression that could lead to cholinergic cell segregation and produce spatial impairments depending on the modification of attentional processes.

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