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Calcium dysregulation and neuroinflammation: Discrete and integrated mechanisms for age-related synaptic dysfunction

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Abstract

Some of the best biomarkers of age-related cognitive decline are closely linked to synaptic function and plasticity. This review highlights several age-related synaptic alterations as they relate to Ca^{2+} dyshomeostasis, through elevation of intracellular Ca^{2+} , and neuroinflammation, through production of pro-inflammatory cytokines including interleukin-1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α). Though distinct in many ways, Ca^{2+} and neuroinflammatory signaling mechanisms exhibit extensive cross-talk and bidirectional interactions. For instance, cytokine production in glial cells is strongly dependent on the Ca^{2+} dependent protein phosphatase calcineurin, which shows elevated activity in animal models of aging and disease. In turn, pro-inflammatory cytokines, such as TNF, can augment the expression/activity of L-type voltage sensitive Ca^{2+} channels in neurons, leading to Ca^{2+} dysregulation, hyperactive calcineurin activity, and synaptic depression. Thus, in addition to discussing unique contributions of Ca^{2+} dyshomeostasis and neuroinflammation, this review emphasizes how these processes interact to hasten age-related synaptic changes.

Keywords

Aging; plasticity; synapse; Ca^{2+} ; neuroinflammation; cytokine

1. Introduction

Severe deficits in cognition (*i.e.* dementia) are not inevitable outcomes of brain aging, but are more symptomatic of neurodegenerative diseases such as Alzheimer's disease (AD).

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Brain aging is generally associated with mild impairments in cognitive function, especially in situations or tasks that depend on the hippocampus. Declarative (semantic/episodic) memory undergoes a normal age-related decline (Fleischman et al., 2004; Margolis and Scialfa, 1984; Ronnlund et al., 2005) that is structurally linked to the hippocampus and associated regions (Leritz et al., 2006). The connections of neural circuits within the hippocampus change in strength with behavioral inputs to store and retrieve memories, but these abilities shift with age, tending to favor reductions in synaptic strength and more rapid forgetting (for review, see Burke and Barnes, 2010; Foster, 2012).

This review highlights evidence linking age-related cognitive decline to changes in hippocampal synaptic function and how these changes can arise specifically from the dysregulation of Ca^{2+} and neuroinflammatory signaling mechanisms. Though decades old, the Ca^{2+} and neuroinflammation hypotheses remain viable and highly useful frameworks for guiding experimental gerontology research and for developing nootropics and other treatments for improving quality-of-life in the elderly. Moreover, increasing evidence suggests that Ca^{2+} and neuroinflammatory signaling mechanisms interact extensively, with distinct outcomes in different neural cell types. These observations should stimulate new avenues of research and provide new opportunities to develop and test more integrative theories of brain aging.

2. Synaptic plasticity

2.1 Long-term potentiation and long-term depression

Most synapses in mammals rapidly adjust their signaling properties in response to changes in cellular activity, such as sensory inputs from environmental stimuli. This plasticity is absolutely necessary for establishing appropriate synaptic connections during neural development and is widely regarded as a physiological mechanism for learning and memory (for review, see Bailey et al., 2000). Activity-dependent strengthening of synaptic connections was envisioned more than 60 years ago by Donald Hebb, who proposed that the presynaptic neuron's repeated firing could exert lasting effects in the postsynaptic neuron and the whole synapse, resulting in increased synaptic stability (Hebb, 1949).

The hippocampus is widely studied with respect to synaptic function and plasticity because of its critical involvement in learning/memory, its discrete cytoarchitecture, and its vulnerability to aging, injury, and neurodegenerative disease. Moreover, hippocampal slices from isolated tissue are relatively easy to prepare, retain much of their basic circuitry, and remain viable for hours. Two well-known and well-characterized types of synaptic plasticity contribute to activity-dependent adaptation of neuronal circuits in the hippocampus—long-term potentiation (LTP) and long-term depression (LTD). LTP is the strengthening of synapses, and typically requires high frequency activation of presynaptic afferents, while LTD is the weakening of synapses usually resulting from lower levels of presynaptic activation.

Bidirectional modulation of synaptic efficacy provides an ideal mechanism for learning and memory. LTP/LTD, like memory, are long-lasting, enduring for hours in acute slices or for days in intact animals (Barrionuevo and Brown, 1983; Bliss and Lomo, 1973; Morris, 1989; Dudek and Bear, 1992; Mulkey and Malenka, 1992; O'Dell and Kandel, 1994). Learning and LTP/LTD are also input specific, associative, and reversible (Levy and Steward, 1979; McNaughton et al., 1978; Mulkey and Malenka, 1992). Abundant experimental evidence shows that synaptic plasticity and learning/memory share the same fundamental mechanisms. For instance, blockade of hippocampal N-methyl-D-aspartic acid receptors (NMDARs) impairs learning in rodents when given prior to training (Morris, 1989; Morris et al., 1986), but enhances memory when given after training on hippocampal dependent

tasks (Norris and Foster, 1999; Villarreal et al., 2002). Thus, like LTP and LTD, learning and forgetting each depend critically on NMDARs (discussed below). Learning and synaptic plasticity also occlude one another under certain conditions (Barnes et al., 1994; Moser et al., 1998; Rioult-Pedotti et al., 2000). Moreover, acquisition of spatial learning tasks and/or exposure to enriched environments is associated with increased synaptic responses in the hippocampus, similar to LTP (Foster et al., 1996; Moser et al., 1993; Sharp et al., 1985). Because of these observations and many others, changes in hippocampal synaptic plasticity and function have received much attention as a neurologic mechanism for impaired cognition in animal models of aging, injury, and disease.

At glutamatergic synapses of the hippocampus, the best characterized forms of LTP and LTD involve two key receptor subtypes: α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPA) and NMDARs. Other forms of LTP/LTD that depend on voltage-sensitive Ca^{2+} channels (VSCCs), metabotropic glutamate receptors, and other mechanisms have also been described. For a review of NMDAR-independent forms of LTP and LTD, see Citri and Malenka (2008) and Johnston et al. (1992). AMPARs and NMDARs are both subtypes of glutamate receptors, permeable to Na^+ and K^+ . A subgroup of AMPARs and all NMDARs are also permeable to Ca^{2+} . When the postsynaptic membrane is hyperpolarized to near resting values, NMDARs are unable to conduct current due to blockade of its channel pore with Mg^{2+} . Local membrane depolarizations, triggered primarily by AMPAR currents, expel Mg^{2+} from the NMDAR channel, and permit Ca^{2+} entry into the postsynaptic cell. LTP and LTD both require Ca^{2+} influx through NMDARs, though to differing levels. LTP generally necessitates extensive membrane depolarization and a large surge in postsynaptic Ca^{2+} , while LTD occurs in response to more modest depolarizations and smaller Ca^{2+} influxes. Differing Ca^{2+} signals recruit divergent biochemical cascades. Protein kinases, especially Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), promote LTP induction and maintenance by increasing the activity and/or levels of glutamate receptors in the plasma membrane through direct actions on receptor proteins, cytoskeletal elements, or other accessory proteins, or transcriptional regulators, such as the cAMP response element binding protein (CREB) (Josselyn and Nguyen, 2005; Malinow and Malenka, 2002). For LTD, smaller elevations in Ca^{2+} favor the dephosphorylation of many of the same substrates through phosphatase activation, namely the Ca^{2+} /calmodulin dependent protein phosphatase, calcineurin (CN), and protein phosphatase 1 (PP1), which is indirectly stimulated by CN activity. The relative balance in activity of protein kinases and phosphatases not only regulates the magnitude and duration of synaptic changes, but also helps maintain the functional status of the synapse under basal conditions. For comprehensive reviews on the molecular mechanisms of LTP and LTD see Citri and Malenka (2008; Malenka, 2003; Malenka and Bear, 2004). For illustration of these processes, refer to Figure 1.

2.2 Aging changes in synaptic plasticity

It has been more than 30 years since synaptic plasticity alterations were first reported in the aged hippocampus (Barnes, 1979; Landfield and Lynch, 1977). Early studies reported that aged animals could express hippocampal synaptic LTP at levels comparable to that seen in younger animals; however, LTP in aged animals was labile and tended to decay much more rapidly. Importantly, this decay was shown to correlate very well to forgetting on hippocampal-dependent memory tasks (Barnes, 1979; Barnes and McNaughton, 1985). While studies have shown that LTP induction and magnitude remain intact during aging, especially with intense stimulation protocols (Chapman et al., 2010; Deupree et al., 1991; Kumar et al., 2007; Landfield et al., 1978; Moore et al., 1993; Norris et al., 1996), others have reported aging-related deficits, including an increased induction threshold (Burgdorf et al., 2011; Deupree et al., 1993; Moore et al., 1993). While these differences may be

attributable to methodological variation, such as different stimulation protocols, different ion concentrations in buffers, or different animal strains, the general consensus is that there is an LTP deficit with age, particularly in regard to threshold of induction and maintenance.

The first investigations of LTD during aging were conducted in the mid-1990s (Foster and Norris, 1997; Norris et al., 1996). These studies showed that aged rats are more susceptible to LTD-induction, relative to adult rats. Through similar mechanisms, the more labile LTP at hippocampal synapses of aged rats is prone to reversal during bouts of low frequency synaptic activation (Norris et al., 1996). Later work showed that the magnitude of LTD in aged rats correlates with the extent of memory dysfunction, as measured by the Morris Water Maze (Foster and Kumar, 2007). While these observations have been largely confirmed by subsequent studies from several different research groups, (Foy et al., 2008; Hsu et al., 2002; Norris et al., 1998a; Sama et al., 2012; Vouimba et al., 2000) other studies did not detect LTD in aged animals or did not find an age difference (Billard and Rouaud, 2007; Kollen et al., 2010; Lee et al., 2005). Like LTP, these discrepancies may be attributable to differences in experimental protocol, especially in regard to synaptic stimulation frequencies and extracellular Ca^{2+} content (see Norris et al., 1996; Foster and Norris, 1997; Kumar et al., 2007; Mathis et al., 2011). For stimulus frequencies near the induction threshold and for extracellular $\text{Ca}^{2+}/\text{Mg}^{2+}$ ratios close to 1:1, aged animals generally show increased susceptibility to LTD, without a change in maximal levels of depression (Kumar et al., 2007).

3. Ca^{2+} dysregulation

3.1 Mechanisms for neuronal Ca^{2+} dysregulation during aging

For synaptic plasticity to proceed in a discrete and efficient manner, it requires the activation of the appropriate biochemical cascades, and exquisite Ca^{2+} regulation—a process that is markedly compromised during aging. Compared to hippocampal neurons from young adult animals, neurons from aged animals show elevations in Ca^{2+} levels during repetitive activation (for review, see Thibault et al., 2007). Aging-related changes in Ca^{2+} dynamics have been measured in soma and dendritic compartments of hippocampal pyramidal neurons (Thibault et al., 2001; Hemond and Jaffe, 2005; Oh et al., 2013) and *are at least partly* attributable to increased Ca^{2+} influx across the plasma membrane (Oh et al., 2013). Elevated Ca^{2+} transients have also been observed in the dendritic spines of young adult mice with AD pathology (Goussakov et al., 2010), but it's unclear whether similar spine Ca^{2+} changes occur as a result of normal aging. Interestingly, elevated Ca^{2+} influx during short-duration bursts of action potentials appears to be compensated by an age-related increase in Ca^{2+} buffering. Nonetheless, the buffering capacity of aged neurons becomes “overwhelmed” by elevated Ca^{2+} influx during sustained activity (Oh et al., 2013) leading to Ca^{2+} dysregulation. A primary source for elevated Ca^{2+} in aged hippocampal neurons appears to be ryanodine-receptor (RyR) gated intracellular stores (Gant et al., 2006), which are positively coupled to L-type VSCCs. It has been shown that the expression and/or function of L-VSCCs is elevated in the hippocampus during aging (Norris et al., 2010; Thibault and Landfield, 1996; Veng et al., 2003) and inversely correlated to cognitive status (Thibault and Landfield, 1996). Moreover, blockade of L-VSCCs improves neurologic function in aged subjects across multiple species including rats, rabbits, mice, humans, and non-human primates (Deyo et al., 1989; Moyer and Disterhoft, 1994; Norris et al., 1998b; Paran et al., 2010; Sandin et al., 1990; Straube et al., 1990; Thompson et al., 1990; Tsukuda et al., 2008; Veng et al., 2003; Wafar et al., 2010). In addition to L-VSCCs and ryanodine receptors, other Ca^{2+} signaling/regulatory mechanisms including a variety of receptors, pumps, binding proteins, and intracellular organelles undergo alterations with aging (for reviews, see Magnusson, 2012; Michaelis et al., 1984; Murchison and Griffith, 2007; Stutzmann and Mattson, 2011; Thibault et al., 2007; Toman and Fiskum, 2011; Yamaguchi,

2012). Changes in any, or all, of these mechanisms is likely to influence the amount of Ca^{2+} in the cell and disrupt the normal function of Ca^{2+} -dependent synaptic plasticity mechanisms (Foster, 2007; Foster and Norris, 1997). These observations are consistent with the long-standing hypothesis (see Disterhoft et al., 1994; Gibson and Peterson, 1987; Khachaturian, 1987; Landfield, 1987) that Ca^{2+} dyshomeostasis during aging involves the disruption of many regulatory mechanisms, ultimately causing neurologic dysfunction and increasing vulnerability to neurodegenerative disease (also see Green and LaFerla, 2008; Stutzmann, 2007). Refer to Figure 1 for a depiction of these regulatory mechanisms.

3.2. Neuronal Ca^{2+} dysregulation and synaptic alterations with aging

Extensive evidence suggests that age-related alterations in synaptic plasticity are directly linked to Ca^{2+} dyshomeostasis. In hippocampal slice experiments, age-related changes in synaptic plasticity are highly sensitive to bath $\text{Ca}^{2+}/\text{Mg}^{2+}$ ratios. Increasing bath Mg^{2+} levels improves short-term frequency potentiation and blocks LTD in aged rats, while increasing bath Ca^{2+} in adult rat slices causes “aging-like” alterations in the synaptic measures (Landfield et al., 1986; Norris et al., 1996). Chelation of intracellular Ca^{2+} using BAPTA-AM in aged rat hippocampal slices also improves LTP induction (Tonkikh et al., 2006). At least some of these effects are linked to the function of L-VSCCs and resulting changes in Ca^{2+} -induced calcium release. Indeed, blockade of L-VSCCs and RyRs normalizes membrane excitability and short-term plasticity, lowers the threshold for LTP-induction, and prevents LTD in aged rats (Moyer et al., 1992; Norris et al., 1998b; Thibault et al., 2001; Thompson et al., 1990), suggesting that age-related elevations in neuronal Ca^{2+} shift the plasticity thresholds in favor of LTD.

Changes in Ca^{2+} regulation during aging appear to affect synaptic plasticity thresholds through disruption of protein kinase/phosphatase signaling cascades. The protein phosphatase CN has more rapid activation kinetics than other Ca^{2+} dependent enzymes, including protein kinases involved in LTP (*e.g.* CaMKII) (Klee, 1991). Age-related elevations in Ca^{2+} levels therefore appear to favor the activation of CN-dependent signaling cascades and the dephosphorylation of critical plasticity regulators, such as CREB (Foster, 2007; Foster et al., 2001; Foster and Norris, 1997). Similar to raising the bath Ca^{2+} level, overexpression of active CN in young animals induces aging-like deficits in LTP (Winder et al., 1998). Conversely, blockade of CN activity and its downstream regulators *in vivo* increases synaptic strength in aged animals (Hsu et al., 2002; Norris et al., 1998a), facilitates LTP (Jouveneau and Dutar, 2006), and leads to improvements in spatial memory tasks (Graff et al., 2010; Malleret et al., 2001). In addition to increases in phosphatase activity, age-related alterations in synaptic plasticity may also relate to changes in Ca^{2+} -dependent protein kinases (Govoni et al., 2010). Impaired membrane localization and/or shifts in the dendritic-to-somal ratios of protein kinase C (PKC) have been reported in the hippocampus with aging and is associated age-related spatial cognition deficits (Battaini et al., 1995; Colombo et al., 1997; Fordyce and Wehner, 1993; Pascale et al., 1998). CaMKII mRNA and protein expression decrease in hippocampus and cortex with normal aging, though they increase in animal models of disease (Zhang et al., 2009). Moreover, the autophosphorylated, activated form of CaMKII is redistributed from synapses and dendritic arbors to the perikarya in postmortem hippocampal tissue from humans with mild cognitive impairment and AD (Reese et al., 2011). Together, these results highlight the importance of the phosphatase/kinase balance in maintaining synaptic plasticity thresholds throughout life.

The age-related shift in plasticity thresholds towards higher phosphatase activity and lower LTD induction thresholds may also have major ramifications on Ca^{2+} regulation. CN stimulates the upregulation of numerous proteins involved in Ca^{2+} homeostasis and signaling, including inositol (1, 4, 5) triphosphate receptors (IP3Rs) and several Ca^{2+} transporters (Carafoli et al., 1999; Graef et al., 1999). Moreover, CN activity appears to be

permissive for L-VSCC activity with aging in neurons *in vitro* and *in vivo* (Norris et al., 2002; Norris et al., 2010). Elevated CN activity and expression in brain therefore may be a cause and consequence of Ca^{2+} dysregulation during aging.

4. Neuroinflammation

4.1. Mechanisms and role in synaptic dysfunction

In addition to neuronal Ca^{2+} dysregulation, another commonly investigated mechanism for altered synaptic function in aging and age-related diseases is increased neuroinflammation (Rao et al., 2012). Glial cells, especially microglia and astrocytes, are the major effectors of immune/inflammatory signaling in the brain (Akiyama et al., 2000) (see Figure 2). Both cell types undergo characteristic morphologic changes with neuroinflammation, a process generally referred to as glial activation (or glial reactivity, or gliosis) which is found in most forms of neurologic injury and disease (Verkhratsky et al., 2012b). Activated microglia typically proliferate with injury/disease and can take on any number of morphologic phenotypes ranging from hypertrophied and ramified to amoeboid in shape (Colton and Wilcock, 2010; Olah et al., 2011; Varnum and Ikezu, 2012). As myeloid lineage cells, microglia are immune/inflammatory powerhouses that release a broad array of cytokines and free radicals. In their amoeboid form, microglia can serve as macrophages to promote the removal of dead cells, protein aggregates, and other debris from the CNS (McGeer and McGeer, 1995). Unlike microglia, astrocytes have a neural lineage, are far more abundant, and provide numerous indispensable metabolic functions that promote neuronal viability and CNS homeostasis (Verkhratsky et al., 2012b). Though astrocytes have historically received less attention than microglia in the realm of neuroinflammation, astrocytes also undergo clear morphological changes with injury and disease (*e.g.* hypertrophy of cell body and processes) and release a wide array of cytokines and other immune/inflammatory factors (Ridet et al., 1997; Sofroniew, 2009). As such, astrocytes are increasingly recognized for their ability to coordinate immune/inflammatory signaling in the CNS and also for their potential to drive neurologic dysfunction due to aging and/or disease (Brambilla et al., 2009; Farina et al., 2007; Furman et al., 2012; Okada et al., 2006; Sofroniew, 2009; Verkhratsky et al., 2012b).

A strong association between chronic neuroinflammation and neurologic dysfunction has been established in multiple experimental models across numerous labs. Early studies found that stimulation of glial activation and cytokine production in otherwise healthy adult animals using lipopolysaccharide endotoxins impairs performance on a variety of cognitive tasks (Hauss-Wegrzyniak et al., 2000a, 2000b) and disrupts LTP at hippocampal synapses (Hauss-Wegrzyniak et al., 2002; Kelly et al., 2003). Conversely, inhibition of neuroinflammation in animal models of injury and disease generally helps to preserve cognitive and synaptic integrity. For instance, non-steroidal anti-inflammatory drugs (NSAIDs), and other novel anti-inflammatory reagents have been shown to prevent LTP deficits and/or ameliorate hippocampal-dependent cognitive impairment in AD mouse models (Kotilinek et al., 2008; Bachstetter et al., 2012). Similar effects in AD mice have been reported with anti-inflammatory polyphenolic compounds found in a variety of fruits and vegetables, (Gong et al., 2013; Wang et al., 2012; Ho et al., 2012). Improvements in synaptic strength and LTP with polyphenols were specifically associated with elevations in phospho-CREB levels (Ho et al., 2012; Wang et al., 2012). Synaptic and cognitive enhancement in AD mice have also been demonstrated to result from the selective inhibition of astrocyte activation using an adeno-associated virus-mediated gene delivery approach (Furman et al., 2012).

Of the major cytokines linked to neuroinflammation, interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) are perhaps the best characterized. Both factors play a role in

normal brain development (Merrill, 1992) and have numerous beneficial effects on neuronal viability and neurologic function when present at low concentrations (Goshen et al., 2007; Schmid et al., 2009; Stellwagen and Malenka, 2006). However, with heightened neuroinflammation, elevated levels of IL-1 and TNF can trigger and maintain numerous deleterious changes in the brain, many of which extend to synapses and synaptic function (Barnum and Tansey, 2011; Lynch, 1998; Macdonald et al., 2000; Mrak and Griffin, 2000; Pickering et al., 2005). Alterations in synaptic plasticity, including reduced LTP have been observed in healthy CNS tissue following acute application of IL-1 or TNF (Bellinger et al., 1993; Cunningham et al., 1996; Katsuki et al., 1990; Tancredi et al., 1992). Conversely, treatments that reduce IL-1 or TNF levels, or inhibit cytokine receptor activation, generally improve indices of synaptic function and/or neuronal viability in experimental models of neuroinflammation and disease (Bachstetter et al., 2012; Kelly et al., 2001; McCoy et al., 2006; Sama et al., 2012; Sama et al., 2008). These effects are likely caused by signaling within the neurons and surrounding glial cells.

Similar to other cell types, neurons express receptors for IL-1, TNF, and many other cytokines (Czirr and Wyss-Coray, 2012) that, in turn, stimulate the activation of one or more members of the mitogen activated protein (MAP) kinase family (Kelly et al., 2003; Pickering et al., 2005). Several studies have described interactions between MAP kinases and glutamate receptors and other classic plasticity-related pathways shown in Figure 1 (*e.g.* see Pickering et al., 2005). Activation of p38 MAP kinase, in particular, seems to play important roles in the internalization of AMPA-type glutamate receptors (Boudreau et al., 2007; Zhong et al., 2008) and the interference of CREB phosphorylation (Tong et al., 2012), suggesting an important role in the weakening of synaptic efficacy, symptomatic of aging and memory dysfunction. Consistent with this possibility, an early study by Lynch and colleagues reported elevated p38 activity in the hippocampus of aged rats in conjunction with reduced LTP amplitude (O'Donnell et al., 2000). Subsequent work has shown that LTP deficits due to inflammatory mediators, including cytokines and amyloid beta peptides, are strongly attenuated by p38-inhibiting compounds (Butler et al., 2004; Li et al., 2011; Wang et al., 2004; Wang et al., 2005). Conversely, activation of p38 appears to synergize with CN activity to induce LTD and synapse loss in experimental models of AD (Hsieh et al., 2006).

4.2 Role of neuroinflammatory mechanisms in age-related synaptic dysfunction

Though neuroinflammation has been most commonly investigated in CNS injury and disease, it has also been long appreciated as a consequence of “normal” aging (Bilbo et al., 2012; Mrak and Griffin, 2005; Pizza et al., 2011). The first reports of glial activation in the aging brain were published decades ago (Geinisman et al., 1978; Landfield et al., 1977; Samorajski, 1976; Sturrock, 1977; Vaughan and Peters, 1974). Subsequently, numerous studies have described age-related changes in other glial activation markers including expression of pro-inflammatory cytokines, such as IL-1 and TNF (Murray and Lynch, 1998; Sheng et al., 1996; Tha et al., 2000). In the early 2000s, massively parallel technologies, such as gene microarrays, demonstrated that the global transcriptional signature of aging brain is dominated by elevations in inflammatory signaling pathways (Blalock et al., 2003; Lee et al., 2000). Changes in inflammatory markers can arise as early as middle age (Blalock et al., 2003; Kadish et al., 2009) and are correlated with impaired synaptic function and/or cognitive impairment (Blalock et al., 2003; Lynch, 1999; Murray and Lynch, 1998). Intervention-type studies performed on aged animals suggest that neuroinflammation is not only a correlate, but a likely cause of impaired neurologic function. Non-steroidal anti-inflammatory drugs, like celecoxib, have been shown to improve hippocampal-dependent learning in middle aged rats concurrent with a reduction in hippocampal cytokine levels (Casolini et al., 2002). Improvements in cognitive function, synaptic strength, and/or LTP have also been reported for aged rodents exposed to a variety

of other anti-inflammatory treatments including minocycline (Griffin et al., 2006), resveratrol (Joseph et al., 2008; Ranney and Petro, 2009) and flavonoid-rich diets (Coultrap et al., 2008; Goyarzu et al., 2004; Malin et al., 2011).

Pro-inflammatory cytokines affect baseline synaptic activity in a variety of conditions, and they appear likely to mediate at least some of the detrimental effects of neuroinflammation on aging synapses (Lynch, 1998; Pickering et al., 2005). Antagonizing IL-1, either with the IL-1 receptor antagonist, or with the anti-inflammatory cytokine, IL-4, reverses LTP deficits (Nolan et al., 2005) and improves memory performance in an aging-dependent manner (Frank et al., 2010). Similar benefits have also been reported for aged animals treated with TNF inhibiting drugs (Paredes et al., 2010; Sama et al., 2012).

Several recent studies suggest that different receptor mechanisms for IL-1 and TNF could play unique roles in the modulation of synaptic function and neuronal viability during aging. Signaling through the IL-1 receptor relies heavily on other partnering proteins, such as the IL-1 receptor accessory protein (IL-1RAcP) (Cullinan et al., 1998). Its newly characterized “b” isoform, termed IL-1RAcPb, is present only in neurons, preferentially responds to low concentrations of IL-1, and preferentially activates Src kinase pathways associated with enhanced NMDAR activity (Huang et al., 2011). In contrast, the more conventional IL-1RAcP, which is ubiquitously expressed, appears to preferentially activate p38 cascades when IL-1 levels are elevated, leading to impaired synaptic function and viability (Huang et al., 2011). For the TNF system, different receptors (TNFRs) similarly regulate distinct intracellular signaling cascades. TNFR1, which shows greater affinity for soluble TNF (Grell et al., 1998), contains a cell death domain in its cytosolic tail, and is coupled to cytotoxic caspase-dependent signaling cascades. Conversely, TNFR2, which binds more tightly to transmembrane TNF (Grell et al., 1995), is preferentially coupled to pro-survival pathways. For a review of TNFR signaling mechanisms and functions see McCoy and Tansey (2008). Consistent with these divergent signaling mechanisms, primary neurons that express TNFR1 in the absence of TNFR2, show enhanced susceptibility to excitotoxicity in the presence of TNF, whereas TNFR2-expressing neurons show increased resistance to excitotoxicity when TNF is present (Marchetti et al., 2004). Interestingly, recent work revealed an aging-related reduction in hippocampal protein levels for TNFR2 but not TNFR1 (Sama et al., 2012), suggesting that TNFR1 is the dominant pathway for TNF signaling during aging. Furthermore, chronic intracranial infusions of the novel TNF/TNFR1 inhibitor XPro1595 improved learning acquisition rates, blocked the induction of LTD, and prevented the loss of GluR1 type glutamate receptors in the hippocampus of aged rats (Sama et al., 2012). The results highlight the complexity of neuroinflammatory signaling in brain and suggest that the development of highly specific, and perhaps more efficacious anti-inflammatory treatments, could result from an increased understanding of individual cytokine messengers and their pathway specific interactions.

5. Interactions between Ca^{2+} dysregulation and neuroinflammation

5.1 Neuroinflammation and the link to Ca^{2+} dysregulation in neurons

As described above, neuroinflammation can adversely affect synaptic function and plasticity through the activation of neuronal MAP kinases. However, it deserves noting that neuroinflammatory mediators can also strongly modulate neuronal Ca^{2+} signaling and homeostasis, which can, in turn, impact synapses. Numerous Ca^{2+} signaling mechanisms in neurons including IP3Rs, RyRs, NMDARs, and VSCCs appear to be sensitive to local cytokine levels and/or cytokine receptor activation (see Table 1). Sensitivity of Ca^{2+} signaling mechanisms to cytokines may partly account for the beneficial effects of polyphenol rich diets on Ca^{2+} clearance in aged rat synaptosomal preparations (Joseph et al., 1999). For some major cytokine species, the impact on neuronal Ca^{2+} signaling is highly

similar to the effects of brain aging. For instance, elevated TNF levels trigger enhanced Ca^{2+} release from intracellular stores (Park et al., 2008; Pollock et al., 2002) and increase L-type VSCC expression/function in primary neuronal cultures (Furukawa and Mattson, 1998). Moreover, chronic blockade of TNF/TNFR1 signaling in the hippocampus of intact aging rats reduces L-VSCC activity in CA1 neurons and suppresses the induction of hippocampal LTD (Sama et al., 2012), shown previously to have a key L-VSCC-sensitive component (Norris et al., 1998b). That neuronal TNF receptors appear necessary for LTD induction in aged animals (also see Albeni and Mattson, 2000) suggests a close relationship to neuronal CN signaling pathways. In non-neuronal cell types, like astrocytes, CN activation is strongly induced by multiple cytokine factors, including TNF (Fernandez et al., 2007; Furman et al., 2012; Sama et al., 2008). TNF also appears to regulate CN-dependent apoptotic cascades in neuroblastoma cells (Alvarez et al., 2011). TNF, CN, and L-VSCC interactions in neurons could provide yet another critical junction for the Ca^{2+} and neuroinflammation hypotheses of aging (for an overview, see Figure 3). However, while existing data implicates TNF in L-VSCC regulation, no studies to our knowledge have investigated the specific linkage between neuronal TNF receptors and elevated CN activity with brain aging.

5.2. Ca^{2+} dysregulation and the link to neuroinflammatory signaling in glial cells

In an interesting parallel to neurons, changes in neuroinflammation with aging and disease may have strong ties to altered Ca^{2+} signaling mechanisms in glia. Glia are generally considered electrically non-excitabile cells. Nevertheless, both astrocytes and microglia express diverse and highly regulated Ca^{2+} signaling machinery that allows them to respond to their local environment and to communicate with neighboring cells via gap junction networks and releasable factors (Farber and Kettenmann, 2006; Verkhratsky et al., 2012a). Elevated levels of glutamate, ATP, cytokines, and numerous other inflammatory mediators in the extracellular milieu all can induce elevated Ca^{2+} levels in glial cells (*e.g.* see Beskina et al., 2007; Cornell-Bell et al., 1990; Glaum et al., 1990; Holliday and Gruol, 1993; James et al., 2011; Koller et al., 1996). Astrocytes, which are in close contact to nearly every excitatory synapse in the brain, seem to be especially reliant on Ca^{2+} signaling and show marked Ca^{2+} dysregulation as a function of aging and/or disease.

Relative to astrocytes in healthy nervous tissue, activated astrocytes in aged animals, or in experimental models of amyloid pathology exhibit higher resting Ca^{2+} levels, bigger Ca^{2+} transients, and/or more frequent Ca^{2+} fluctuation (Kuchibhotla et al., 2009; Lin et al., 2007; Vincent et al., 2010). For aged animals, elevated Ca^{2+} responses in astrocytes have been attributed to reduced uptake into mitochondrial stores (Lin et al., 2007). However, it remains possible that other Ca^{2+} regulatory mechanisms, such as IP3Rs, RyRs, Ca^{2+} -ATPases, and VSCCs are also disrupted in astrocytes during aging, injury, and disease. For instance, L-VSCCs, which exhibit low expression levels in “resting” astrocytes, are prominently expressed in activated astrocytes following acute CNS injury (Westenbroek et al., 1998). This observation is intriguing because, as discussed earlier, L-VSCCs appear to play a predominant role in neuronal Ca^{2+} dysregulation during aging. However, it remains unclear whether astrocytic L-VSCC expression is increased as a function of aging.

In addition to regulating the release of neurotransmitters and neuropeptides from astrocytes (*i.e.* gliotransmission), elevated glial Ca^{2+} transients also modulate inflammatory responses, including cytokine production and release (Canellada et al., 2008; Choi et al., 2001; Fernandez et al., 2007; Norris et al., 1994; Sama et al., 2008). Some inflammatory-related mediators, such as the S100 family members, are themselves Ca^{2+} -binding proteins that exhibit increased activity in the presence of Ca^{2+} (Donato, 2001). Most other cytokines and inflammatory mediators are indirectly induced by Ca^{2+} through the activation of a variety of signaling cascades involving CN, CaM kinases, and PKC, among others. CN is an interesting case because it is highly expressed in activated astrocytes during aging, injury,

and disease (Abdul et al., 2010; Abdul et al., 2009; Celsi et al., 2007; Hashimoto et al., 1998; Norris et al., 2005), but is only weakly expressed in astrocytes of young healthy animals (Goto et al., 1986; Norris et al., 2005). Thus, astrocytic CN appears to be a biomarker of sorts for astrocyte activation. CN induces cytokine expression in astrocytes and microglia through the activation of the nuclear factor of activated T-cells (NFAT) (Canellada et al., 2008; Fernandez et al., 2007; Nagamoto-Combs and Combs, 2010; Sama et al., 2008): a transcription factor well-characterized for its pivotal roles in lymphocyte activation, immune responses, and phenotype switching (Crabtree and Olson, 2002; Horsley and Pavlath, 2002; Macian, 2005). Hyperactivation of CN/NFAT activity in normal astrocytes recapitulates many of the loss- and gain-of function phenotypes associated with astrocyte activation including cellular hypertrophy, increased expression of intermediate filament proteins, loss of high affinity glutamate transport, and induction of numerous inflammatory mediators and cytokines (Abdul et al., 2009; Canellada et al., 2006; Fernandez et al., 2007; Norris et al., 2005; Perez-Ortiz et al., 2008; Sama et al., 2008). Since many of the cytokines induced by CN also stimulate Ca^{2+} elevations in glial cells, the CN/NFAT pathway can maintain its own activation and propagate to other nearby glial populations through positive feedback signaling (Sama et al., 2008). Thus, similar to its positive-feedback role in neuronal Ca^{2+} dysregulation, CN appears to be both a cause and a consequence of glial activation, and as such, may be a central mechanism for chronic neuroinflammation found in aging and age-related neurodegenerative disease.

6. Summary and Conclusions

The Ca^{2+} and neuroinflammation hypotheses provide alternate explanations for increased susceptibility to synaptic dysfunction, cognitive decline and neurodegenerative disease with aging. Both hypotheses have been supported by abundant data collected from diverse experimental models, and both undergo continual refinement. Though discrete in nature, Ca^{2+} and neuroinflammatory signaling mechanisms also interact at multiple levels in different neural cell types. One of the many questions that remain unanswered is: Which comes first: Ca^{2+} dysregulation or increased neuroinflammation? Gene microarray studies on transcriptional changes across the lifespan show that elevations in immune/inflammatory regulators (including levels for TNF family members) begin to emerge in rat hippocampus as early as six-months-of-age (Kadish et al., 2009). In contrast, common indices of CA1 neuronal Ca^{2+} dysregulation (i.e. increased CICR and augmented Ca^{2+} -dependent afterhyperpolarizations) do not appear until approximately 12-months-of-age in the same animal model. These observations would seem to suggest that low levels of neuroinflammation are present before Ca^{2+} dysregulation arises, which, in turn, is consistent with the hypothesis that neuroinflammation precipitates Ca^{2+} dysregulation. However, caution is needed with this interpretation as Ca^{2+} measurement technology, as applied to in situ brain slices, may lack the sensitivity to detect very subtle changes in Ca^{2+} dynamics. Of course, it's also possible that Ca^{2+} dysregulation in neuronal microdomains (e.g. dendritic spines) or in non-neuronal cell types (e.g. astrocytes and microglia) occur as early, or even earlier, than inflammatory transcriptional changes. Further investigation of Ca^{2+} /neuroinflammatory interactions, the temporal progression of these interactions, and the specific molecular pathways/cell types involved will surely lead to more comprehensive theories of brain aging and perhaps stimulate novel strategies for treating age-related memory decline and/or reducing the risk of developing neurodegenerative diseases.

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Highlights

Age related cognitive deficits are linked to alterations in synaptic function and plasticity

The Ca^{2+} and neuroinflammation hypotheses have provided frameworks for synaptic dysfunction

Though discrete in nature, Ca^{2+} signaling and inflammatory mechanisms are also intertwined

Understanding Ca^{2+} /inflammatory interactions may lead to the development of novel nootropics

Figure 1.

A. Synaptic Plasticity. Long-term potentiation (LTP) and long-term depression (LTD) involve the activation of two glutamate receptors, α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPA; green) and N-methyl-D-aspartic acid receptors (NMDARs; blue). Both are permeable to Na⁺ and K⁺, while a subgroup of AMPARs and all NMDARs are permeable to Ca²⁺. Upon membrane depolarization by AMPARs, NMDARs expel a Mg²⁺-block (red), and permit Ca²⁺ entry into the postsynaptic cell. Both forms of plasticity require Ca²⁺ influx through NMDARs, though LTP generally requires a large surge in postsynaptic Ca²⁺, and LTD generally requires smaller Ca²⁺ influxes. As a result, the differing Ca²⁺ signals activate divergent biochemical cascades. Protein kinases, especially Ca²⁺/calmodulin-dependent protein kinase II (CaMKII; orange oval), have been strongly implicated in LTP, where they are involved in the phosphorylation (small yellow circle) and subsequent membrane insertion of glutamate receptors. Smaller elevations in Ca²⁺ are involved in LTD induction and activate protein phosphatases, namely Ca²⁺/calmodulin dependent protein phosphatase, calcineurin (CN; black circle), and/or protein phosphatase 1 (PP1; lavender triangle), which can be stimulated by CN activity. The balance in activity of protein kinases and phosphatases regulates the magnitude/duration of synaptic changes, and helps maintain the functional status of the synapse under basal conditions.

B. Ca²⁺ dysregulation. Synaptic plasticity requires the activation of the appropriate biochemical cascades, and exquisite Ca²⁺ regulation. Under normal conditions, there are numerous mechanisms regulating intracellular Ca²⁺ concentrations. These include: voltage sensitive Ca²⁺ channels (VSCCs; aqua), a variety of receptors on the cell surface (NMDARs; light blue) or receptors on intracellular organelles which store Ca²⁺ (IP3Rs and ryanodine receptors), pumps (SERCA Ca²⁺; purple), binding proteins (calreticulin, BiP/grp78, grp94, and calnexin; royal blue), and intracellular organelles which store Ca²⁺ (endoplasmic reticulum and mitochondria). All of these mechanisms are impaired with aging, leading to increases in Ca²⁺ entry/release, and decreased Ca²⁺ expulsion/sequestration, leading to an elevation in Ca²⁺ concentration.

Figure 2. Neuroinflammation

Many astrocytes and microglia evidently morphologic changes from a “resting state” (green/blue) to an “activated state” (red/brown) under conditions of injury, disease, or aging (lightning bolt, yellow). When in a “resting state,” normal functions of glia include ion monitoring, glutamate clearance, and neurite guidance. Once astrocytes and microglia undergo a phenotype switch these functions are impaired and glia begin to produce and release immune/inflammatory mediators. The loss of glutamate transport and ion monitoring, together with the release of immune/inflammatory mediators, can lead to impaired synaptic plasticity, neuronal viability, and cognitive function.

Figure 3. The intersection of Ca^{2+} dysregulation and neuroinflammation

Ca^{2+} dysregulation in glia, especially astrocytes, can increase calcineurin (CN) activity and lead to the production and release of inflammatory factors. These factors can then initiate activation of the MAP kinase signaling pathways (p38) and Ca^{2+} dysregulation in neurons, leading to increased CN activity. Changes in neuronal Ca^{2+} signaling can further perpetuate Ca^{2+} dysregulation, synaptic plasticity deficits, and cognitive impairments.

Table 1**Effects of inflammatory modulators on mechanisms of Ca²⁺ regulation in neurons**

This table highlights references that have investigated the impact of pro- or anti-inflammatory modulators on neuronal Ca²⁺ signaling. While the interaction of these signaling pathways has support in the literature, it is noteworthy that most mechanisms have only been investigated in one or a few studies.

Inflammatory Modulator	Ca ²⁺ Mediator	Effect	Reference(s)
<i>Pro-inflammatory</i>			
IL-1	Total Ca ²⁺		De et al., 2002; Shu et al., 2007; Wuchert et al., 2009
	Total VSCC	activity	Plata-Salaman and Ffrench-Mullen, 1992, 1994
	L-VSCCs	activity	Zhou et al., 2006a
		protein expression	Zhou et al., 2006a
	N-VSCCs	activity	Gambino et al., 2007; Zhou et al., 2006b
		protein expression	Zhou et al., 2006b
	NMDARs	activity	Huang et al., 2011; Kawasaki et al., 2008; Liu et al., 2013; Viviani et al., 2003; Yang et al., 2005
	AMPARs	activity	Liu et al., 2013
		surface expression	Lai et al., 2006
IL-2	Total VSCC	activity	Plata-Salaman and Ffrench-Mullen, 1993; Song et al., 2002
	NMDARs	activity	Shen et al., 2006
IL-6	Total Ca ²⁺		Fan et al., 2009; Gruol and Nelson, 2005; Nelson et al., 2004; Nelson et al., 2002; Ott et al., 2010
	Total VSCC	activity	Ma et al., 2012
	L-VSCCs	activity	Ma et al., 2012
		protein expression	Vereyken et al., 2007
	AMPARs	activity	Nelson et al., 2002
	NMDARs	activity	Orellana et al., 2005; Qiu et al., 1995; Qiu et al., 1998
TNF-	Total Ca ²⁺		Ott et al., 2010; Wuchert et al., 2009
	Total VSCC	activity	Furukawa and Mattson, 1998
		activity	Czeschik et al., 2008; Hagenacker et al., 2010
	N-VSCCs	activity	Motagally et al., 2009
		mRNA	Motagally et al., 2009
		surface expression	Motagally et al., 2009
	L-VSCCs	activity	Furukawa and Mattson, 1998; Soliven and Albert, 1992
	NMDARs	activity	Kawasaki et al., 2008; Wheeler et al., 2009
		activity	Furukawa and Mattson, 1998
	AMPARs	activity	Kawasaki et al., 2008
		activity	Furukawa and Mattson, 1998
		surface expression	Beattie et al., 2002; Lai et al., 2006; Leonoudakis et al., 2008; Ogoshi et al., 2005; Stellwagen et al., 2005; Stellwagen and Malenka, 2006; Yin et al., 2012
	IP3	activity	Park et al., 2008
	RyR	activity	Pollock et al., 2002; Rogers et al., 2006

Inflammatory Modulator	Ca ²⁺ Mediator	Effect	Reference(s)
LPS	Total Ca ²⁺		Murakami et al., 2009; Ott et al., 2010
<i>Anti-inflammatory</i>			
IL-1ra	Total Ca ²⁺		Viviani et al., 2006
	NMDARs	phosphorylation	Viviani et al., 2006; Zhang et al., 2008b; Zhang et al., 2008c
	AMPARs	protein expression	Chu et al., 2010
IL-10	AMPARs	protein expression	Savina et al., 2013
	IP3	activity	Turovskaya et al., 2012
XPro	L-VSCCs	activity	Sama et al., 2012
	AMPARs	protein expression	Sama et al., 2012
NSAIDs	Total Ca ²⁺		Gardam et al., 2008
	Total VSCC	use inactivation	Gardam et al., 2008
	NMDARs	activity	Peng et al., 2003
	AMPARs	activity	Kohno, 2011
Resveratrol	Total Ca ²⁺		Gong et al., 2007; Yanez et al., 2011
	L-VSCCs	activity	Li et al., 2005
	AMPARs	activity	Gao et al., 2006; Zhang et al., 2008a
	NMDARs	activity	Gao et al., 2006
Curcumin	Total Ca ²⁺		Matteucci et al., 2011
	NMDARs	phosphorylation	Matteucci et al., 2005
		protein expression	Matteucci et al., 2011
		protein expression	Xu et al., 2009
Other polyphenols	Total Ca ²⁺		Yin et al., 2009; Zhang et al., 2012
			Ahn et al., 2011; Bae et al., 2002; Ge et al., 2007; Han et al., 2008; Ibarretxe et al., 2006; Lee et al., 2003)
	Total VSCC		Li et al., 2010
	L-VSCCs	activity	Zhang et al., 2012
	AMPARs	phosphorylation	Matsuzaki et al., 2008
		activity	Matsuzaki et al., 2008
		mRNA	Schroeter et al., 2007
		protein	Schroeter et al., 2007
	RyR	activity	Feng et al., 2010; Lin et al., 2007