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GDF11 reverses mood and memory declines in aging

Patrick T. Piantadosi & Andrew Holmes

Aging is known to be associated with a decline in memory and mood, but the molecular mechanisms that underlie these changes remain unclear. Moigneu, Abdellaoui and colleagues show that growth differentiation factor 11 reverses deficits in these functions in aged mice, pointing the way towards a novel pro-mnemonic and antidepressant therapeutic target.

Changes in memory and mood are hallmarks of aging. As a result, there is intense interest in identifying molecular factors that underlie the depressed mood and deterioration of memory that accompany aging in some individuals[1]. A study presented in *Nature Aging* by Moigneu, Abdellaoui and colleagues[2] identifies growth differentiation factor 11 (GDF11) as a potentially key regulator of both age-related memory decline and increased depression-related behavior in mice. Uncovering this role for GDF11 advances our understanding of the connection between aging, memory and mood disorders, and – perhaps most excitingly – raises the prospect of targeting GDF11 as a means to improve the diagnosis and treatment of these ailments.

GDF11 is a member of the transforming growth factor-β (TGFβ) superfamily that is involved in tissue formation during embryonic development[3]. Administering GDF11 has previously been shown to reverse age-related cardiac hypertrophy and skeletal muscle degeneration, and also to improve cerebral vasculature and protect against cerebral hemorrhage[4–7]. These findings have led to the emerging view that GDF11 could act as a rejuvenating factor in various aged organs[8]. In parallel, a group led by Pierre-Marie Lledo has shown that circulating GDF11 protein levels are depleted in aged, relative to young, mice[9] – although some studies report opposite trends[10]. On the basis of these observations, the group's new study, undertaken by Moigneu, Abdellaoui and colleagues, set out to investigate whether increasing levels of GDF11 could have beneficial effects on memory and mood in aged mice (Fig. 1).

The authors began by assessing the behavioral effects of chronic GDF11 treatment using a procedure that the same group had previously shown[9] restores the depleted circulating GDF11 levels that are evident in aged (22-month-old) mice, as compared to young counterparts (3–4 months old). The authors tested the effects of this treatment regimen on performance in three behavioral assays for memory: the novel-object recognition test, novel-object location test and a spatial novelty-based version of the Y-maze test. In each of these tests, aged mice treated with vehicle exhibited poorer performance than similarly treated young mice. Notably, the GDF11-treated aged mice, by contrast,

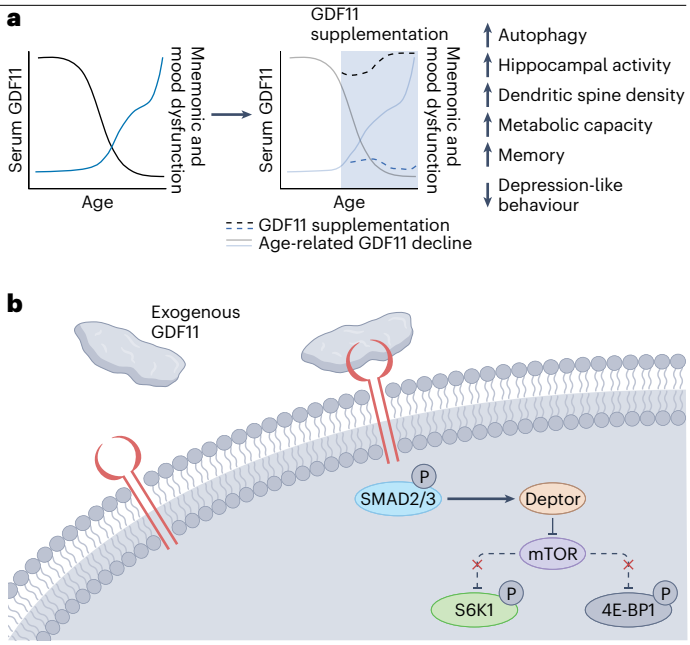

Fig. 1 | GDF11 supplementation reverses age-related deficits in mood and memory. a, Age-related decline in serum GDF11 is associated with impairments in memory and anxio-depressive-like behaviors, which can be ameliorated in aged mice through chronic treatment with exogenous GDF11 supplementation. **b**, Mechanistically, GDF11 acts on hippocampal neurons, binding to TGFβ superfamily receptors to increase Deptor, inhibiting mTOR and thus promoting autophagy. This cascade of events results in an improvement in memory and the anxio-depressive-like phenotype in aged mice by promoting hippocampal neuronal metabolic capacity and synaptic health.

performed at levels indistinguishable from their younger counterparts, demonstrating that restoring GDF11 levels was sufficient to reverse the age-related decline in performance on these tasks.

Next, Moigneu, Abdellaoui and colleagues turned their attention to examining the effects of GDF11 on a comprehensive battery of mouse behaviors that are known to be sensitive to clinically efficacious antidepressants, including the tail suspension, splash-induced grooming and sucrose preference tests[11]. In an analogy with their findings on memory performance, the authors found that the heightened 'depressive-like' phenotype observed in aged mice was reversed by GDF11 treatment. Conversely, GDF11 did not alter the heightened anxiety-like behavior that was evident in aged mice, nor did it affect indices of gross motor function – ruling out the possibility that the antidepressant-like effect of GDF11 was an artifact of a more-general change in motor ability in the aged mice. In fact, the authors further showed that GDF11 treatment in young mice was able to mitigate the 'anxio-depressive-like' state

produced by chronic administration of the 'stress hormone' corticosterone in drinking water.

The marked ability of chronic GDF11 treatment to restore memory and depression-related abnormalities in aged mice led Moigneu, Abdellaoui and colleagues to delve into the question of the underlying mechanisms involved. Here, the authors were guided by their previous work showing that neurogenesis in the subgranular zone of the hippocampal dentate gyrus (a region known to contribute to some forms of memory and depression-related behaviors) displays elevations in neurogenesis and vascular blood flow in response to rejuvenating factors related to young mice[5]. In the new study, they found that neural stem cells and immature neurons (indices of neurogenesis) in the subgranular zone of aged mice were increased through as little as nine days of GDF11 treatment. GDF11 treatment also normalized the aging-induced elevation in neural senescence to the level seen in young mice, as evidenced by a reduction in the expression of the senescence-related markers SA-βGal, p16 and p19ARF.

Autophagic processes are known to become impaired with aging — a change that has been related to the diminished neurogenic potential that is typical of older animals[12]. Moigneu, Abdellaoui and colleagues found that autophagic proteins, including beclin 1 (a key molecular initiator of the autophagic process), are decreased in the hippocampus of aged mice. GDF11 treatment again mitigated these changes. These findings are consistent with a pro-autophagic function of GDF11 in the central nervous system, extending previous work that has shown that this growth factor can stimulate autophagy in peripheral tissues such as smooth muscle cells[13] and skeletal muscle fibers[7]. Given these widespread effects, a corollary question is whether the effects of systemic GDF11 administration on brain and behavior observed here are attributable to direct actions in the brain or to indirect, peripherally mediated effects.

This issue was addressed by chronically (over the course of two weeks) delivering GDF11 into the lateral ventricle and showing that this produced the same pro-mnemonic and antidepressant-like effects in aged mice as did systemic administration. The same was largely true of autophagic processes. The effects of systemic and central administration diverged when it came to measures of hippocampal neurogenesis — ventricular delivery of GDF11 did not increase markers of neurogenesis. One possible explanation for this discrepancy is that the pro-neurogenic effect of systemic GDF11 relied upon recruitment of an unknown circulating factor that is capable of crossing the blood–brain barrier. Indeed, recent data suggest that GDF11 natively opposes adult hippocampal neurogenesis[14]. Regardless, this dissociation suggests that the behavioral effects of GDF11 are not causally dependent on the neurogenic properties of the growth factor, but instead are coincident with its ability to increase autophagy.

The finding that neurogenesis is not necessary for the positive effect of GDF11 on behavior led the authors to assess its effects on the function of mature neurons. Working with cultured hippocampal neurons, the authors observed that incubation with GDF11 increased the expression of the immediate–early gene *Fos* and promoted dendritic outgrowth. Both pieces of data suggest that this crucial growth factor can directly activate hippocampal neurons, a fact which the authors confirmed by demonstrating GDF11-induced phosphorylation of the canonical TGFβ signaling pathway. As the authors had observed with systemic and intra-cranial GDF11 exposure, autophagic proteins (including beclin 1) were again significantly upregulated in GDF11-exposed hippocampal cultures.

Collectively, these various lines of evidence suggest an intriguing link between autophagic processes and neuronal activation, but do not confirm whether autophagy is indeed necessary for the neural responses induced by GDF11. To answer this question, the authors turned to a short hairpin RNA approach to disrupt beclin 1, again in hippocampal cultures. After first determining that the GDF11-induced increase in spine density was diminished by disruption of beclin 1, they then blocked the late stage of the autophagic process by incubating cultured neurons in bafilomycin A1, which blocks autophagosome–lysosome fusion. Bafilomycin A1 treatment attenuated the ability of GDF11 to increase metabolic capacity and induce FOS in hippocampal neurons, providing support for the hypothesis that stimulation of autophagic processes underpins the neuronal effects of GDF11. It will be fascinating to build upon these in vitro findings to examine whether GDF11 affects neuronal activity in vivo.

Working with primary neuron cultures enabled the current study to drill down into the mechanisms that mediate the effects of GDF11 on autophagic processes. By using bulk RNA sequencing of cultured neurons, the authors found that GDF11 treatment altered gene pathways linked to mTOR, a known regulator of autophagy. Of particular note, protein levels of Deptor (an mTOR inhibitor) were upregulated by GDF11 treatment, and the phosphorylation of downstream kinase targets of mTOR were decreased. This pattern of changes suggests a model in which GDF11 inhibits mTOR activity and thus indirectly promotes hippocampal neuronal autophagy. As with all hypothetical models, this one will require follow-up investigation, but it clearly provides a roadmap for future work.

Neurological and psychiatric conditions associated with impairments in memory and disordered mood are leading causes of morbidity, and a growing concern in aging populations. The findings presented here by Moigneu, Abdellaoui and colleagues advance our understanding of the molecular factors at play as behavioral disturbances emerge with advancing age. Moreover, by implicating GDF11 in memory and depression-related behavior, this study suggests that this growth factor may be a mechanistic link between the two. This is particularly intriguing in light of evidence that individuals with major depressive disorder are almost twice as likely to present with dementia later in life[15]. Relatedly, in a tantalizing observation, the current study found lower circulating levels of GDF11 in young adults suffering from major depressive disorder. On the basis of these findings, it is tempting to speculate about whether therapeutically targeting GDF11 could break this link, bringing about clinical benefits to both mood and memory. Further research in the coming years will hopefully see this idea put to the test.

Patrick T. Piantadosi & Andrew Holmes ✉
Laboratory of Behavioral and Genomic Neuroscience, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, USA.
✉e-mail: Andrew.Holmes@nih.gov

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Competing interests
The authors declare no competing interests.