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REVIEW OPEN ACCESS

DHA (omega-3 fatty acid) increases the action of brain-derived neurotrophic factor (BDNF)

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Abstract – Neurons have high energy needs, requiring a continuous supply of glucose from the blood. Tight regulation of glucose metabolism in response to stimuli is essential for brain physiology. Glucose metabolism and cerebral blood flow are closely coordinated during neuronal activity to maintain proper brain function. In a previous article, we have already detailed the mechanisms by which the PI3K/Akt signaling pathway is involved in the efficiency of glucose uptake by stimulating GLUT-1 action and NO-mediated vasodilation. In this article, we now clarify how the activation of BDNF helps to stimulate the IRS-1/PI3K/Akt signaling pathway and upregulates NMDA receptor activity. In short, high-frequency neuronal activity induces the secretion of BDNF, whose presence boosts this important pathway. DHA, *via* the PPARα-RXRα and PPARɣ-RXRα heterodimers, is involved in the critical regulation of BDNF activation. As a preferential ligand of PPARs and RXRα, DHA plays an important role in the gene expression of *CREB* and *CPE*, and it is involved in the regulation and expression of *tPA,* as well as the inhibition of *PAI-1*. BDNF boosts the IGF-1/estradiol/PI3K/Akt signaling pathway, and DHA boosts the action of BDNF.

Keywords: BDNF / CREB / PPAR / RXR / DHA

Résumé – Le DHA (acide gras oméga-3) augmente l'action du facteur neurotrophique dérivé du cerveau (BDNF). Les neurones ont un besoin énergétique élevé, nécessitant un apport continu de glucose par le sang. Une régulation étroite du métabolisme du glucose en réponse à des stimuli est essentielle pour la physiologie du cerveau. Le métabolisme du glucose et le flux sanguin cérébral sont étroitement coordonnés pendant l'activité neuronale afin de maintenir le bon fonctionnement du cerveau. Dans un article précédent, nous avons déjà détaillé les mécanismes par lesquels la voie de signalisation PI3K/Akt est impliquée dans l'efficacité de l'absorption du glucose en stimulant l'action de GLUT-1 et la vasodilatation *via* le monoxyde d'azote. Dans cet article, nous expliquons comment l'activation du BDNF contribue à stimuler la voie de signalisation IRS-1/PI3K/Akt et à augmenter l'activité du récepteur NMDA. Globalement, une activité neuronale à haute fréquence induit la sécrétion de BDNF et l'intervention de celui-ci stimule cette voie majeure. Le DHA, *via* les hétérodimères PPARα-RXRα et PPARɣ-RXRα, est impliqué dans la régulation critique de l'activation du BDNF. En tant que ligand préférentiel des PPARs et RXRα, le DHA joue un rôle important dans l'expression de *CREB* et *CPE*, ainsi que dans la régulation, l'expression et l'inhibition respectivement, des gènes *tPA* et *PAI-1*. Le BDNF stimule la voie de signalisation IGF-1/estradiol/PI3K/Akt, et le DHA renforce les actions du BDNF.

Mots clés : BDNF / CREB / PPAR / RXR / DHA

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Highlight

- DHA, preferential agonist ligand of the PPARα-RXRα and PPARɣ-RXRα heterodimers, is involved in the critical regulation of BDNF activation
- DHA plays an important role in the gene expression of CREB and CPE, and is involved in the regulation and expression of tPA, as well as the inhibition of PAI-1

1 Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor found in the brain and periphery. This protein, which is encoded by the *BDNF* gene, helps to support the survival of existing neurons, and it encourages the growth and differentiation of new neurons and synapses through axonal and dendritic sprouting. It plays an important role in the activity-dependent regulation of synaptic structure and function, particularly in glutamatergic synapses. In the brain, it is active in the hippocampus, cortex, cerebellum, and basal forebrain – areas that are vital to learning, memory, and higher cognition. It stands out due to its high level of expression. Data demonstrate the ability of BDNF to stimulate glucose utilization in response to increased energy demand (Burkhalter *and al.,* 2003) by increasing the expression of the neuronal glucose transporters *GLUTs* (Arora *et al*., 2020); this *GLUT* mRNA expression is dependent on the concentration of BDNF (Burkhalter *and al.,* 2003). BDNF upregulates the expression of neuronal *NO synthase* (nNOS) and increases the production of NO (Biojone *et al.,* 2015; Kolarow *et al.,* 2014; Xiong *et al.,* 1999). It should be noted that low levels of BDNF coincide with impaired glucose metabolism. BDNF has specific and dose-response protective effects on neuronal toxicity induced by amyloid-β 42 (Arancibia *et al.,* 2008). Decreased BDNF levels are a pathogenic factor involved in Alzheimer's disease and depression, but also in type 2 diabetes (Krabbe *et al.*, 2007). Several studies have shown the impaired synaptic plasticity of glutamatergic synapses in people suffering from diseases where compromised BDNF function has been observed, such as Huntington's disease, schizophrenia, depression, anxiety, bipolar disorder etc. (Carvalho *et al.,* 2008).

We have already detailed the mechanisms by which the PI3K/Akt signaling pathway is involved in the efficiency of glucose uptake by stimulating GLUT-1 action and NO-mediated vasodilation (Majou, 2018). We will now clarify how the activation of BDNF supports free estradiol and free insulin-like growth factor-1 (IGF-1) in stimulating the IRS-1/PI3K/Akt signaling pathway and upregulates NMDA receptor activity. Then we will show the major role of DHA in the concentration-dependent stimulatory action of BDNF.

2 The mechanisms of BDNF's action

Like IGF-1, BDNF is a trophic factor required for the viability and normal function of various neuronal cells. The biological actions of BDNF are mediated by a high-affinity receptor, tyrosine kinase B (TrkB). The binding of IGF-1 to the IGF-1R and of BDNF to TrkB cause a conformational change to these receptors, inducing the autophosphorylation of their tyrosine residues (Hubbard *et al.,* 2000; Revest *et al.,* 2014). These two receptors in turn phosphorylate various intracellular substrates, such as IRS-1 and Shc in the PI3K/Akt signaling pathway. IGF-1 rapidly stimulates the tyrosine phosphorylation of IRS-1 and its association with PI3K; however, its effect on the tyrosine phosphorylation of Shc is weak. Conversely, BDNF differentially upregulates the protein levels of the NR1, NR2A and NR2B NMDA receptor subunits, by a mechanism that is sensitive to transcription and translation inhibitors, and their delivery to the plasma membrane. BDNF thereby upregulates NMDA receptor activity in neurons and increases the potential for calcium influx (Caldeira *et al.,* 2007). Moreover, BDNF induces a rapid surface translocation of AMPA receptors (Narisawa-Saito *et al.,* 2002; Fig. 1).

High-frequency activation of glutamatergic synapses triggers the release of BDNF. This release depends on the activation of postsynaptic ionotropic glutamate receptors and on postsynaptic Ca^{2+} influx (Hartmann *et al.,* 2021). An increase in synaptic activity and intracellular calcium induces the expression of the *BDNF* gene (Finkbeiner, 2000). Furthermore, it has been suggested that DHA upregulates BDNF because a DHA deficiency reduces *BDNF* expression in the frontal cortex, cyclic AMP response element binding protein (CREB) transcription factor activity and mitogen-activated protein kinase (MAPK) activity (Rao *et al.,* 2007); the opposite has been shown in rats with a DHA-enriched diet (Wu *et al.,* 2008), and a high-DHA maternal diet increases the mRNA expression of *BDNF*, *TrkB* and *CREB*, as well as the protein concentration of pCREB in the fetal-brain as gestation progresses (Akerele *et al.,* 2020; Balogun *et al.,* 2014; Hashimoto *et al.,* 2017). These phenomena can be explained as follows (Fig. 1). The transcriptional regulation of the *BDNF* gene's promoter activity is carried out *via* the phosphorylated PPARα-RXRα/CREB pathway. *CREB* is regulated by the phosphorylated PPARα-RXRα heterodimer, bound to its preferential agonist ligand DHA, at the transcriptional level. A PPAR-responsive element has been identified in the *CREB* promoter (Roy *et al*., 2013). Phosphorylation, exclusively on serine residues, increases the transcriptional activity of PPARα, *via* the-MAPK pathway (Majou, 2021). Upon activation by the Ca^{2+}/calmodulin complex, activated CaM kinases autophosphorylate each other at threonine residue 286 (Ohsako *et al.,* 1991). Phosphorylated CaMKII phosphorylates CREB at a particular residue, serine 133, and calcium-dependent phosphorylation of Ser133 is required for CREB-mediated transcription (Sheng *et al.,* 1991). When activated, the CREB protein recruits other transcriptional coactivators, such as the coactivator CBP/p300, to bind to CRE promoter 5's upstream region (Shaywitz *et al.,* 1999; Yan *et al.,* 2016).

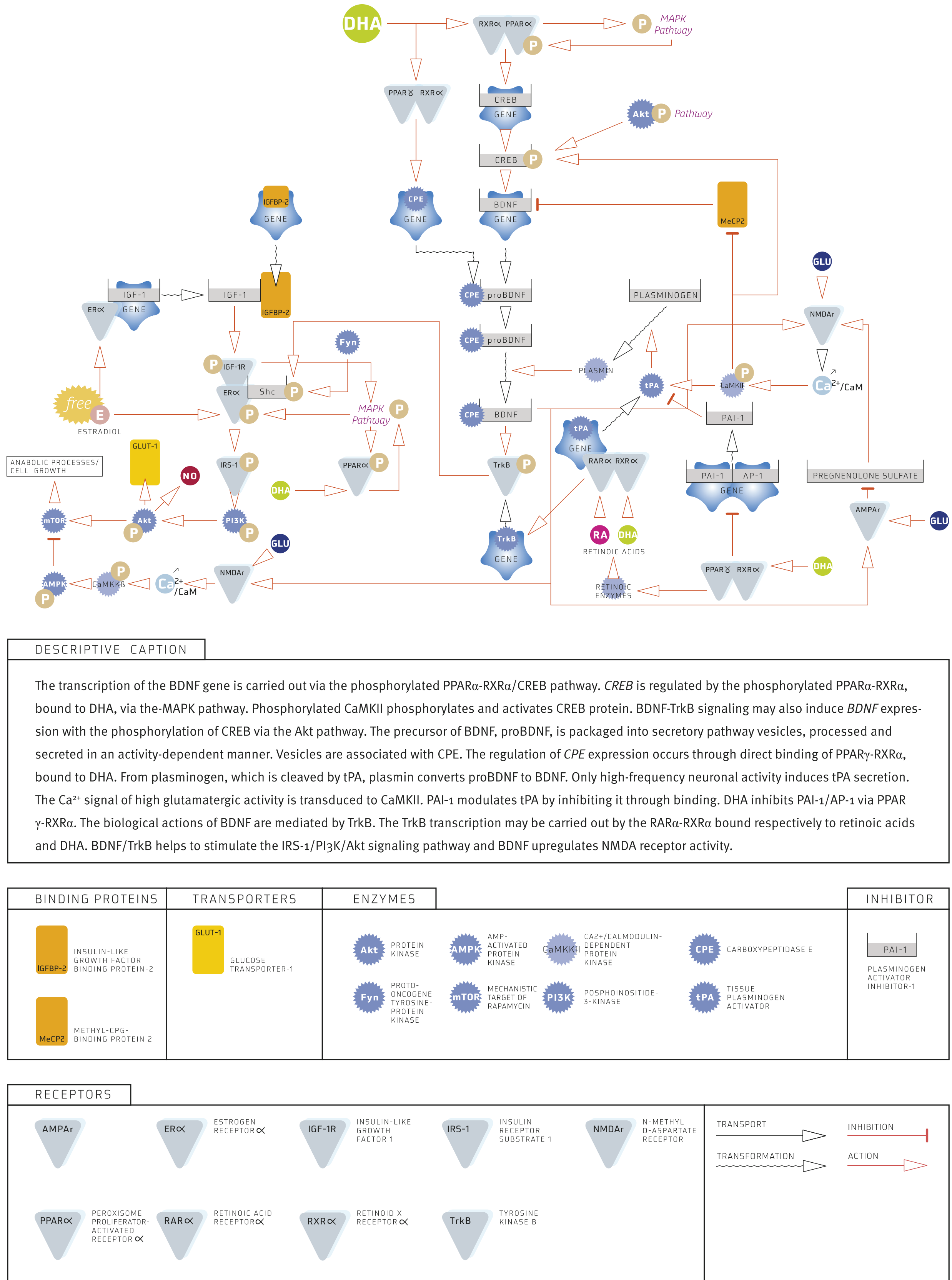

Fig. 1. Role and regulation of BDNF.

Remarkably, BDNF seems to be capable of modulating its own expression levels in neurons, forming a transcriptional positive feedback loop (Esvald *et al.,* 2020). BDNF-TrkB signaling may induce *BDNF* gene expression with the phosphorylation of CREB *via* the Shc (phosphorylated by BDNF/TrkB)/Shc/IRS-1/PI3K/Akt pathway (Peltier *et al.,* 2007). We have been aware of the interaction between BDNF and sex steroids for decades, and some sex steroids, such as estrogen, have a positive regulatory effect on *BDNF* expression and signaling (Chan *et al.,* 2017). Estrogens increase BDNF levels in the prefrontal cortex and the hippocampus (Luine *et al.,* 2013). According to Spencer-Segal *et al.* (2012), free estradiol activates ERα, which mediates the effects on behaviors involving the hippocampus at least in part *via* Akt and TrkB signaling. These results are linked with the *BDNF* transcriptional autoregulation described above. We can hypothesize that free estradiol increases the phosphorylation of CREB *via* the PI3K-Akt signaling pathway. CREB phosphorylation appears to depend on basic brain activity (PI3K/Akt pathway) and stimulation (Ca^{2+}/CaMKII pathway). The effects of these two pathways seem to be cumulative, modulated and limited (Fig. 1).

The precursor of BDNF, proBDNF, is packaged into regulated secretory pathway vesicles, processed and secreted in an activity-dependent manner. From plasminogen, which is cleaved by tissue plasminogen activator (tPA), the extracellular protease plasmin converts proBDNF to BDNF (Pang *et al.,* 2004) and the BDNF pro-peptide, the N-terminal fragment of proBDNF. Only high-frequency neuronal activity induces tPA secretion (Van den Eijnden-Schrauwen *et al.,* 1997), but it does not increase tPA mRNA levels (Gualandris *et al.,* 1996). The Ca^{2+} signal of high glutamatergic activity is transduced to CaMKII (Bramham *et al.,* 2007). BDNF vesicles are associated with carboxypeptidase E (CPE), a proneuropeptide/prohormone-processing enzyme, also known as neurotrophic factor-α1 (NFα1), in hippocampal and cortical neurons. The luminal domain of CPE's membrane form acts as a receptor to sort BDNF into the regulated secretory pathway vesicles (Lou *et al.,* 2005; Park *et al*., 2008). The regulation of *CPE* expression occurs through direct binding of PPARγ-RXRα to the *CPE* promoter (Thouennon *et al.,* 2015).

tPA transcription is induced by the RARα-RXRα heterodimer (Bulens *et al.,* 1995; Borel *et al.,* 2010) with all-trans retinoic acid (ATRA) and 9-cis-retinoic acid for RARα and only 9-cis-retinoic acid, in competition with DHA, for RXRα. The induction is mediated by a specific retinoic acid response element (RARE) located in the promoter region of target genes. This *tPA* expression is also related to DHA. Indeed, PPARγ turns on retinoic acid synthesis by inducing the expression of retinol and retinal-metabolizing enzymes such as retinol dehydrogenase 10 (RDH10) and retinaldehyde dehydrogenase type 2 (RALDH2). PPARγ-regulated expression of these enzymes leads to an increase in the intracellular generation of ATRA from retinol. ATRA regulates gene expression *via* the activation of RARα (Gyöngyösi *et al.,* 2013; Szatmari *et al.,* 2006). It should be highlighted that the same mechanism exists for the expression of the *TrkB* gene. Retinoic acids induce a sustained increase in TrkB mRNA that is accompanied by an increase in TrkB mRNA transcription by the RARα-RXRα heterodimer (Lucarelli *et al.,* 1995), and the PPARγ-RXRα heterodimer is involved in the same way, bound to its preferential agonist ligand DHA. The plasminogen activator inhibitor-1 (PAI-1) modulates tPA by inhibiting it through binding. Therefore, the tPA/PAI-1 system is an important regulator of the BNDF/proBDNF ratio. Increased *PAI-1* expression and activity contribute to Aβ accumulation by inhibiting tPA (Liu *et al.,* 2011) and impairing BDNF maturation (Gerenu *et al.,* 2017). Conversely, the suppression of PAI-1 significantly reduces brain Aβ load (Akhter *et al.,* 2018), and neuronal tau hyperphosphorylation is reverted (Gerenu *et al.,* 2017). The PAI-1 inhibitors augment tPA and plasmin activity, and significantly lower plasma and brain Aβ levels (Jacobsen *et al.,* 2008). The presence of c-Jun-responsive elements in the *PAI-1* promoter has been reported (it is an AP-1-like binding site; Descheemaeker *et al.,* 1992). However, DHA inhibits AP-1 and suppresses AP-1 activation (transcription factor activator protein 1; Liu *et al.,* 2001; Zgórzyńska *et al.,* 2021) *via* PPARɣ (Konstantinopoulos *et al.,* 2007; Fig. 1). Thus, DHA is involved in the regulation and expression of *tPA,* as well as the inhibition of *PAI-1*, and consequently DHA boosts the action of BDNF.

Methyl-CpG-binding protein 2 (MeCP2) binds selectively to *BDNF* promoter III and represses the expression of the *BDNF* gene (Chen *et al.,* 2003). The transcriptional regulation of *BDNF* by MeCP2 is controlled by MeCP2 phosphorylation on serine 421. CaMKII catalyzes this calcium-dependent phosphorylation event (Kolarow *et al.,* 2007) and releases MeCP2 from *BDNF* promoter III, thereby facilitating the transcription and postsynaptic secretion of BDNF (Buchthal *et al.,* 2012; Fig. 1). It is interesting to note that the level of stimulation (Ca^{2+} influx) modulates the regulation of *proBDNF* transcription *via* the release of MeCP2 and the phosphorylation of CREB, and then the conversion of *proBDNF* to BDNF *via* tPA. Above a certain concentration of Ca^2, BDNF activity is modulated by (i) AMP-activated protein kinase (AMPK), whose activation by glutamate inhibits the effects of BDNF on protein synthesis by specifically suppressing the activation of mTOR (mechanistic target of rapamycin) signaling (Ishizuka *et al.,* 2013) and (ii) AMPA receptors (glutamate receptors), which inactivate SULT2B1a, an enzyme that generates pregnenolone sulfate acting on NMDA receptors to accelerate the entry of Ca^{2+} (Fig. 1).

3 DHA as a key regulator of BDNF's action

The role of DHA in the expression of BDNF and in the actions of its protein has been the subject of several experiments. In adult rats or mice, a DHA-enriched diet increases levels of proBDNF and mature BDNF (Jiang *et al.,* 2009; Sable *et al.,* 2013; Sugasini *et al.,* 2020; Vosadi *et al.,* 2014; Wu *et al.,* 2008), as well as in patients with schizophrenia, for example (Pawełczyk *et al.,* 2019). The same applies to the CREB level (Wu *et al.,* 2008). The opposite has also been suggested, *i.e.*, that a DHA deficiency reduces *BDNF* expression in the frontal cortex, as well as CREB and MAPK activity (Rao *et al.,* 2007). And a high-DHA maternal diet increases the mRNA expression of *BDNF*, TrkB and CREB, as well as the protein concentration of pCREB in the fetal-brain as gestation progresses (Akerele *et al.,* 2020; Balogun *et al.,* 2014; Hashimoto *et al.,* 2017).

DHA plays an essential role as a gene transcription modulator *via* transcription factors, in particular peroxisome proliferator activated receptors (PPARs) and retinoid X receptors (RXRs). These transcription factors take the form of PPAR-RXR heterodimers, located within the nucleus and activated by phosphorylation (PPARα) and their respective ligands, which modify their tertiary structures and enable them to bind to the PPRE located in the promoter region of the target genes. DHA is a preferential ligand in comparison to PPARs and RXRs (de Urquiza *et al.,* 2000; Deckelbaum *et al.*, 2006; Diep *et al.*, 2002; Dziedzic *et al.*, 2018; Song *et al.*, 2017). As we have already seen, *CREB* gene expression is regulated by the phosphorylated PPARα-RXRα heterodimer, and *CPE* gene expression is regulated by the PPARγ-RXRα heterodimer. DHA is involved in the regulation and expression of the *tPA* gene, as well as the inhibition of the *PAI-1* gene, through PPARγ-RXRα (Fig. 1).

4 Conclusion

Neurons have high energy needs, requiring a continuous supply of glucose from the blood. Tight regulation of glucose metabolism in response to stimuli is essential for brain physiology. Glucose metabolism and cerebral blood flow are closely coordinated during neuronal activity to maintain proper brain function. The data and mechanisms presented above demonstrate the ability of BDNF-TrkB to stimulate glucose uptake in response to increased energy demand by increasing the expression of the neuronal glucose transporters (GLUTs) and NO-mediated vasodilation through the IGF-1/estradiol/PI3K/Akt signaling pathway. In short, high-frequency neuronal activity induces the secretion of BDNF, whose presence boosts this important pathway.

DHA, *via* the PPARα-RXRα and PPARɣ-RXRα heterodimers, is involved in the critical regulation of BDNF activation. As a preferential ligand of PPARs and RXR, DHA plays an important role in *CREB* and *CPE* gene expression, and it is involved in the regulation and expression of *tPA,* as well as the inhibition of *PAI-1*. BDNF boosts the IGF-1/estradiol/PI3K/Akt signaling pathway, and DHA boosts BDNF action.

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