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Role of activin in cognitive functions, affective behavior and neuronal survival

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Abstract: The multifunctional regulatory protein activin is a member of the transforming growth factor-β family. In the adult brain, activin serves as a neuroprotective factor in acute and chronic brain damage, but it also regulates brain circuits under physiological conditions. This review will highlight activin as a master molecule at excitatory and inhibitory CNS synapses and discuss how synaptic tuning by activin impacts on cognitive functions and affective behavior. By augmenting NMDA receptor function and adjusting spine morphology and density, activin strengthens hippocampal long-term potentiation (LTP), leading to improved performance in rodent learning and memory tasks. Disruption of activin signaling not only impairs cognitive functions, but also engenders a low-anxiety phenotype, which has been linked to alterations in GABAergic inhibition. Finally, accumulating evidence implicates activin as a putative endogenous antidepressant as well as a target of antidepressant treatment.

Keywords: Activin; Hippocampus; Learning and Memory; Anxiety; Depression

Introduction

The German brain researcher Wolf Singer once called the brain an “orchestra without conductor” (Singer, 2005). This statement implies that the brain operates as a highly complex, nonlinear and self-organized system. One telling feature of this system is that it is capable of binding nerve cells, which perform a certain function such as object recognition or memory recall into *ad hoc*, task-related neuronal assemblies. A specific pattern of bioelectrical activity that is highly synchronized in space and time is thought to group the neurons together, which thus become members of the assembly. One might ask what mechanisms are at work when it comes to more prolonged processes, such as the gradual exploration of a new and stimulating environment, a behavior which is expected to promote neuronal plasticity, foster learning and memory, and counteract depression. Or, on an even more extended time scale, what principles serve to maintain the stability of neuronal networks involved in cognitive functions and affective behavior? Here as well, not a single conductor is responsible, but there is evidence for overarching factors which govern and coordinate a multitude of cellular and molecular events. In this review, we will introduce activin as such a master molecule and describe how this factor tunes elements of brain circuits in a fashion that has a direct impact on cognition and mood. We will also demonstrate that activin, beyond its many functions in the normal operations of the brain, serves as a potent neuroprotective factor in acute and chronic brain damage.

Activin and activin receptor signaling

Activin is a member of the large transforming growth factor-β (TGF-β) family (see Box 1). It was originally recognized as an endocrine factor of ovarian origin which augments the release of follicle-stimulating hormone (FSH) from the pituitary gland.

The TGF-β family

The human TGF-β family comprises more than 30 members, including the TGF-βs themselves (TGF-β1-3), the activins and inhibins, the bone morphogenetic proteins (BMPs), the growth and differentiation factors (GDFs), Nodal, Lefty, and Müllerian inhibiting substance (MIS). The factors are small secreted signaling molecules of dimeric structure, which control and regulate the development of many tissues and organs. In the adult, they regulate and coordinate numerous processes in a variety of tissues and organ systems, with a particular emphasis on tissue homeostasis and repair, inflammation and oncogenesis.

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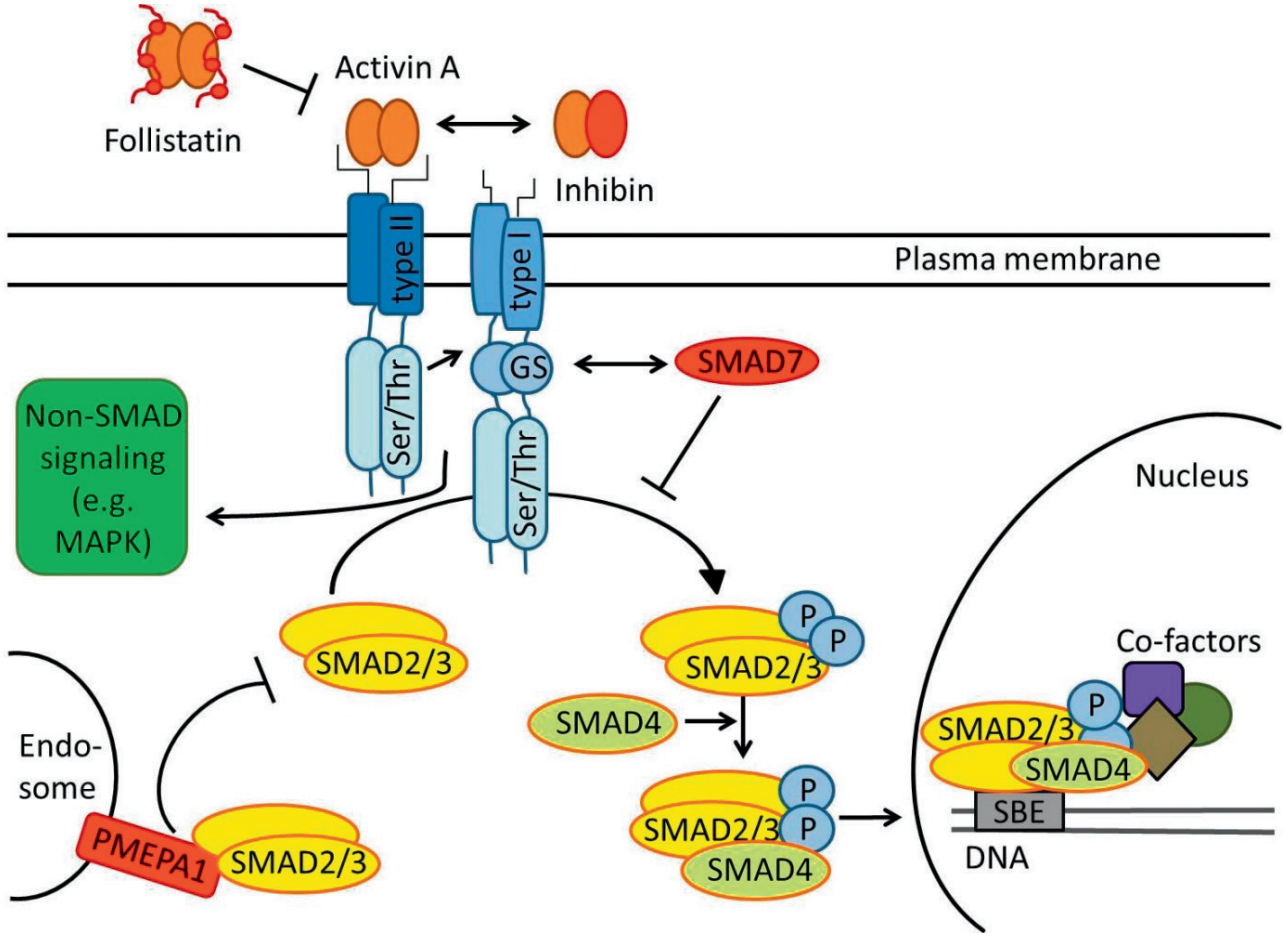

Fig. 1: Schematic drawing of activin receptor signaling pathways. Note that activin signaling is strictly regulated by extracellular inhibitors like follistatin and inhibin, the transmembrane antagonist PMEPA1, and the cytoplasmatic inhibitor SMAD7. All inhibitors are colored in red. For further explanation see text. Abbreviations: MAPK, mitogen-activated protein kinase; PMEPA1, prostate transmembrane protein, androgen induced 1; SBE, SMAD-binding element.

Because the factor counteracted the effect of the previously identified protein inhibin, it was named "activin". By now, activin has been established as a multifunctional regulatory protein with a broad spectrum of biological effects in developing as well as in mature tissues and organ systems. Activin has been shown to play a major role in proliferation, differentiation, apoptosis, inflammation, immunoregulation, tissue homeostasis and repair. Correctly speaking, we should not refer to activin in the singular, since several variants of activin exist. The best characterized activins are the homodimeric proteins activin A and activin B, which contain two disulfide-linked βA- or βB-subunits, respectively (the heterodimer activin AB has one βA- and one βB-subunit). In the brain, activin A is the most abundant and functionally prevailing representative of the activins. For the sake of simplicity, we will therefore denote activin A in this review as activin. After its release from neurons and glial cells, which presumably occurs in a constitutive fashion under homeostatic conditions, activin signals through a tetrameric complex of type II activin receptors (ActRIIA, ActRIIB) and type I receptors (mainly ActRIB, but also ActRIC), which both contain serine-threonine kinase domains. The schematic drawing of Fig. 1 depicts the pathways of activin receptor signaling. Once activin is bound to type II receptors, type I receptors are recruited and trans-phosphorylated, which in turn enables them to phosphorylate the intracellular signaling proteins SMAD2 and SMAD3. After assembling with SMAD4, the SMAD complex translocates to the nucleus, where it regulates the expression of targets genes, which are still mostly unknown in the brain. Importantly, the strength and duration of activin receptor signaling is strictly controlled at several levels. The already mentioned inhibin competes with activin for receptor binding, whereas follistatin intercepts activin and prevents binding. SMAD7 blocks phosphorylation of SMAD2/3 by type I receptors.

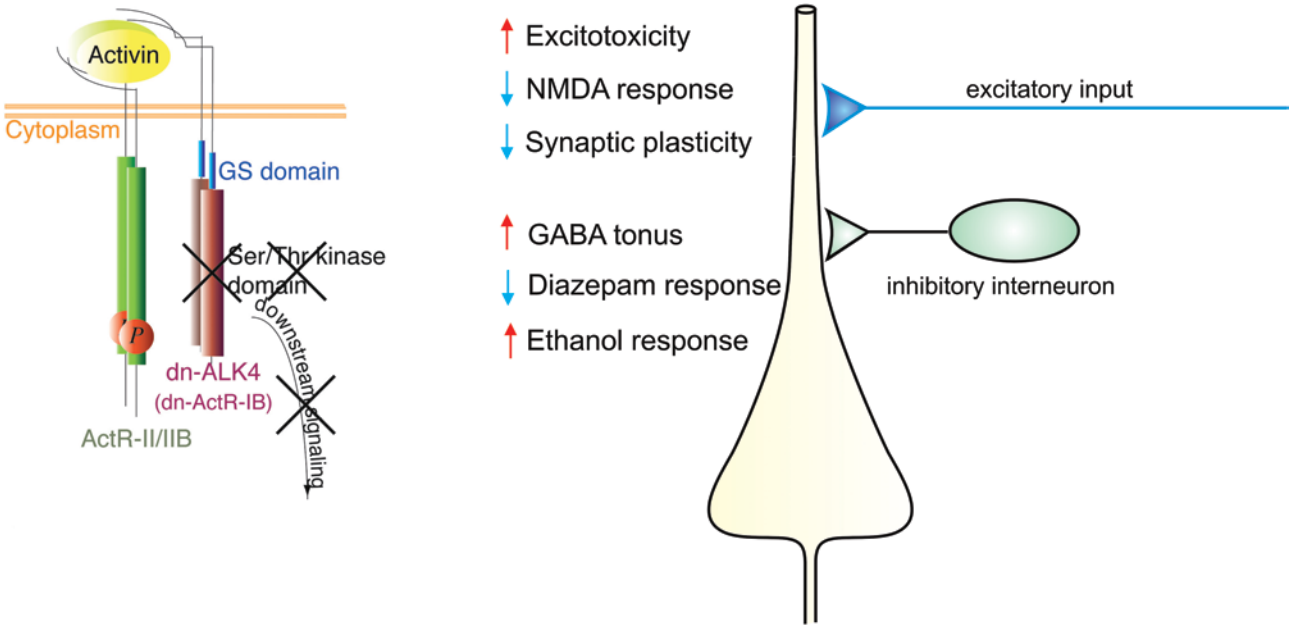

Fig. 2: Activin impacts on synaptic physiology and pharmacology. Summary of major changes at excitatory and inhibitory synapses (right-hand side) after disruption of activin receptor signaling by expression of a dominant-negative mutant of the type I activin receptor IB (dn-ActR-IB, also called dn-ALK4), in which the complete kinase domain of the receptor was deleted (left-hand side).

A similar effect is attributable to the protein PMEPA1. Interestingly, we recently identified *PMEPA1* as one of the first target genes of activin in the brain, suggesting that it serves as a feedback inhibitor of activin signaling (Link et al., 2016a). In addition to the canonical, SMAD-dependent signaling, activin can also activate other pathways, such as the mitogen-activated protein kinase (MAPK) or phosphoinositide-3-kinase (PI3K) signaling cascades.

Activin and the molecular underpinnings of learning and memory

A long lasting enhancement of synaptic transmission at excitatory synapses, which use glutamate to convey information, is widely recognized as an important neurobiological mechanism of learning and memory. The lasting increase in synaptic efficiency is called long-term potentiation (LTP) and considered a neurophysiologic correlate of newly formed memory traces. LTP is induced by specific stimulation patterns, which lead to the activation of NMDA receptors (NMDA-Rs), a subtype of glutamate receptor channels. The influx of Ca^{2+} through NMDA-Rs triggers signaling cascades, which serve to establish LTP. The genetic or pharmacologic suppression of NMDA-R function not only abrogates LTP, but also impairs learning and memory. The causal links between LTP and memory formation have been interrogated most thoroughly in the hippocampus, a brain region essential for spatial and, more so, declarative memory. Several studies have shown that activin promotes LTP and learning in mice (Krieglstein et al., 2011). Disruption of activin signaling in transgenic mice through a postnatal expression of a dominant-negative activin receptor IB (dnActRIB) mutant in forebrain neurons diminished hippocampal LTP (Fig. 2) (Muller et al., 2006). In a similar vein, over-expression of the activin-intercepting protein follistatin (see above) abrogated LTP and impaired the behavioral performance in a context-dependent learning task (Ageta et al., 2010). Notably, activin receptors are present in dendritic spines, where they augment NMDA-R function, and thus LTP, through a non-SMAD-dependent signaling conduit. In addition, activin was found to increase the number of spines and change their shape, thereby also supporting the morphological underpinnings of memory consolidation.

Activin, GABA receptors and anxiety

The above mentioned dnActRIB mice display a pronounced low-anxiety phenotype. This behavioral alteration became particularly prominent in the light-dark exploration test, which explores unconditioned anxiety

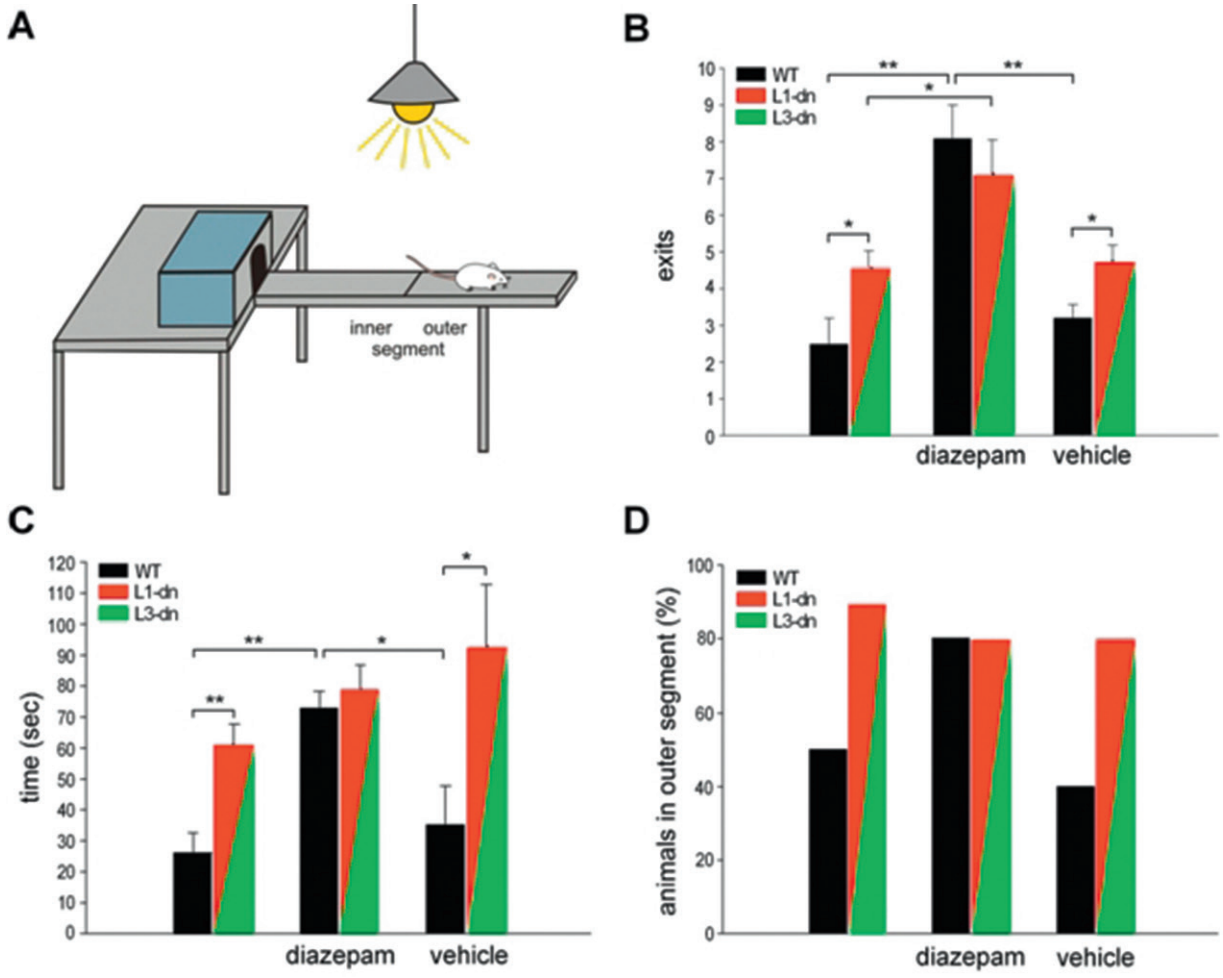

Fig. 3: Low-anxiety phenotype after forebrain-specific disruption of activin receptor signaling. A, Schematic drawing of test apparatus to investigate light-dark exploration behavior. **B-D,** Histograms of exits from the box (**B**), time spent on the open bar (**C**), and percentage of animals entering outer segment (**D**), over a 5 min test period for wild type animals (WT, black columns) and two lines of dnActRIB mice (L1-dn, L3-dn, green/red columns) without treatment (left columns), with diazepam (middle columns) or with vehicle (right columns). Data from the two mutant lines were pooled. * $P < 0.05$, ** $P < 0.01$ (reprinted, with permission, from Zheng et al., 2009).

(Zheng et al., 2009). In this test, the mouse is placed inside a dark box and may either stay in the safe surroundings of the box or explore the well-lit and elevated (and thus aversive) bar, which extends from the opening of the box (Fig. 3). The test subjects mice to a characteristic conflict paradigm between the innate drive to explore a novel environment and the potential threats this environment poses. Whereas wild type mice behaved rather cautiously in this test and left the box only two or three times during a 5 min test period, and then only briefly, dnActRIB mice proved much more curious and venturesome. The anxiety-like behavior of the wild type mice was reduced substantially by diazepam, a benzodiazepine which is in wide clinical use as an anxiolytic drug. In contrast, the already low level of anxiety in dnActRIB mice was not further reduced by diazepam (Fig. 3).

Since the anxiolytic effect of diazepam has been attributed to its action as a positive allosteric modulator of $GABA_A$ receptors ($GABA_A$-Rs), it seemed obvious to explore and compare the physiology and pharmacology of GABAergic synapses in hippocampal slices from wild type and dnActRIB mice (Zheng et al., 2009). In agreement with the behavioral findings from dnActRIB mice, diazepam failed to produce the prominent potentiation of $GABA_A$-R responses that was typically obtained in wild type neurons (Fig. 2). In addition, mutant neurons exhibited a significantly stronger inhibitory tonus compared to their wild type counterparts. This tonus is mediated by extrasynaptic $GABA_A$-Rs and has been implicated in the regulation of anxiety-like behavior. Finally, disruption of activin signaling was found to enhance the G protein-activated, inwardly rectifying K^+ (GIRK) current response to $GABA_B$-R

activation. This finding fits nicely into the picture, since drugs that act as positive modulators at $GABA_B$-Rs exhibit anxiolytic properties. Taken together, the low-anxiety phenotype of dnActRIB mice and their lacking response to diazepam can be ascribed to alterations in $GABA_A$-R and $GABA_B$-R function. It thus appears that activin regulates the properties of the two GABA receptor types in a fashion that ensures a survival-promoting balance between explorative curiosity and the need for safety. Based on their daredevil behavior, we would expect dnActRIB mice, if released in the wild, to become easy prey for cats and other enemies.

Activin, alcohol and drug addiction

Like diazepam, alcohol is a positive allosteric modulator of $GABA_A$-Rs, and this mechanism is thought to make a major contribution to the CNS effects of alcohol, which include anxiolysis. Would activin then regulate the effect of alcohol at $GABA_A$-Rs in a manner similar to that of diazepam? Surprisingly, the opposite is true, in that activin signaling *dampens* the potentiating effect of alcohol at $GABA_A$-Rs (Zheng et al., 2016). In contrast to wild type neurons, dnActRIB neurons proved more sensitive to the effect of alcohol on $GABA_A$-R currents, causing a leftward shift of the dose-response relationship. In other words, disruption of activin signaling makes synaptic $GABA_A$-Rs sensitive to alcohol at concentrations ≤ 30 mM (17 mM equals 0.8‰), which do not normally affect their function (Fig. 2). Activin appears to regulate the alcohol sensitivity of $GABA_A$-Rs through a non-SMAD pathway, which involves protein kinase C epsilon (PKCε). On the behavioral level, alcohol produced stronger sedation in dnActRIB mice than in wild type mice, whereas the reinforcing effects of alcohol were not affected.

A recent study implicated the canonical (SMAD-dependent) signaling pathway of activin in drug craving and relapse after cocaine withdrawal (Gancarz et al., 2015). The authors of this study reported that, after 7 days of cocaine withdrawal, phosphorylation of SMAD3 was strongly and specifically increased in the Nucleus accumbens, an important part of the mesolimbic reward system. Intra-accumbal injection of recombinant activin enhanced drug self-administration, whereas viral over-expression of dominant-negative SMAD3 (dnSMAD3) produced the opposite effect. Notably, dnSMAD3 also prevented the increase in dendritic spines in accumbal neurons, which is normally an important feature of the maladaptive processes underlying the endurance of cocaine-seeking behavior. It is tempting to speculate that cocaine hijacks pathways of activin signaling that are meant to engender synaptic plasticity in support of learning and memory to re-instate drug self-administration.

Activin as an endogenous antidepressant?

In view of the extensive co-morbidity of anxiety and depression, it is not surprising that activin has also been implicated in the latter. Activin signaling is stimulated by antidepressant drugs as well as by electroconvulsive therapy (ECT), which is clinically used in major, pharmacoresistant depression (Link et al., 2016b). The therapeutic benefits of activin signaling are underscored by behavioral tests, in which injection of recombinant activin into the dentate gyrus of rodent hippocampus alleviated depression-like behavior (Dow et al., 2005). In a mouse model of ECT, a massive increase in activin signaling was observed, which was largely restricted to the dentate gyrus (Fig. 4c). This raises the question of whether activin might have an impact on adult neurogenesis in this area, which has been advanced as a target of antidepressant treatment. Injection of activin into the dentate gyrus enhanced indeed neural stem/precursor cell proliferation. According to the (not undisputed) hypothesis that adequate adult neurogenesis in the dentate gyrus is a prerequisite for balanced mood and stable affective behavior, it seems conceivable that the antidepressant efficacy of drugs and ECT is causally linked to the strong induction of activin signaling.

Interestingly, a remarkable activation of activin signaling can also be achieved by behavioral means. If mice were transferred from their regular cages into larger cages enriched with shelters, toys and tunnels, the active exploration of such an enriched environment (EE) led to a substantial rise in activin expression and subsequent signaling (as indicated by increased SMAD2/3 phosphorylation) in the hippocampus within 2 hours (Link et al., 2016a). Activin levels peaked after 4–6 hours and then declined over 24 hours (Fig. 4b). It is worth noting that exposure to EE is recognized as a measure to produce antidepressant-like effects. It seems therefore plausible to assume that the EE-associated induction of activin signaling serves as an endogenous antidepressant mechanism. The same behavioral setting also up-regulated the expression of *bdnf,* albeit to a lesser degree (Fig. 4a). This parallel is remarkable, since BDNF is widely recognized as a major player in synaptic plasticity, learning and memory, as well as in antidepressant treatment. The striking overlap in the

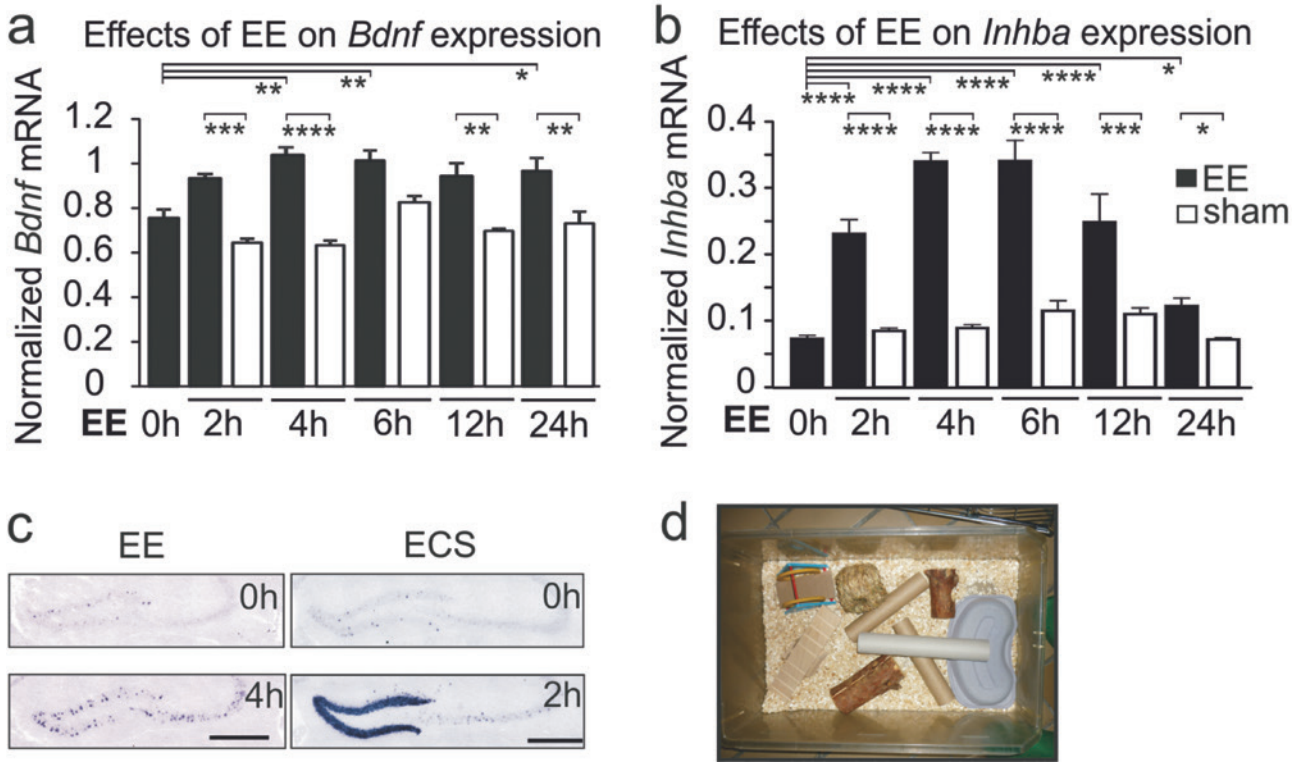

Fig. 4: Exposure of mice to an enriched environment (EE) increased expression of *Bdnf*-mRNA (a) and *Inhba*-mRNA, which encodes the activin βA subunit (b). mRNA levels were determined by RT-qPCR and normalized to the mean of *Tbp*, *Hprt*, and *Rpl13a*. Mice were placed in cages equipped with shelters, toys and tunnels (**d**) and sacrificed at the time points indicated. Production of functionally active activin was confirmed by Western blotting showing increased SMAD2/3 phosphorylation (data not illustrated). (**c**) In-situ hybridization revealed scattered up-regulation of activin βA in the dentate gyrus and the CA3 region of the hippocampus after 4 h of EE (left-hand side). By comparison, electroconvulsive seizures (ECS), a mouse equivalent of electroconvulsive therapy in major depression, produced a dramatic increase in activin βA-mRNA that was mainly confined to the dentate gyrus (right-hand side). (Modified after Link et al., 2016a)

profiles of activin and BDNF suggests that the two factors should be well positioned to exert synergistic effects on cognitive functions and affective behavior.

Activin as a neuroprotective factor

In the brain, activin was initially identified as a neurotrophic and -protective factor, a property that has been confirmed and extended by now in many models of acute and chronic brain injury. Acute focal lesions of the mouse hippocampus induce a strong up-regulation of endogenous activin, which confines the volume of the lesion (Muller et al., 2006). Pre-application of recombinant activin via osmotic mini-pumps into the ventricle proved essential to avert neuronal cell death in the hippocampus after injection of an excitotoxic substance (Tretter et al., 2000). From a clinical point of view, findings from a mouse stroke model are of particular interest, in which a single intracerebroventricular injection of activin was effective in reducing the size of the tissue damage up to 6 hours after the ischemic insult (Mukerji et al., 2009). Activin exhibited also neuroprotective effects in animal models of Parkinson´s disease, suggesting potential therapeutic benefits in neurodegenerative diseases. In an elegant study, Hilmar Bading and co-workers just elucidated an intriguing mechanism, in which the sequential interplay between BDNF and activin diminishes the activation of extrasynaptic NMDA-Rs, which are known to trigger pro-death pathways (Lau et al., 2015). The signaling chain is illustrated in Fig. 5. According to this scheme, any perturbation of the synergistic interaction of BDNF and activin would be expected to tilt the delicate balance between survival-promoting *synaptic* NMDA-Rs and neurotoxic *extrasynaptic* NMDA-Rs towards the latter. If persisting over longer time, the prevalence of signaling through extrasynaptic NMDA receptors might well constitute a major pathogenetic process in neurodegenerative diseases.

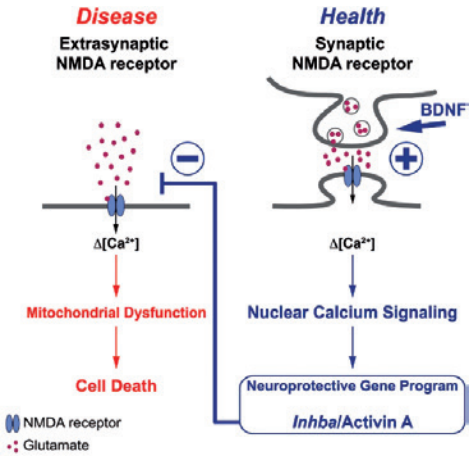

Fig. 5: Schematic drawing of the neuroprotective interplay between BDNF and activin. The synergistic collaboration of the two factors affords neuroprotection by shielding neurons from neurotoxic pathways mediated by the activation of extrasynaptic NMDA receptors. (The graphical abstract was reprinted, with permission, from Lau et al., 2015).

Outlook

The gradual elucidation of the unexpectedly broad spectrum of effects of activin in the normal and diseased brain reveals a number of striking parallels to the profile of the well-established and extensively studied regulatory protein BDNF. The commonalities range from synaptic plasticity, learning and memory to drug addiction, mood disorders and neurodegenerative diseases. It will be an intriguing topic for future research to explore to what extent these factors join forces to achieve common goals in the brain functions they control and protect.

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References

Ageta H., Ikegami S., Miura M., Masuda M., Migishima R., Hino T., Takashima N., Murayama A., Sugino H., Setou M., Kida S., Yokoyama M., Hasegawa Y., Tsuchida K., Aosaki T., Inokuchi K. (2010). Activin plays a key role in the maintenance of long-term memory and late-LTP. Learn Mem *17*: 176–185.

Dow A.L., Russell D.S., Duman R.S. (2005). Regulation of activin mRNA and Smad2 phosphorylation by antidepressant treatment in the rat brain: effects in behavioral models. J Neurosci. *25*: 4908–4916.

Gancarz A.M., Wang Z.J., Schroeder G.L., Damez-Werno D., Braunscheidel K.M., Mueller L.E., Humby M.S., Caccamise A., Martin J.A., Dietz K.C., Neve R.L., Dietz D.M. (2015). Activin receptor signaling regulates cocaine-primed behavioral and morphological plasticity. Nat Neurosci. *18*: 959–961.

Krieglstein K., Zheng F., Unsicker K., Alzheimer C. (2011). More than being protective: functional roles for TGF-beta/activin signaling pathways at central synapses. Trends Neurosci. *34*: 421–429.

Lau D., Bengtson C.P., Buchthal B., Bading H. (2015). BDNF Reduces Toxic Extrasynaptic NMDA Receptor Signaling via Synaptic NMDA Receptors and Nuclear-Calcium-Induced Transcription of inhba/Activin A. Cell Rep *12*: 1353–1366.

Link A.S., Kurinna S., Havlicek S., Lehnert S., Reichel M., Kornhuber J., Winner B., Huth T., Zheng F., Werner S., Alzheimer C. (2016a). Kdm6b and Pmepa1 as Targets of Bioelectrically and Behaviorally Induced Activin A Signaling. Mol Neurobiol *53*: 4210–4225.

Link A.S., Zheng F., Alzheimer C. (2016b). Activin Signaling in the Pathogenesis and Therapy of Neuropsychiatric Diseases. Front Mol Neurosci. *9*: 32.

Mukerji S.S., Rainey R.N., Rhodes J.L., Hall A.K. (2009). Delayed activin A administration attenuates tissue death after transient focal cerebral ischemia and is associated with decreased stress-responsive kinase activation. J Neurochem *111*: 1138–1148.

Muller M.R., Zheng F., Werner S., Alzheimer C. (2006). Transgenic Mice Expressing Dominant-negative Activin Receptor IB in Forebrain Neurons Reveal Novel Functions of Activin at Glutamatergic Synapses. J Biol Chem 281: 29076–29084.

Singer W. (2005). Das Gehirn – ein Orchester ohne Dirigent. MaxPlanckFORSCHUNG *2/2005*: 15–18.

Tretter Y.P., Hertel M., Munz B., ten Bruggencate G., Werner S., Alzheimer C. (2000). Induction of activin A is essential for the neuroprotective action of basic fibroblast growth factor in vivo. Nat Med *6*: 812–815.

Zheng F., Adelsberger H., Muller M.R., Fritschy J.M., Werner S., Alzheimer C. (2009). Activin tunes GABAergic neurotransmission and modulates anxiety-like behavior. Mol Psychiatry *14*: 332–346.

Zheng F., Puppel A., Huber S.E., Link A.S., Eulenburg V., van Brederode J.F., Muller C.P., Alzheimer C. (2016). Activin Controls Ethanol Potentiation of Inhibitory Synaptic Transmission Through GABAA Receptors and Concomitant Behavioral Sedation. Neuropsychopharmacology *41*: 2024–2033.

Bionotes

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