

# BDNF expression in GABAergic interneurons

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Brain-derived neurotrophic factor (BDNF) is a major neuronal growth factor that is widely expressed in the central nervous system. It is synthesized as a glycosylated precursor protein, (pro)BDNF and post-translationally converted to the mature form, (m)BDNF. BDNF is known to be produced and secreted by cortical glutamatergic principal cells (PCs); however, it remains a question whether it can also be synthesized by other neuron types, in particular, GABAergic interneurons (INs). Therefore, we utilized immunocytochemical labeling and reverse transcription quantitative PCR (RT-qPCR) to investigate the cellular distribution of proBDNF and its RNA in glutamatergic and GABAergic neurons of the mouse cortex. Immunofluorescence labeling revealed that mBDNF, as well as proBDNF, localized to both the neuronal populations in the hippocampus. The precursor proBDNF protein showed a perinuclear distribution pattern, overlapping with the rough endoplasmic reticulum (ER), the site of protein synthesis. RT-qPCR of samples obtained using laser capture microdissection (LCM) or fluorescence-activated cell sorting (FACS) of hippocampal and cortical neurons further demonstrated the abundance of BDNF transcripts in both glutamatergic and GABAergic cells. Thus, our data provide compelling evidence that BDNF can be synthesized by both principal cells and INs of the cortex.

BDNF

FACS

GABAergic interneurons

RT-qPCR

hippocampus

laser capture microdissection

neocortex

## 1. Introduction

Author provide compelling evidence for BDNF gene expression not only in PCs, but also in GABAergic INs of the hippocampus and the neocortex. Our immunocytochemical findings demonstrated that, in addition to the mature protein form of BDNF being present in both GABAergic and glutamatergic neurons, its precursor form, proBDNF, was also present in the majority of INs and PCs examined. Importantly, proBDNF, with its perinuclear distribution, colocalized strongly with lamin, which selectively labels the nuclear envelope and perinuclear ER cisternae, the site of protein synthesis in the ER. Finally, using independent cell purification techniques, LCM in the tissue slices and FACS of dissociated cells, to specifically purify hippocampal and cortical PCs and INs, we could robustly demonstrate the presence of BDNF transcripts in both neuronal populations and thus, finally confirm the presence of BDNF mRNA in GABAergic neurons.

## 2. Technical Considerations

LCM is a technique increasingly employed for mRNA expression studies in physiological and pathological conditions and it allows for targeted sampling of specific neuronal subpopulations from brain tissue samples [1]. In our study, we adapted this method to obtain samples of glutamatergic PCs and GABAergic INs from the hippocampus for BDNF gene expression profiling by combining it with RT-qPCR. During the procedure, we aimed to minimize RNA degradation, by omitting histochemical or immunocytochemical processing of the tissues, to visualize specific neuron types; instead, we relied on endogenous fluorescence marker expression in transgenic mouse lines. Additionally, we shortened the time to dissecting the tissue slices, significantly reducing the total number of recovered cells per experiment. The modified LCM approach can, thus, be used to efficiently collect individual cell populations or even single cells from very thin, methanol-fixed sections from transgenic mice expressing fluorescent markers.

Author used LCM to focus on BDNF expression in the cell bodies of cortical neurons. To control for potential mRNA contamination from neuropils, we took samples of the surrounding tissue making sure that no neuronal cell bodies were captured. Indeed, in these samples, we did not detect *Emx1* and *GAD67* transcripts. They detected the expression of *GFAP* gene product in some of them, plausibly due to the presence of astrocytes and their processes, which occupy approximately 5% of the neuropils in the CA1 stratum radiatum [2][3], intermingling with dendrites, axons and synapses; however, independent of the presence or absence of *GFAP* signal, BDNF was not detected in these control samples from neuropils.

Real-time RT-qPCR is a well-established method for the analysis of DNA and RNA molecules, even in previously fixed samples [4]. For the detection of gene amplification, we used SYBR Green in the real-time PCR assay, which provides a rapid and accurate alternative to the 'TaqMan' approach [5][6]. SYBR Green is a non-coupled fluorescent dye and generally binds to any dsDNA [7]. All primers, for the gene of interest, used in our study were empirically validated by doing an actual RT-qPCR experiment and inspecting the melting point curve. In addition, a standard curve for individual primers was run in order to estimate the efficiency of the PCR primers. All primer pairs were designed carefully such that they could not non-specifically amplify other genomic targets. For BDNF, our gene of interest, we chose a primer optimized for the amplification of exon IX BDNF, since it is known that the BDNF gene comprises nine exons, but the coding sequence (CDS) resides solely in exon IX, with the other exons being involved in protein shuttling and subcellular localization [8]. Thus, the eight upstream exons drive the transcription of multiple BDNF splice variants that encode an identical BDNF protein in a regional and cell type-specific manner [9][10]. Since, we wanted to analyze the somatic gene expression in two main neuron populations, we chose the somatic markers, *Emx1* and *GAD67*, for glutamatergic and GABAergic neuron types, respectively. As the reference gene, we used class III  $\beta$ -tubulin, which is known to be expressed in all neuron types [11].

### 3. BDNF Precursor Protein Localized not only to Glutamatergic Principal Cells, but also to GABAergic Hippocampal Interneurons

proBDNF protein, a precursor of the mature form of BDNF, is present in the two main hippocampal neuron populations, glutamatergic neurons and GABAergic INs. Moreover, the immunolabeling for proBDNF highly

overlapped with that of lamin, a marker of the nuclear envelope and ER perinuclear cisternae, the area where protein synthesis takes place. We take these results as a strong indicator that proBDNF could be synthesized in both of these neuronal groups.

The mature form of BDNF has been previously detected in cortical GABAergic INs [12]. Our present results confirmed this finding and demonstrated that the majority of hippocampal INs show substantial levels of immunoreactivity for the ~14 kDa mature protein. It has been shown that BDNF can be taken up by neurons from the extracellular space [13][14]. As principal cells produce and release high levels of BDNF [15][16], the ability of cortical INs to synthesize the protein has remained an open question [17][18].

Our immunocytochemical results now provide further evidence for the possible synthesis of BDNF in INs. First, the 34 kDa proBDNF protein was also found to be present at high levels in ~84% of hippocampal INs. The proBDNF protein is generally regarded as an intracellular precursor of BDNF, which can be cleaved by furin (the abundant protein convertase present in all cells) or pro-convertases to produce the secretable mature form [19][20]. There is some evidence that proBDNF might also be released and an alternative extracellular cleavage by metalloproteinases and plasmin may exist [20][21][22]. Thus, endocytosis, similar to that of mBDNF, may explain the observed presence of proBDNF in INs, if readily released by hippocampal PCs [23]. A contradicting observation, however, argues that dentate gyrus GABAergic INs are unable to respond to proBDNF [24][25], thus may not be able to take up this form of the protein, even if available in the extracellular space. This is consistent with the fact that proBDNF can interact only with the p75 receptor [57], but most INs, except for the parvalbumin ones, are devoid of the receptor [24][26]. In fact, this receptor would be needed to mediate the endocytotic uptake of proBDNF, too.

The second piece of our immunocytochemical results which points to a possible synthesis of BDNF was the perinuclear colocalization of proBDNF with lamin, in the area where protein synthesis takes place. This was in stark contrast to the more diffuse cytoplasmic localization of mBDNF observed in our study. Indeed, if proBDNF was taken up by INs from the extracellular space, a similar cytoplasmic or an endosomal localization would be expected. While not a definitive evidence, our data on the perinuclear localization and the high level of proBDNF, comparable to that detected in PCs, convergently suggested the endogenous production of the protein in hippocampal INs.

## 4. BDNF RNA is Expressed in Both Glutamatergic Neurons and GABAergic Interneurons in the Cortical Structures.

It is generally assumed that only glutamatergic PCs express BDNF mRNA [15][27][16][28]. And showed that hippocampal GABAergic INs express BDNF mRNA and, thus, can produce BDNF themselves, further supporting our immunocytochemical evidence. This finding also converged with results of a recent in situ hybridization (ISH) study demonstrating that, while endogenous BDNF transcripts primarily localized to the somatic compartments of putative principal neurons in pyramidal and granular cell layers, they can be also detected in neurons scattered in the dendritic layers of hippocampal subfields [17]. While the authors did not identify the latter as GABAergic neurons, the high number of these scattered labeled cells indicated that they must include at least some types of

INs [29][30]. Indeed, in our VGAT-YFP and VGAT-YFP x NexCre-Ai9 transgenic mice, we observed very little RFP-positive, displaced, glutamatergic neurons in the dendritic layers, the stratum oriens and radiatum, but high numbers of YFP-positive GABAergic INs were observed.

Expert used LCM to dissect the somata of YFP-positive INs from these two dendritic layers to avoid contamination by glutamatergic PCs and compared these to YFP-negative and RFP-positive samples of PCs from the cell body layers of the CA1 and CA3 areas, and the DG. An RT-qPCR assessment of these samples confirmed the expression of BDNF transcripts, as well as the glutamatergic marker *Emx1* in PCs, whereas *GAD67* expression was absent or very low in CA1 and CA3 PCs. In dentate granule cells, *GAD67* expression was intermediate high, consistent with the fact that these cells can, in addition to glutamate, co-release GABA [31][32][33]. In contrast, in our sample of INs, we reliably obtained signals for BDNF RNA and for the GABA-synthesizing enzyme *GAD67*, whereas *Emx1* was absent from most of these samples indicating the lack of contamination by glutamatergic PCs. Finally, our RT-qPCR results of control samples obtained from cell body-free hippocampal neuropils showed no traces of BDNF, *Emx1* or *GAD67*, providing support to the validity of our samples. Our results obtained from FAC sorting showed converging results and supported the notion that cortical INs can express BDNF mRNA transcripts.

Data further showed that endogenous expression of BDNF was relatively low, especially in INs, compared to the neuronal marker and primarily localized to the somatic compartment. Thus, our results did not support the idea of substantial BDNF mRNA transport to dendritic and axonal processes [34][35][36]. The absent signal in neuropils implied that, under basal (unstimulated) conditions, there was a limited potential for local translation of BDNF mRNA. The lack of BDNF signal in our samples from neuropils further suggested that BDNF mRNA is not present in astrocytes. Even in samples of neuropils in which GFAP mRNA was detected, indicating the presence of harvested astrocytes, BDNF gene product was consistently absent. These findings were in line with published data that muscimol manipulation cannot upregulate BDNF mRNA in glial cultures [37].

Data from LCM and FACS supported the immunocytochemistry results and they convergently suggested that the two main cortical neuron classes, glutamatergic and GABAergic, can synthesize BDNF.

## 5. Functional Implications for BDNF Synthesized By Interneurons

The evidence that cortical GABAergic INs can also produce BDNF, presented in this study, raises new questions about possible autocrine and paracrine actions of mature BDNF and its precursor. This question fits into the broader debate on whether proBDNF can be secreted and has any biologically relevant activity. In fact, previously, it was assumed that only the mature form of BDNF could be secreted and was biologically active, whereas proBDNF, localized intracellularly, served only as an inactive precursor. Accumulating evidence shows that both proBDNF and mBDNF can be released and are active, with important functions in various developmental and physiological processes [38][39][40]. Moreover, the proBDNF and mBDNF forms have been suggested to serve opposing effects via the p75 neurotrophin receptor (p75NTR) and TrkB receptors, respectively [38][39][40]; while mature BDNF promotes neuronal survival, differentiation, synaptic plasticity and long-term potentiation (LTP),

proBDNF may induce apoptosis and growth cone retraction, reduce dendritic spine density and facilitate long-term depression (LTD) in hippocampal slices [41]. The proBDNF form has been further shown to reduce the intrinsic excitability of pyramidal cells of the entorhinal cortex and can thereby modulate memory functions and seizure propensity [42].

The effects of BDNF on the GABAergic system appear to be more diverse. Mature BDNF can enhance, but also reduce, inhibitory synaptic transmission by modulating presynaptic GABA release [43] or by up- or down-regulating postsynaptic GABA<sub>A</sub> receptor expression [44][45]. A recent study also found a bidirectional effect of proBDNF on GABAergic synaptic activity in the hippocampus, which was dependent on NMDA receptor activation [46]. Beyond synaptic transmission, mature BDNF has also been found to decrease the excitability of GABAergic INs via activation of TrkB, whereas no cellular effects were observed for proBDNF [24]. While these diverse effects may reflect developmental stage- and brain region-specific actions of the neurotrophins [47], an important aspect to consider is the morphological, physiological and molecular heterogeneity of the GABAergic system. In fact, the large number of IN types [29][30] would require a rigorous, systematic analysis of the modulatory effects of both BDNF and the precursor protein on their cellular and synaptic functions.

In summary, expert provided evidence indicating that BDNF can be synthesized as a precursor in the two main neuronal populations of the mouse hippocampus and neocortex. While proBDNF is likely to constitute an intermediate step in the synthesis of BDNF, it may also provide a neurotrophic environment necessary for the continuous degenerative/regenerative process inherent in the hippocampal GABAergic system; however, the mechanism by which endogenous proBDNF can affect INs under competitive environments needs to be explored.

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