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Review

Physiological functions of non-apoptotic caspase activity in the nervous system

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ABSTRACT

Caspases are cysteine proteases that play important and well-defined roles in apoptosis and inflammation. Increasing evidence point to alternative functions of caspases where restricted and localized caspase activation within neurons allows for a variety of non-apoptotic and non-inflammatory processes required for brain development and function. In this review, we highlight sublethal caspase functions in axon and dendrite pruning, neurite outgrowth and dendrite branches formation, as well as in long-term depression and synaptic plasticity. Importantly, as non-apoptotic activity of caspases is often confined in space and time in neurons, we also discuss the mechanisms that restrict caspase activity in order to maintain the neuronal networks in a healthy and functional state.

Contents

1. Introduction

Caspases belong to a family of cysteine proteases which have important functions in apoptosis, a form of programmed cell death, and inflammation. Caspases are expressed in a wide range of organisms. Initially identified in worms, 18 mammalian homologs of the *C. elegans* Cell death protein 3 (CED-3) have been described to date. However, the set of caspases expressed within mammals is heterogeneous [1]. Pro-apoptotic caspases are responsible for the proteolytic cleavage of hundreds of caspase substrates in response to pro-apoptotic stimuli, ultimately leading to the controlled fragmentation of cellular components, a process essential for the removal of unwanted or damaged cells by specialized phagocytes [2]. In the context of inflammation, a subset of caspases are responsible for the proteolytic maturation of well-defined pro-inflammatory cytokines, as well as the initiation of an inflammation specific form of cell death called pyroptosis [3]. In healthy cells, caspases are expressed as inactive zymogen and their activation, which is usually initiated by proteolytic cleavage, is tightly regulated.

While the mechanisms controlling caspases activation and their targets are well established in the context of apoptosis and inflammation, accumulating evidence also support a non-apoptotic and

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non-inflammatory function of caspases. These functions comprise differentiation and cell fate determination (including differentiation of stem cells and terminal differentiation of keratinocytes, erythroblasts and myoblasts) as well as cell proliferation and tissue regeneration as a result of non-cell autonomous effect on survival and proliferation [4,5]. In addition, caspases exerts non-apoptotic function in the nervous system [5–9]. Over the recent years, studies have demonstrated that restricted and localized caspase activation within neurons allows for a variety of processes that are relevant to neuronal development and function. In this review, we briefly summarize our understanding of caspase activation before exploring the physiological sublethal roles of caspases in the nervous system. We illustrate the roles of caspases in shaping neuronal networks during development and reshaping neuronal connectivity during maturation of the nervous system. We finally discuss the mechanisms that potentially confine and restrict caspase activation in the nervous system.

2. Pathways for caspase activation

Apoptotic caspases can be subdivided into initiator and effector caspases where initiator caspases (caspase-2, -8, -9 and -10) are activated within molecular platforms and are responsible for the direct proteolytic activation of effector caspases (caspase-3, -6 and -7). These effector caspases are responsible for the cleavage of hundreds of cellular substrates and are the real effectors of the apoptotic program. Two molecular platforms, activated by two different pro-apoptotic pathways, are known to activate the apoptotic initiator caspases [4].

The extrinsic, or death receptor, pathway is initiated by ligand-dependent stimulation of cell surface receptors of the tumor necrosis factor (TNF) superfamily, including TNF receptor-1 (TNFR1), Fas/CD95, TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (TRAILR1, TRAILR2), death receptor 3 (DR3), and DR6. Upon ligand-induced trimerization, these receptors, identified by the presence of a death domain and commonly called death receptors, engage into the formation of a death-inducing signalling complex called DISC. This platform consists in the trimerized receptor, the adaptors Fas associated via death domain (FADD) and/or TNFR1-associated death domain protein (TRADD) and the pro-caspase-8 or −10. Within the DISC, pro-caspase-8 homodimerizes and undergoes auto-proteolytic activation. Fully activated caspase-8 can in turn, cleave and activate the effector caspase-3, −6 and −7 [10].

Alternatively, the intrinsic, or mitochondrial, pathway originates from the detection of intracellular stress and involves a signalling cascade leading to mitochondrial outer membrane permeabilization (MOMP) and release of proteins, such as cytochrome *c* and second mitochondria-derived activator of caspases (SMAC), from the mitochondrial intermembrane space. Members of the B cell lymphoma-2 (Bcl-2) family, which are characterized by the presence of Bcl-2 homology (BH) domains, play a key role in the control of MOMP. The pro-apoptotic members Bax and Bak are the effectors of this family, forming pores in the mitochondrial outer membrane upon oligomerization, allowing the release of mitochondrial proteins. Their activation is inhibited by interactions with anti-apoptotic members of the family (e.g. Bcl-2, Bcl-xl, Mcl-1, Bcl-b, Bcl-w, A1), while members containing a single BH domain, the so-called BH3-only proteins (e.g. Bid, Bim, Puma, Noxa, Bad, Bmf, Hrk, Bik), promote the activation of Bax and Bak by either direct interaction and/or inhibition of the anti-apoptotic Bcl-2 proteins [11,12]. In the cytosol, cytochrome *c* promotes the assembly of another caspase activating platform: the apoptosome. The adaptor apoptotic protease activating factor 1 (APAF-1) oligomerizes upon binding to cytosolic cytochrome *c* and ATP, promoting the recruitment and activation of pro-caspase-9. Formation of the apoptosome subsequently promotes the proteolytic activation of pro-caspase-3, -6 and -7 [13].

3. Pruning of axons and dendrites

During development, neurons extend their axons to innervate their target regions often resulting in superfluous connections. This outgrowth phase is followed by a regressive phase where excessive or inappropriate axons, dendrites and synapses are eliminated while suitable connections are maintained. The selective elimination of unwanted axons, dendrites, and synapses is known as pruning and occurs without the death of the parent neuron [14,15]. Pruning is essential for the refinement of neuronal connectivity and establishment of a mature and functional network. In vertebrates, pruning takes place largely during early postnatal development. Classical examples of developmental pruning occur in response to limited neurotrophic factors for sensory and sympathetic neurons, at the neuromuscular junction, in the midbrain where retinal ganglion cells project their axons as well as in the cortex and hippocampus [14,15]. During insect metamorphosis, large-scale pruning allows larval processes to remodel and form adult-specific connections [16]. Evidence that caspase activity is required for developmental pruning has emerged from both genetic and biochemical studies in multiple models.

Caspase function in pruning was first shown in the Drosophila model. During metamorphosis, remodelling of class IV sensory neurons innervating the epidermis involves the elimination of larval dendrites and the subsequent regrowth of adult-specific dendrites. Mutants of the initiator caspase Death regulator Nedd2-like caspase (DRONC) fail to prune the larval dendrites of these sensory neurons [17,18]. In this context, pruning requires Death-associated APAF1-related killer (DARK), the fly homolog of APAF-1 that is necessary for activating caspases *via* the apoptosome complex. Moreover, overexpression of p35, the baculovirus inhibitor of effector caspases, also inhibits dendritic pruning, suggesting that effector caspases are also important for dendrite pruning during metamorphosis [18]. Importantly, unlike in the context of cell death, caspase activity is spatially restricted to the dendrites of neurons undergoing pruning [17,18]. Effector caspases have also been implicated in the large-scale pruning of axons of the retinal ganglion cells (RGC) that occurs in the midbrain of mammals. During embryonic development, RGC extend their axons in the superior colliculus but largely overshoot their targets. Neuronal activity promotes the elimination of these inappropriate extensions during the first postnatal week in order to refine the eye-specific projection map [19,20]. In mice deficient in caspase-3, −6, or the caspase-3 target calpastatin, RGC axon projections remain outside of their targeted area in the superior colliculus beyond this refinement period [21,22].

The role of caspases in axon pruning has also been studied in the context of axon degeneration induced by neurotrophic factor deprivation in sensory and sympathetic neurons (Fig. 1). During development, neurotrophin-responsive neurons extend their axons to innervate target regions producing neurotrophins such as Neuronal Growth Factor (NGF). *In vitro*, depletion of NGF induces the apoptotic death of Dorsal Root Ganglia (DRG) and Superior Cervical Ganglia (SCG) neurons [23,24]. However, deprivation of NGF from only the distal axons of these neurons cultivated in compartmentalized chambers (referred to as “local NGF deprivation”), promotes axon pruning without causing neuronal death [25]. The involvement of caspases in axon pruning, initially reported using the caspases inhibitors zVEID and zDEVD [26], was confirmed with the observation that axons of DRG and SCG derived from caspase-3, caspase-6 or caspase-9-deficient mice are protected against axonal NGF deprivation [21,27]. Although caspases are present in

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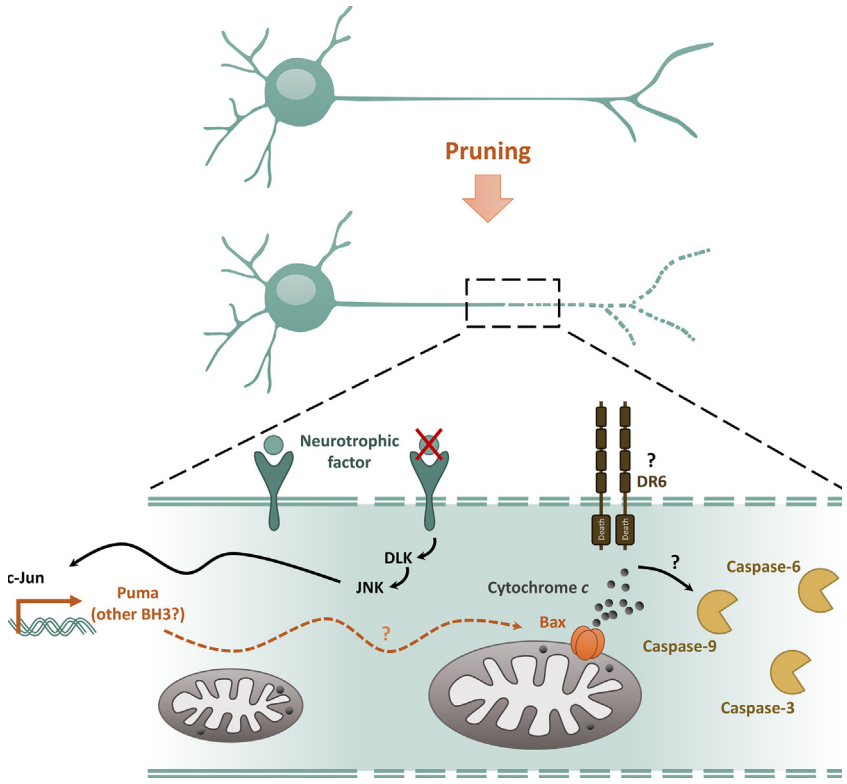

Fig. 1. Non apoptotic role of caspases in axon and dendrite pruning. In absence of neurotrophic factors (i.e. NGF), activation of the JNK pathway by DLK promotes the transcriptional upregulation of Puma, a pro-apoptotic BH3-only members of the Bcl-2 family. This ultimately results in the activation of Bax, mitochondrial depolarization and caspases, leading to local degeneration of the axon. Additionally, the death receptor DR6 might play a role in local activation of the caspase cascade.

both axons and cell bodies [28–31], caspase activation is spatially restricted to the axonal compartment where cleaved caspase-3 and caspase-6 can be detected during pruning [21,27].

The modalities and sequence of caspase activation during axon pruning is not yet well understood. Since addition of the transcription inhibitor Actinomycin D in the soma compartment preserves axons from degeneration, caspase activation during pruning is thought to be regulated by gene transcription [32]. The transcription factor c-Jun was found to be phosphorylated in a JNK- and DLK-dependent manner in the cell bodies of neurons locally deprived of NGF [28,33]. Moreover, chemical inhibition of the MAP kinases p38, JNK or DLK in the axonal compartment prevents axonal pruning, suggesting that these kinases are activated locally at the site of NGF deprivation [32–34]. This signalling pathway most likely triggers the intrinsic mitochondrial pathway of apoptosis as JNK/c-Jun has previously been involved in transcriptional upregulation of the BH3-only proteins Hrk, Bim and Puma that activate the pro-apoptotic members of the Bcl-2 family [23]. Consistent with this model, anti-apoptotic Bcl-2 family members Bcl-xl and Bcl-w protect against axonal degeneration while the BH3-only protein Puma and pro-apoptotic Bcl-2 family member Bax are required for axon pruning [26,27,34–36]. Moreover, cytochrome *c* is released from mitochondria in response to local NGF withdrawal and genetic analysis suggests that caspase-6 activation occurs downstream of caspase-3, caspase-9 and Bax engagement [27]. However, the adaptor APAF-1, is dispensable for axon pruning [27], raising the possibility that caspase activation during axon pruning occurs independently of the apoptosome (Fig. 1).

In mammals, a role for the death receptor DR6 has been implicated in pruning. Genetic studies suggest that DR6 regulates dendritic spine density in cortical neurons in young mice [37,38] and also RGC axon pruning in the superior colliculus [26]. However, the modalities of DR6 activation and its involvement in pruning are still unclear. The extracellular domain of DR6 was initially reported to bind the cleaved amino terminal fragment of amyloid precursor protein (APP), the precursor of Amyloid β in Alzheimer's disease, but the authors subsequently reported that DR6 was rather binding to the extracellular domain 2 of APP [26,39,40]. Interestingly, RGC from APP-deficient mice present pruning defects similar to the DR6-deficient mice and epistasis analysis revealed that RGC pruning defect in DR6-deficient mice was not enhanced by loss of APP, suggesting that APP and DR6 function in the same pathway [40]. Although, in other systems, DR6 was shown to recruit the adaptor protein TRADD and activate Bax in a caspase-8-independent manner [41,42], there have not been any reports of the mechanism by which DR6 may activate caspases in the context of axon pruning. Moreover, the modalities regulating APP-DR6 interaction and the consequences of this interaction during pruning remain to be resolved.

4. Neurite outgrowth and arborization (branching, axonal guidance)

Axon outgrowth, pathfinding and arborization are essential during development in order to establish functional neuronal connectivity. Guidance proteins play a crucial role in this process and mutations in guidance molecules or their receptors have been associated with several neurological disorders including congenital axon guidance disorders, autism and neurodegenerative diseases [43]. Guidance proteins are either secreted or membrane bound factors which are recognized by specific receptors on the surface of neuronal growth cones. They act as attractant or repellent to guide growing axons to their specific target regions during development [43]. Their action is localized, as growth cones of severed axons are still repelled or attracted by these factors [44]. Caspases were first reported to participate in neurite outgrowth and guidance in

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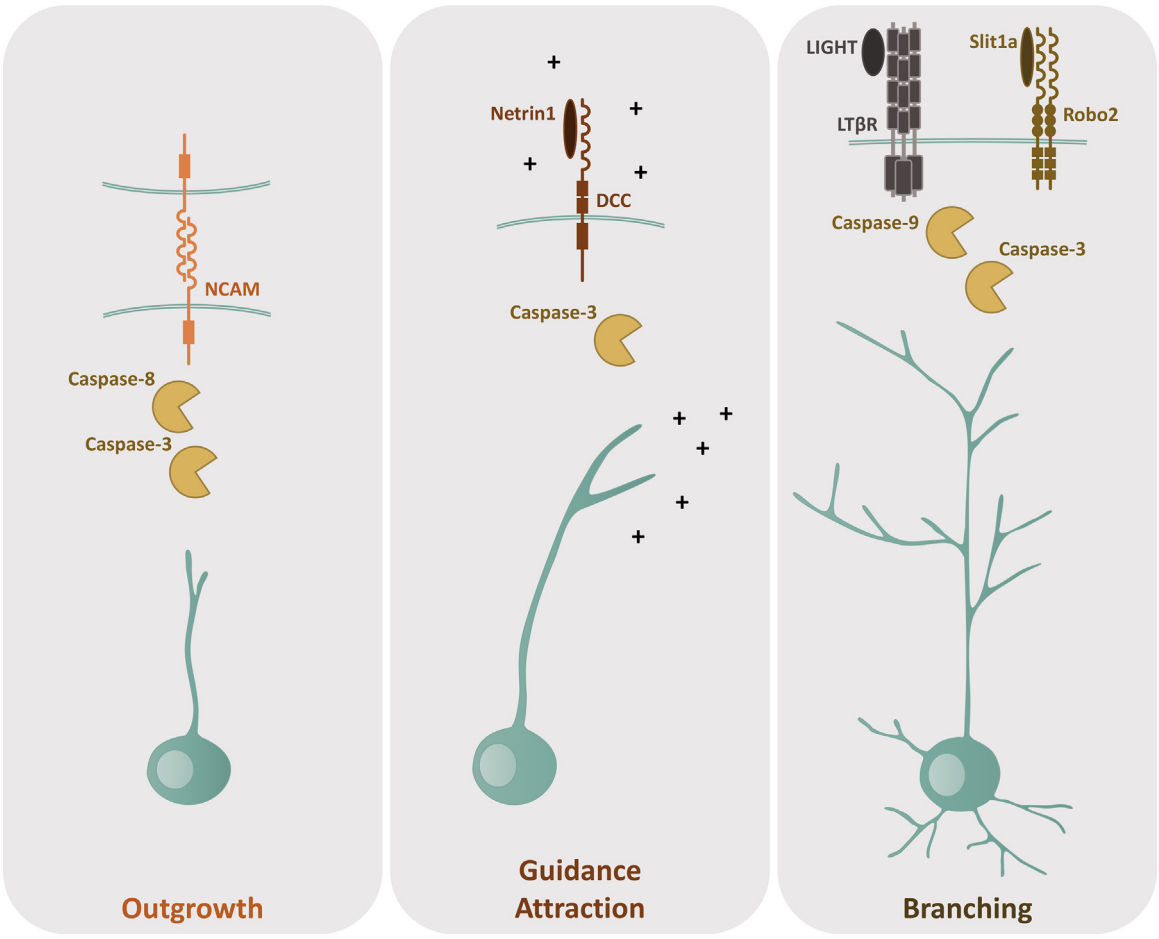

Fig. 2. Non apoptotic role of caspases in neurite outgrowth, axon guidance and branching. Caspases are activated in response to various receptors implicated in neurite outgrowth (NCAM), guidance (DCC in response to its ligand Netrin1- with its chemoattractive ability depicted as +) and branching (lymphotoxin beta receptor (LT-βR) when bound to its ligand LIGHT and Robo2 stimulated by its ligand Slit1a).

the context of Netrin-1 chemoattractant's effect on Xenopus retinal ganglion cells (Fig. 2) [45]. Netrin-1 is a secreted guidance protein which, upon binding to its receptors DCC and UNC5, promotes growth cone attraction or repulsion, respectively [46]. *In vitro*, caspase-3 is rapidly activated in growth cones of retinal neurons stimulated with Netrin-1 and participates in the Netrin-1-mediated attractive chemotrophic effect. Mouse hippocampal neurons also have been reported to express active caspase-3 in their growth cone *in vitro*, and NCAM clustering triggers neurite outgrowth in a caspase-3/8-dependent manner [47]. In addition, developing olfactory bulb of rodents activate caspase-3 in a caspase-9-dependent manner. Interestingly, deficiency in APAF-1 and caspase-9 does not affect the number of olfactory neurons, it rather results in aberrant projection and axon trajectories in olfactory sensory neurons [48].

Slit constitute another family of guidance molecules that are able to activate caspases upon binding to their Robo receptors. Similar to many guidance proteins, the outcome of Slit-Robo signalling is highly dependent on the context. It has been reported to have both attractive and repulsive effect on growing axons, as well as both permissive and repressive effect on arborization during development [49–51]. *In vivo*, Slit1a and its receptor Robo2 stimulate local caspase-3 activity in zebrafish embryonic retinal ganglion cells, in absence of neuronal death (Fig. 2). In this context, caspase-3 activity is restricted spatially – at branching points but not in dendrites or cell bodies – and temporally – over a short period of time when arborization is most dynamic. Time-lapse imaging revealed that caspase-3 is activated upon branch formation and promotes both branch formation and retraction. Further, Slit1a, Robo2, caspase-9 and caspase-3 cooperate in a pathway required for maintaining newly formed branch tips and presynaptic terminal in a dynamic, unstable phase [52]. A Bax/Bak/caspase pathway seems to be also involved in controlling axonal branching at postnatal stages. Skilled movement acquisition during early postnatal development requires motor circuit reorganization through refinement of corticospinal axons connectivity. A recent study found caspase-3 to be activated in a Bax/Bak-dependent manner in axons of corticospinal neurons in the spinal cord of neonatal mice. Early postnatal inactivation of Bax/Bak in motor cortex results in increased axonal branches in the spine of these animals once they reach adult age. As a result, refinement of connectivity is lost and animals fail to acquire fine voluntary movements [53]. Although neuronal activity is known to be a prerequisite for branch formation [54], the upstream signalling pathways responsible for caspase activation in this context is currently unknown.

To the best of our knowledge, there is currently no report of activation of non-apoptotic caspase function in response to other type of guidance proteins, including Semaphorins, Ephrins and Repulsive Guidance Molecules (RGMs) in neurons. However, several members of these proteins or their receptors have been reported to induce caspase activation and apoptosis. For instance, Semaphorin 3A induces caspase-dependent cell death in sympathetic neurons through binding to its receptors PlexinA3 and Neuropilin-1 [55,56]. Additionally, overexpression of Neogenin, the receptor for RGMs, has been shown to induce apoptosis in neural tube of chick embryos and immortalized neuroblasts [57]. Overexpression of Ephrin-A5 in neurons expressing its receptor EphA7

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induces caspase-3 activation and apoptosis in cortical progenitors [58]. Therefore, it is possible that in a context of local activation, these guidance molecules trigger caspase activation to promote their repulsive or attractive effect. Differential outcome of local *versus* global receptor stimulation has been observed in the case of the TNF receptor superfamily member lymphotoxin beta recetor (LT-βR). LIGHT stimulate cell death upon binding to its receptor LT-βR in non-neuronal and motoneuron cultures [59,60]. Conversely, when locally applied to the axons of motoneurons, LIGHT promotes axonal outgrowth and branching [60]. Moreover, the outgrowth and branching promoting effect of LIGHT can be inhibited by the use of the caspase-9 inhibitor LEHD. Rather surprisingly however, the DEVD inhibitor has no effect in the same experimental conditions [60].

Axonal injury often permits neurons to survive and is sometimes associated with sprouting at the axon tip, allowing formation of a growth cone and axon extension. Axon segments which are separated from their cell bodies are able to regrow, suggesting that axonal regeneration most likely is a local process [61]. Although inhibition of caspases has been reported to promote regeneration by inhibiting apoptosis [62–64], there is evidence that axon stabilization and axon regeneration are antagonistic phenomenon [65]. Rather counterintuitively, caspases have been reported to promote regenerative neurite outgrowth in response to injury. For instance, caspase-3 inhibition reduces growth cone formation and axonal regeneration following *in vitro* axotomy in dorsal root ganglion cells from embryonic and postnatal rats [66]. In *C. elegans*, axonal outgrowth in response to *in vivo* axotomy of motor and mechanosensory neurons is reduced in the APAF-1 homolog CED-4 and in the caspase homolog CED-3 inactive mutants [67]. Also, upon sciatic nerve crush in mice, LIGHT expression is stimulated in B lymphocytes and LIGHT is involved in neuromuscular junction regeneration. However, it remains unknown whether caspases are required for this regenerative function of LIGHT as observed during LIGHT-induced outgrowth and branching [60].

Exactly how caspases are activated in the context of axonal outgrowth and arborization and how they promote outgrowth and arborization is largely unknown. A few guidance receptors have been reported to recruit caspases, including the EphrinA receptors EphA7 and EphA4 which are able to recruit caspase-8 [68] and the Netrin-1 receptor DCC which is able to interact with caspase-3 and caspase-9 [69]. However, NCAM is the only receptor that has been shown to recruit caspase-8 in the context of neurite outgrowth [47]. Although members of the UNC5 receptors family possess a death domain in their cytoplasmic portion [70], it is currently unknown if this domain play any role in caspase activation.

5. Long-term depression and synapse plasticity

Synaptic plasticity plays a major role in developmental maturation of neuronal circuits as well as in experience-dependent remodelling of neuronal circuits. Durable synapse modification in response to neuronal stimulation can result in enhanced or reduced synaptic strength and is known as Long-Term Potentiation (LTP) or Long-Term Depression (LTD), respectively [71]. Activity-dependent change in synaptic strength is largely recognized as a mechanism associated with spatial learning and memory in the hippocampus, fear memory in the amygdala, task memory in the cortex and learning in the cerebellum [72]. The best characterized form of LTP and LTD is experienced by excitatory synapses in response to L-glutamate. Glutamate binds notably to N-methyl-D-aspartate receptor (NMDA) receptors (NMDARs), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors (AMPARs) and metabotropic glutamate receptors (mGluRs) and triggers an increase in calcium in the stimulated spine. The outcome of calcium entry is a gain in AMPAR expression at the synapses experiencing LTP [73] while AMPA receptors are internalized at synapses undergoing LTD [74]. Modulation of synaptic strength during LTP and LTD is also associated with remodelling of dendritic spine size and density which are increased during LTP and reduced during LTD. Similar to synaptic strength, spine shrinkage during activity-dependent LTD requires NMDAR and calcium-calcineurin signalling [75,76].

The use of caspase inhibitors *in vivo* has uncovered a functional role for caspases in long-term spatial memory formation [77], in avoidance learning [78] and in auditory memory formation [79]. Consistently with a role for caspases in memory formation, active caspase can be detected in the hippocampus [77] and cortex [78] of mice. As would be anticipated, caspase activation seems to be transient and restricted to postsynaptic structures in these contexts [79,80]. Mechanistically, NMDAR-LTD is inhibited in hippocampal neurons from caspase-3-deficient mice, suggesting that this effector caspase plays an active role in NMDAR-dependent LTD [81] and caspase-3 is sufficient to reduce synaptic strength [80]. The role of caspases in synapse plasticity might not be restricted to excitatory glutamatergic synapses as there is also genetic evidence that CED-4/APAF-1 participates in inhibitory GABAergic synapse elimination in worms [82]. Although caspase-3 deficiency has been shown to have no impact on high frequency stimulation-induced LTP in mice hippocampal neurons [81], it is possible that caspases regulate LTP in different contexts. Long exposure to caspase inhibitors have been reported to inhibit LTP in rat hippocampal neurons [83] but also in snail parietal neurons [84], reports that have not been confirmed genetically. Contradictive studies have however suggested that caspases could negatively regulate LTP in hippocampal neurons, either directly using inhibitors in the context of high-frequency stimulation [85] or in response to LTP antagonists such as amyloid β [86] or aluminium [87].

Caspase-3-dependent control of synaptic plasticity relies on Bax-mediated mitochondrial membrane permeabilization in order to promote NMDAR-LTD (Fig. 3) [80,81] as well as the amyloid β-mediated inhibition of LTP, which is also NMDAR-dependent [88]. Similar to apoptotic triggers [89], NMDA induces Bad dephosphorylation in a calcineurin-dependent manner to promote its activation and relocation to mitochondria in hippocampal slices [80]. Calcium influx through NMDAR, which is essential for LTP and LTD, therefore also triggers a signalling pathway leading to caspase-3 activation to promote NMDAR-LTD or inhibition of LTP. Consistent with a transient activation of caspase-3 in response to synaptic activity, activated Bad and Bax, and also released cytosolic cytochrome *c*, are similarly short lived in this context [80]. The transitory nature of this pathway may be required to maintain caspase-3 activity at a low level in order to prevent neurons from undergoing apoptosis [80] and it is possible that neurological synapses activate a negative feedback loop to restrain caspase-3 activation in these situations. In other cellular context such as immunological synapse between activated dendritic cells and T lymphocytes, a similar glutamate-NMDAR-calcium pathway triggers sustained caspase-3 activation and apoptosis [90].

Several possible roles for effector caspases have been suggested in the context of synaptic plasticity. While the outcome of LTP/LTD converges on controlling the expression of AMPAR at the surface of synapses, there is evidence to support a role of caspase-3 in the regulation of AMPAR distribution. Deficiency in the pro-apoptotic proteins that have been implicated in LTD, including, Bad, Bax and caspase-3, result in impairment of NMDAR-induced AMPAR internalisation in hippocampal neurons [80,81]. How caspase-3 could mediate this effect is not exactly known. Han and colleagues have identified the synaptic protein Gap43 as a caspase-3 substrate for which its caspase-dependent cleavage seems to be required for LTD and AMPAR internalisation in hippocampal neurons [91]. Caspase-3 could also promote AMPAR internalisation *via* increased activation of its substrate calcineurin [92], which is required for

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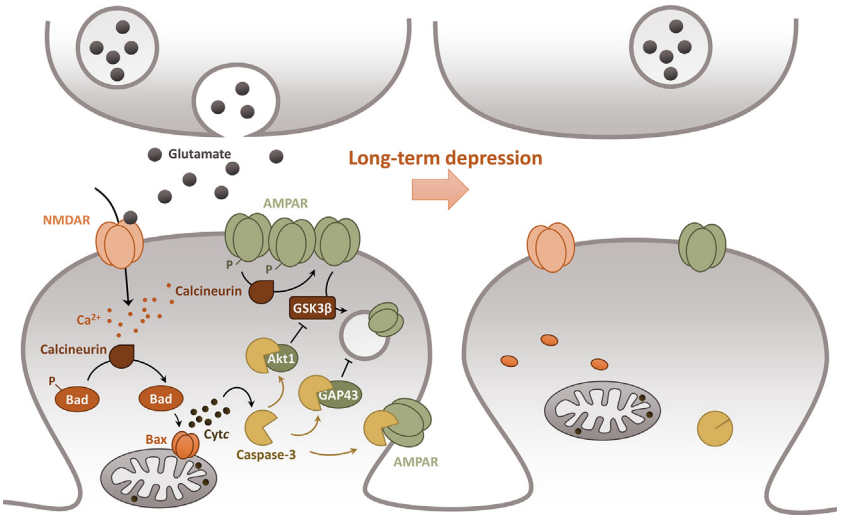

Fig. 3. Non apoptotic role of caspases in long-term depression (LTD). Caspases participate in synaptic plasticity of glutamatergic synapses by promoting the downregulation of AMPA receptor expression from the synaptic surface. In response to NMDA receptor-induced calcium entry, calcineurin dephosphorylates Bad, thereby stimulating Bax-induced mitochondrial depolarization and caspase-3 activation. Possible roles for caspase-3 in LTD include direct role in AMPAR endocytosis either by activation of GSK3β via proteolysis of Akt1, or by GAP43 cleavage. Alternatively, caspase-3 may directly process and inactivate AMPAR.

NMDAR-induced endocytosis of AMPAR during LTD [74]. As an alternative mechanism to caspase-mediated AMPAR internalisation, it has been suggested that caspases directly cleave AMPAR subunits as this has been observed in apoptotic hippocampal neurons in response to amyloid β, staurosporine or starvation [93,94]. Another substrate of caspase-3 recognized to influence LTD and LTP is Akt1. During apoptosis, caspase-mediated cleavage of Akt1 results in loss of Akt1 kinase activity [95]. In the context of synaptic plasticity, cleavage of Akt1 is required for NMDAR-LTD as well as for amyloid β-mediated repression of LTP [81,86]. The PI3K-Akt1 pathway is known to antagonize LTD and to repress the activity of GSK3β [96]. Because GSK3β is activated and required for NMDAR-LTD [96] as well for amyloid β-mediated inhibition of LTP [86], it is possible that caspase-3 promotes LTD and suppress LTP *via* repression of Akt1 and promotion of GSK3β activity (Fig. 3).

Dendritic spine density remodelling that occurs during LTP and LTD [75,76] is another aspect of synaptic plasticity involving caspase-3 activity [97]. In response to neuronal activity, the neurotrophin BDNF is secreted as a precursor (proBDNF), which binds the neurotrophin receptor p75NTR. ProBDNF is processed by extracellular proteases to its mature form (mBDNF), which binds the TrkB receptor [98]. BDNF has been reported to play a role in hippocampal memory both in humans and in rodents [99]. ProBDNF and mBDNF have opposite effects on synaptic strength and synaptic density remodelling. Mature BDNF increases spine density and promotes LTP in a TrkB-dependent manner [100,101]. Conversely, proBDNF has been shown to promote NMDAR-LTD though its receptor p75NTR, which localizes at synapses [102]; proBDNF can also decrease dendrite arbor complexity and spine density [97,103]. ProBDNF signalling triggers the mitochondrial pathway and caspase-3 activation that is required for its ability to promote the reduction in spine density [97]. Although the role of caspase-3 in proBDNF-induced LTD has not been directly assessed, these combined studies strongly support a role for caspases in synaptic plasticity and memory formation.

6. How is non-apoptotic caspase activity confined and restricted in neurons?

As illustrated in the case of pruning, dendrite branches formation and synaptic plasticity, non-apoptotic caspase function is often restricted in time and space whether to dendrites during pruning, branching points during arborization or postsynaptic buttons during LTD. Localized activation of caspase in living neurons contrasts with global caspase activity observed during apoptosis and can only be achieved if regulatory mechanisms limit caspase activity in order to prevent the loss of neurons that would occur in response to widespread caspase activation [5].

Several mechanisms have been described to restrict caspase function in neurons (Fig. 4). The best characterized regulators of caspase function in neurons belongs to the family of Inhibitor of Apoptosis Proteins (IAP). IAPs are identified by the presence of Baculovirus IAP Repeat (BIR) domains which mediate protein–protein interactions. Several IAPs, including those involved in caspase regulation, also possess a Really Interesting New Gene (RING) domain that confers IAPs an E3 ligase activity [104]. IAPs interfere with caspase function either by direct binding or by promoting their ubiquitination and occasionally their degradation. For example, Drosophila DIAP1 restricts both the initiator caspase DRONC, either in its monomeric inactive form or as part of the apoptosome [105–107], and the activated effector caspase death related ICE-like caspase (DRICE) [108–110], through ubiquitination. DIAP2, on the other hand, only ubiquitinates activated DRICE [111,112]. Protein ubiquitination is often associated with proteasomal degradation. However, degradation of caspases is rarely observed as a consequence of ubiquitination by DIAPs. DRONC targeting to the proteasome pathway only seems to occur in the context of the apoptosome following ubiquitination by DIAP1 [113]. Otherwise, DIAP1 or DIAP2 rather promote non-degradative ubiquitination and inactivation of DRICE or monomeric DRONC [105,109,111]. Mammals express several IAPs, of which only X-linked inhibitor of apoptosis (XIAP) can efficiently interfere with a specific set of caspases, namely, caspase-9, −3 and −7 [114]. Unlike DIAP1 and DIAP2, XIAP does not seem to target caspases for ubiquitination but rather inhibits caspases activity by direct binding, obstructing the catalytic site of caspase-3 and −7 or the homo-dimerization domain of caspase-9 [115–118].

The efficiency of IAPs at preventing caspase activation and apoptosis in different mammalian cells is variable. In neurons however, IAPs play a major role in keeping caspases inactive and protecting neurons from death [30,119,120]. Interestingly, the increased effectiveness of XIAP in restricting caspases in neurons is not because of high XIAP expression but rather due to low levels of the adaptor APAF-1 in neurons, which limits the extent of caspase activation

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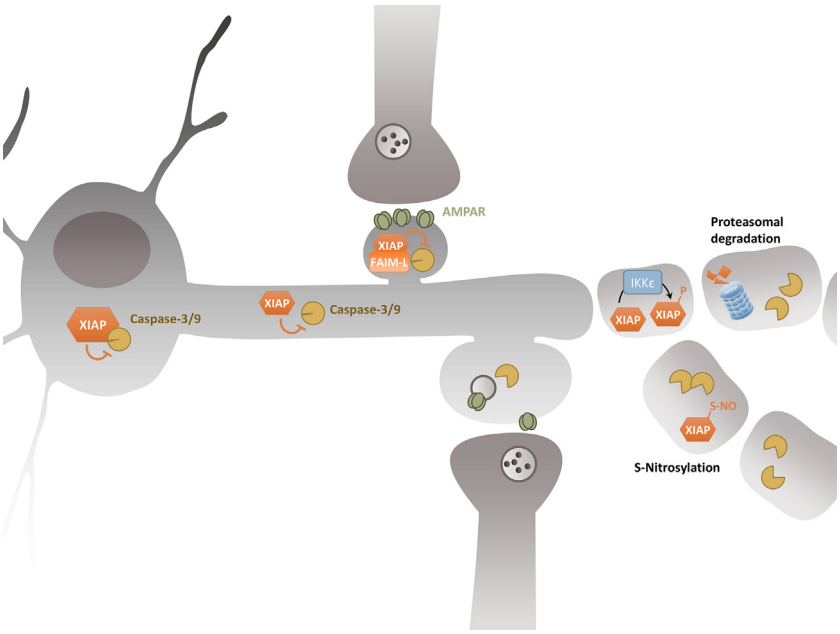

Fig. 4. XIAP restricts caspase activity during non apoptotic contexts. Caspases-3, −7 and −9 are kept inactivated by XIAP in neurons therefore restricting caspase activation where and when it is needed. Proposed mechanisms for releasing caspases from XIAP control include proteasomal degradation of XIAP stimulated by IKKε and XIAP inactivation by S-nitrosylation.

allowing for strict control by XIAP [121]. IAPs also protect the cell bodies when local caspase activity is triggered in the dendrites, thus keeping caspase activity localized during dendrite elimination [120]. XIAP was also shown to restrict caspase-3 activation and axon degeneration in the NGF deprivation model of axon pruning *in vitro* [27]. Consistent with this function of XIAP, neurons innervating the skin of mice deficient in XIAP have reduced axonal length, while overexpression of XIAP prevents pruning [30]. Finally, XIAP was shown to restrict AMPA receptor internalisation and caspase-3 activation during long-term depression [81,122,123].

Interestingly, one mechanism that allows for the restricted caspase activation is by degradation of IAPs in localized region. For example, caspase-3 activation during pruning of dendrites from sensory neurons during fly metamorphosis requires degradation of DIAP1 by the proteasome [17]. XIAP stability was recently shown to be enhanced by a brain-specific isoform of Fas Apoptotic Inhibitory Molecule (FAIM-L). Endogenous FAIM-L notably interferes with AMPA receptor internalisation in the context of LTD, while overexpression of FAIM-L is able to stabilize XIAP, inhibit caspase-3 activation and prevent LTD as well as pruning [122].

These observations suggest that IAPs function is tightly regulated in neurons. IAPs are stabilized when and where caspase function needs to be repressed, and conversely, IAPs are inactivated when and where limited caspase activity is required. Although proteasomal degradation of XIAP and DIAP1 has been shown to be required for effector caspases activation during pruning [17], very little is known about the mechanisms controlling XIAP or DIAP1 to allow for local caspase activity under physiological conditions in neurons. In the context of apoptosis, IAPs activity and stability is regulated by their inhibitory proteins, which in mammals include the protease Omi/HtrA2 and the IAP antagonist Smac/DIABLO, and in flies, Grim, Hid, Reaper and Sickle. These mitochondrial proteins are characterized by the presence of a conserved IAP-binding motif (IBM), necessary for binding and antagonizing IAPs [124]. In addition, the septin ARTS (Apoptosis-Related protein in the TGF-β Signaling pathway) was found to antagonize XIAP through a different mechanism [125]. ARTS, which also localizes at mitochondria, binds XIAP via a different motif and recruits the E3 ligase Siah1 to XIAP. Ubiquitination of XIAP by Siah1 results in XIAP degradation and promotion of apoptosis [126]. The role of these IAP antagonists in the activation of non-apoptotic function of caspases remains obscure. Interestingly, Hid has been implicated in non-apoptotic activation of caspases in neurons as tight control of Hid levels during larval remodelling of class IV sensory neurons is required to attain an balanced degree of dendritic growth and retraction [127].

Other modifications of XIAP or DIAP1 have also been shown to alleviate their inhibition on caspase activity. For instance, XIAP and DIAP1 can be phosphorylated by the IKKε kinase. In Drosophila, inactivation of IκB kinase ε (IKKε) suppress Reaper-induced cell death, suggesting that IKKε is activated downstream of the IAP antagonist [128]. Both mammalian and fly IKKε interact with, phosphorylate and mediate proteasomal degradation of XIAP or DIAP1 respectively, therefore promoting caspase-3/DRONC activation [128,129]. Interestingly, fly IKKε was suggested to affect the non-apoptotic function of caspases during development rather than developmental cell death [128]. Further studies will be required to determine if IKKε is also activated and recruited to XIAP in response to release of IAP antagonists in the cytosol and if this kinase participate in caspase activation in neuronal physiology. Another posttranslational modification that can promote the inactivation of XIAP is S-nitrosylation. S-nitrosylation of XIAP impairs its ability to inhibit caspase-3. It is however unclear how S-nitrosylation affects XIAP function as it was shown to either not affect or reduce XIAP E3 ligase function [130,131]. Functionally, XIAP S-nitrosylation reduces XIAP capacity to inactivate caspase-3 in response to NMDA-induced excitotoxicity [131], suggesting that local S-nitrosylation of XIAP might be involved in restricted caspase activation during long-term depression. Consistently, Alzheimer's disease which is associated with increase LTD, synaptic loss and synaptic caspase-3 activity [86,132], is also associated with increased S-nitrosylated XIAP [131].

7. Perspectives for the future

Nearly 25 years after the discovery of caspase function during apoptosis [133], the most unexpected aspects of caspase function that have emerged is the finding that many of the same caspases that can induce cell death are also activated in physiological con-

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texts of neuronal pruning, axon guidance, and synaptic plasticity. While the function of caspases in these non-apoptotic situations in the brain is now firmly established, several important question remain unanswered. Exactly how are caspases activated in these physiological contexts? Are the mechanisms the same as seen during apoptosis? Are these differences in how caspases are activated during dendritic or axonal pruning, or axon guidance, or synaptic plasticity? How is caspase activity restricted, both spatially and temporally, in these situations so as to avoid apoptosis? While the importance of the XIAP in restricting caspases in several of these situations has become clear, are there other mechanisms? Most importantly, do these caspase restraining mechanisms in non-apoptotic physiological contexts become less effective and ultimately contribute to the neuronal loss in the pathological contexts of neurodegeneration?

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