Agonistic encounters in aged male mouse potentiate the expression of endogenous brain NGF and BDNF: possible implication for brain progenitor cells’ activation

Marco Fiore, Tiziana Amendola, Viviana Triaca, Paola Tirassa, Enrico Alleva and Luigi Aloe
Istituto di Neurobiologia e Medicina Molecolare, CNR, viale Marx, 43/15, 00137 Rome, Italy
Laboratorio di Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanità, viale Regina Elena, 299, 00161, Rome, Italy

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Abstract

The condition of dominance or submission following agonistic encounters in the adult male mouse is known to differentially affect brain nerve growth factor, a neurotrophin playing a role in brain remodeling, in the fine tuning of behaviour and in the regulation of the basal forebrain cholinergic neurons. During development and adult life nerve growth factor regulates brain expression of neurotransmitters and the stimulation of progenitor cells (stem cells) which, under different external stimuli, may differentiate into neuronal and/or glial cells promoting the recovery of the injured brain. However, little information is available for the aged brain. Thus in the present study we investigated the effect of the social status (‘dominance’ vs. ‘submission’) in the aged mouse on the presence of nerve growth factor, brain-derived neurotrophic factor, choline acetyltransferase, neuropeptide Y and progenitor cells of selected brain regions. We found that aged dominant mice showed increased brain-derived neurotrophic factor in the subventricular zone and hippocampus and increased choline acetyltransferase in the septum and basal nuclei, which were associated with increased presence of progenitor cells in the subventricular zone. Conversely, in aged subordinate mice the data showed a marked brain increase in nerve growth factor in the subventricular zone and hippocampus, choline acetyltransferase in the septum and basal nuclei and neuropeptide Y in the hippocampus and parietal cortex. The possible functional implications of these findings are discussed.

Introduction

Neurotrophins, a family of proteins including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT 3) and NT 4/5, exert an important role in promoting the survival and differentiation of neurons under physiological and pathological conditions (Barde, 1994; Thoenen, 1995; Connor & Dragunow, 1998). NGF is the best characterized neurotrophin and is expressed both in the peripheral (PNS) and in the central nervous system (CNS) (Levi-Montalcini, 1987; Thoenen, 1991; Ebendal, 1992). Within the CNS, NGF mainly regulates the basal forebrain cholinergic neurons which send topographically organized projections to the hippocampus and cerebral neocortex. BDNF is more widely distributed in the CNS (Barde, 1990, 1994; Thoenen, 1991, 1995) and has survival-promoting actions on a variety of CNS neuronal cells including hippocampal and cortical neurons, cholinergic neurons and nigral dopaminergic neurons.

Both NGF and BDNF have been shown to participate in the fine tuning of behaviour (Alleva et al., 1993; Smith, 1996) and in the physiological regulation of cognitive processes during both development and ageing (Rylett & Williams, 1994; Thoenen, 2000). It has been shown that NGF is involved in the mechanisms controlling coping reaction to stress (Aloe et al., 2002) and repeated experiences of defeat and submission significantly enhance the level of NGF compared with the dominant, attacking male mouse (Alleva et al., 1993). The increased amount of NGF in subordinate mice does not correlate with either the number of attacks received or the defensive reactions opposed to them, suggesting that other stimuli, e.g. of a psychological nature, are implicated in the mechanisms triggering the NGF release. The results of these studies have led to the hypothesis that fear and anxiety-like conditions might be associated with activation of NGF-releasing or NGF target cells (Aloe et al., 2002).

NGF has also been shown to influence the endogenous proliferating and/or differentiating cells of aged mice (Fiore et al., 2002) present in certain brain regions such as the subventricular zone (SVZ). These cells have the capability after appropriate stimuli to differentiate into glial or neuronal cells (Alvarez-Buylla & Garcia-Verdugo, 2002). This effect may be elicited by neurotrophic factors, enriched environment, physical activity and stressful experiences (Gage, 2002). However, little information is available on the presence of proliferating cells in the aged brain. Thus, because the establishment of a dominant or subordinate status upon interpale aggressive behaviour in the mouse has been shown to modify the basal levels of NGF, we measured in dominant or subordinate fighting aged mice the presence of NGF and BDNF in selected brain regions. We also studied whether or not the condition of dominance or submission was associated with changes in neuropeptides regulated by neurotrophins (Croll et al., 1994), such as choline acetyltransferase (ChAT) and neuropeptide Y (NPY) which play a role in ageing and behavioural regulation, and with changes in differentiating stem cells in the brain stained with the Ki67 antibody (Calza et al., 1998; Kee et al., 2002).

Materials and methods

Animals

Aged CD-1 mice were purchased by Harlan-Nossan, Italy, at 12 months of age and were thereafter kept under standard conditions at our...