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Susceptibility of the cerebral cortex to spreading depolarization in neurological disease states: The impact of aging

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ABSTRACT

Secondary injury following acute brain insults significantly contributes to poorer neurological outcome. The spontaneous, recurrent occurrence of spreading depolarization events (SD) has been recognized as a potent secondary injury mechanism in subarachnoid hemorrhage, malignant ischemic stroke and traumatic brain injury. In addition, SD is the underlying mechanism of the aura symptoms of migraineurs. The susceptibility of the nervous tissue to SD is subject to the metabolic status of the tissue, the ionic composition of the extracellular space, and the functional status of ion pumps, voltage-gated and other cation channels, glutamate receptors and excitatory amino acid transporters. All these mechanisms tune the excitability of the nervous tissue. Aging has also been found to alter SD susceptibility, which appears to be highest at young adulthood, and decline over the aging process. The lower susceptibility of the cerebral gray matter to SD in the old brain may be caused by the age-related impairment of mechanisms implicated in ion translocations between the intra- and extracellular compartments, glutamate signaling and surplus potassium and glutamate clearance. Even though the aging nervous tissue is thus less able to sustain SD, the consequences of SD recurrence in the old brain have proven to be graver, possibly leading to accelerated lesion maturation. Taken that recurrent SDs may pose an increased burden in the aging injured brain, the benefit of therapeutic approaches to restrict SD generation and propagation may be particularly relevant for elderly patients.

1. Introduction

1.1. Occurrence of spreading depolarization (SD) in neurological diseases

Spreading depolarization (SD) is a wave of massive depolarization of a critical mass of neurons and presumably glia cells, which – together with a concomitant depression of spontaneous brain electrical activity – propagates across the cerebral gray matter at a low rate of 2–8 mm/min (Leao, 1944; Somjen, 2001). Not long after its discovery, SD was speculated to correspond with scotomas of migraine with aura on the basis of a similar rate of propagation (Milner, 1958), although no direct proof could be gathered at the time to indisputably support the claim. Consequently, SD was considered for decades as an experimental curiosity, or a model for neurovascular coupling, the latter due to the evolution of an associated, robust cerebral blood flow (CBF) response. The CBF response to SD generally consists of an initial, brief vasoconstriction, followed by a remarkable, transient, and then a less obvious late hyperemia, which are succeeded by a long lasting oligemia. The final, oligemic element of the CBF response is typically obvious in the non-ischemic cortex in case a prior SD event was not generated within the preceding hour. The presence and weight of each, distinct phase in the CBF response may vary in different species, and is subject to the metabolic state of the tissue, establishing a spectrum of CBF response types ranging from the spectacular dominance of peak hyperemia to ruling vasoconstriction known as spreading ischemia (Ayata and Lauritzen, 2015).

SD in a patient – rather than in experimental model systems – was first captured during the aura phase of a migraine attack. In fact, an epiphenomenon, spreading oligemia was revealed by positron-emission tomography (PET) (Lauritzen et al., 1983). Later the full CBF response to SD (i.e. including both hyperemia and oligemia) was confirmed in migraine patients by functional magnetic resonance imaging using blood oxygen level detection (fMRI-BOLD) techniques (Hadjikhani et al., 2001). The clinical evidence were highly significant, but still

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Abbreviations

BK	large-conductance Ca^{2+} activated K^+ channel
Cav	voltage-gated calcium channel
CBF	cerebral blood flow
DC potential	direct current potential
DCI	delayed cerebral infarctions
EAAT	excitatory amino acid transporter
ECoG	electrocorticogram
eNOS	endothelial nitric oxide synthase
GFAP	glial fibrillary acidic protein
IL-1β	interleukin-1β
Kir	inward rectifier potassium channel
Kv	voltage-gated potassium channel
Nav	voltage-gated sodium channel
NMDA	N-methyl-D-aspartate
NO	nitric oxide
nNOS	neuronal nitric oxide synthase
SAH	subarachnoidal hemorrhage
SD	spreading depolarization
TBI	traumatic brain injury
TNFα	tumor necrosis factor-α

indirect, since the CBF variation characteristic of SD, rather than SD itself (the primary, electrophysiological event), was identified. Still, SD has been justly acknowledged to accompany the aura phase of migraine (Ayata, 2010), and the associated transient depression of neural activity has been linked to neurological symptoms such as scintillations and scotomas (Goadsby et al., 2017; Milner, 1958). Although it is still debated, SD may sensitize the trigeminovascular system, activate meningeal nociceptors, and thereby contribute to migraine headache itself, as well (Ayata, 2009; Goadsby et al., 2017).

The first, direct indication for SD to occur in the human brain was presented by multiparametric monitoring of the cerebral cortex of severe traumatic brain injury (TBI) patients. The synchronous acquisition of CBF, extracellular K^+ concentration ($[K^+]_e$), direct-current (DC)-potential, electrocorticogram (ECoG) and changes in NADH redox state unequivocally confirmed that SD, in association with injury, evolves in a recurrent fashion in the human brain (Mayevsky et al., 1996, 1998). Subsequently, the systematic monitoring of SD in acute brain injury patients (i.e. TBI, subarachnoid hemorrhage - SAH, malignant ischemic stroke) took off starting with a landmark study (Strong et al., 2002). The most reliable approach to detect SD has since become the use of subdural surface electrode strips left in place for up to several days after the neurosurgical intervention to alleviate the primary traumatic or ischemic insult (Dreier et al., 2017). Because the recording of SDs with scalp electrodes requires further validation (Hartings et al., 2014), SD monitoring at present remains predominantly invasive, limited to acute brain injury patients requiring craniotomy. These studies keep delivering highly valuable data on the pattern of evolution and injurious potential of SD, and promote SD as an indicator or mediator of ongoing secondary damage (Dreier et al., 2017; Hartings et al., 2017).

1.2. Contribution of SD to lesion progression

Following SAH, delayed cerebral infarctions (DCI) (i.e. focal neurological deterioration, new ischemic lesions and related neurological symptoms) arise unpredictably, typically 5–14 days following the initial injury. DCI was originally attributed to vasospasm in the proximal large vessels, but, more recently, the additional contribution of microthrombus formation and microvascular hypoperfusion was revealed (Rowland et al., 2012). Microvascular hypoperfusion, in particular, was suggested to be caused by clusters of SD (Dreier et al., 2006). Such SDs may be coupled with inverse hemodynamic response and concomitant tissue hypoxia, deepening the metabolic crisis of the tissue and leading to ischemic lesion progression (Bosche et al., 2010; Dreier et al., 2009). The inverse hemodynamic response to SD has also been observed in TBI patients, and presented as a novel mechanism of secondary brain injury (Hinzman et al., 2014). As further support for the injurious potential of recurrent SDs, the high number of SDs and the total depolarization time were closely associated with DCI development, independent of vasospasm (Dreier et al., 2006; Woitzik et al., 2012).

Recently, repetitive SDs – in clusters or alone - have also been identified in patients suffering malignant ischemic stroke (Pinczolits et al., 2017; Woitzik et al., 2013). In focal cerebral ischemia, repetitive SDs are thought to arise from the border of the penumbra and the ischemic core (Bere et al., 2014; Kao et al., 2014), probably initiated by hypotensive or hypoxic transients (von Bornstadt et al., 2015). These SDs may increase the chance of infarct maturation by converting viable penumbra tissue to the core beyond repair (Hartings et al., 2017). The coincidence between the severity of ischemic damage and SD occurrence was corroborated by the linear correlation between the total depolarization time or SD frequency with infarct maturation in rodent focal ischemia models (Back et al., 1994, 1996; Dijkhuizen et al., 1999; Takano et al., 1996). In order to determine the direction of causality, SDs elicited experimentally distant to ischemic foci were shown to propagate to penumbra-like tissue and increase the size of the ischemic infarct (Busch et al., 1996), verifying that SDs may contribute to ischemic lesion progression.

1.3. Age as a risk factor for neurological diseases in which SD is relevant

Taken that SD emerges as a potent mechanism of secondary brain injury in patients, it is of great interest what conditions favor SD occurrence. In neurological disorders implicating SD (i.e. migraine with aura, or acute brain injury including TBI, SAH, and malignant ischemic stroke), age is known as an independent risk factor for the incidence and prevalence of the disorders (Fig. 1). For example, the age-dependent prevalence of migraine has been shown to be bimodal, as migraine incidence peaks at the age of 19 and 48 years in men, and at the age of 25 and 50 in women (Victor et al., 2010) (Fig. 1). Among the general population, TBI has a peak incidence during childhood (falls), adolescence (motor-vehicle accidents) and geriatric age (falls) (Bruns and Hauser, 2003) (Fig. 1). Further, SAH is one of the most common types of stroke in young adults, and younger age is an established risk factor

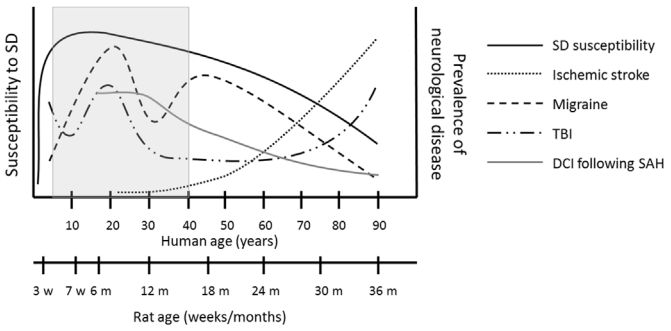

Fig. 1. The age-related alteration of spreading depolarization (SD) susceptibility against the prevalence of neurological diseases, in which SD is implicated as a pathophysiological phenomenon. Note, that data underscoring the modification of SD susceptibility over the lifespan are predominantly based on experimental SD elicitation. In order to compare data from clinical and experimental research, the secondary x-axis represents the rat lifespan matched with human (Sengupta, 2013). Gray area highlights the time period, over which increased SD susceptibility coincides with the increased prevalence of neurological diseases, such as migraine, traumatic brain injury (TBI) and delayed cerebral ischemia (DCI) following subarachnoid hemorrhage (SAH).

for secondary lesion progression in SAH, caused by proximal large artery vasospasm (Charpentier et al., 1999; Rabb et al., 1994) and DCI (Crobeddu et al., 2012; de Rooij et al., 2013; Magge et al., 2010) (Fig. 1). Finally, aging significantly predicts poor patient outcomes after ischemic stroke (Chen et al., 2010; Liu and McCullough, 2012). The incidence and poor outcome of stroke steeply rises with age (Chen et al., 2010) (Fig. 1). In this context, the impact of age on stroke pathophysiology has been the target of intensive research in order to understand the reason for the increased susceptibility of the aged brain to stroke-related injury, yet the potential contribution of SD has remained largely unexplored.

In recent years, outstanding and comprehensive reviews focusing on different aspects of SD have been published: the pharmacological profile of SD (Pietrobon and Moskowitz, 2014); the linkage between migraine, stroke and SD (Dreier and Reiffurth, 2015); the aspects of hemodynamic response to SD (Ayata and Lauritzen, 2015) and the pivotal role of SD during ischemic injury (Hartings et al., 2017). Here we set out to provide an overview on the susceptibility of the nervous tissue to SD, with a principal focus on age.

2. Aging and the susceptibility of the nervous tissue to SD

2.1. SD triggered experimentally

The neonatal brain appears to be too immature to sustain experimentally triggered SD. In the intact rat cortex, SD can be first initiated from postnatal days 12–15 (Bures, 1957; Richter et al., 1998; Schade, 1959). The threshold of SD elicitation was thought to decrease until adulthood, and expected to decrease further with aging, theoretically due to the shrinkage of the extracellular space (Somjen, 2001). However, the latter view on aging appears to be superseded by accumulating experimental evidence. First, the rate of SD propagation was shown to decelerate in the aging rodent brain (Guedes et al., 1996). Also, increasingly higher concentration of KCl was required to trigger SD in brain slices obtained from middle-aged rats with respect to young adults (Maslarova et al., 2011), and in the old versus young anesthetized rat cerebral cortex (Menyhart et al., 2015, 2017b). Further, the same, incessant, standard trigger (1 M KCl) produced a lower number of recurrent SDs in the middle-aged with respect to the young adult cerebral cortex in anesthetized rats (Farkas et al., 2011). Finally, a more sensitive, refined experimental approach dissected that between the ages of 7–30 weeks of rats - corresponding to adolescence and young adulthood in humans (Sengupta, 2013) – progressively increasing electrical charge was necessary to elicit SD, especially when the cortex suffered of global forebrain ischemia (Hertelendy et al., 2017). In the non-ischemic cortex, the elevating electric threshold of SD elicitation coincided with increasing dendritic spine density, which might outline an association between SD threshold and the fine histological and possibly neurochemical organization of the cortex (Hertelendy et al., 2017).

In further support for the concept that the aged nervous tissue is less able to sustain SD, additional experimental results may be lined up. In the full band ECoG, SD is seen as a transient, spreading depression of activity (Leão, 1944) – unless the ECoG is already isoelectric prior to SD occurrence due to a severe insult (Hartings et al., 2011). The duration of the ECoG depression in the non-ischemic rat cerebral cortex may last for over 2 min in the young, but for only half of this time duration in middle-aged animals (Farkas et al., 2011). The shortening of the SD-related ECoG depression appears to be evident first in the low frequency components (delta and theta bands) at middle-age (7 months old) (Hertelendy et al., 2017), and concerns all frequency bands at old age (18 months old) (Makra, 2018). These data have been interpreted to depict a narrower SD wave front in space, standing for a smaller volume of nervous tissue involved in SD at a given point in time (Farkas et al., 2011; Hertelendy et al., 2017; Makra, 2018).

Another read-out to be taken as an indicator for the susceptibility of the nervous tissue to SD is the distance covered by SD before coming to a halt. Indeed, some SD events are gradually extinguished over their course of propagation, rather than traversing the entire cortical surface, as demonstrated by multimodal experimental imaging studies (Bere et al., 2014; Kaufmann et al., 2017; Menyhart et al., 2017a). Even though not documented so far, we observed that in old (18 months old) rats, experimentally triggered SDs are more likely to terminate after having propagated only a few millimeters away from the site of elicitation than in young (2 months old) rats.

2.2. SD that occurs spontaneously in response to hypoxia/ischemia

Even though these studies consistently demonstrated that SD events are less likely to occur or evolve fully with aging (Fig. 1), the experiments relied on provoking SD experimentally (i.e. by the application of high concentration KCl or electrical stimulation), rather than evaluating the likelihood of spontaneous SD evolution as it takes place in acute brain injury. The distinction between experimentally triggered and spontaneously generating SDs may be important, because their pharmacology is different, and thus the share of specific ion channels in their igniting mechanisms may not be identical (Pietrobon and Moskowitz, 2014). In addition, the share of ion channels in supporting the generation and propagation of SD is dependent on the metabolic conditions of tissue (Dreier and Reiffurth, 2015). This is best illustrated by the observations that NMDA receptor antagonism effectively blocks SD in well-nourished tissue (Marrannes et al., 1988), but fails to do so under severe ischemic conditions (Hertle et al., 2012). Accordingly, contemplating the age specific pattern of spontaneous SD occurrence adds new perspectives. To begin with, the earliest age when spontaneous SD was shown to emerge due to asphyxia proved to be as early as postnatal day 4 (Hansen, 1977) – in contrast with postnatal days 12–15 determined as the youngest age in which SD can be triggered experimentally (Bures, 1957; Richter et al., 1998; Schade, 1959). The impediment for SD to evolve in such a young brain was, however, confirmed by a remarkable 20 min delay of SD onset with respect to asphyxia initiation, in contrast with the 1.5 min delay observed in adult rats (Hansen, 1977) – the longer delay possibly indicating a better tolerance of the nervous tissue against deleterious insults. Towards the other end of the life span, the frequency of spontaneous, recurrent SDs was, likewise, found significantly lower in the old (23–25 months old) than in young (1.5 months old) and the middle-aged (9 months old) rat brain in a model of focal cerebral ischemia (Clark et al., 2014). This finding stands in agreement with the above data gathered using experimental SD initiation. The reason for the low SD frequency at old age could not be identified with certainty, but SDs that are often long-lasting in the old brain considerably postponed – if not altogether prevented – the occurrence of subsequent SDs, which offered a plausible explanation (Clark et al., 2014). Indeed, the duration of transient SD triggered under ischemia appeared to be longer-lasting in the old rat brain as compared with the young (Menyhart et al., 2015). Further, in the focal ischemia model not only the higher incidence of long-lasting SDs was characteristic among the old animals than in the younger ones, but also the larger cortical surface involved in these prolonged SD events (Clark et al., 2014). Apparently, the recovery from SD in the old brain appears to be hampered. This may point towards or underlie the increased vulnerability of the old brain to ischemic conditions, and the pathophysiologic role SD is suggested to play in injury progression.

Curiously, in another study, the generation of a spontaneous SD in immediate response to bilateral common carotid artery occlusion was more frequently encountered in old animals than in their young counterparts (Menyhart et al., 2017b). Reflecting on the evidence presented here so far, this observation may seem perplexing at first, yet it is, in fact, complementary, and makes the interpretation of existing data more subtle. It must be appreciated that the spontaneous occurrence of SD in these experiments was strongly associated with a severe drop of perfusion (to 7–23% of baseline flow), rather than with age

itself, the serious perfusion deficit being more frequent among the old rats (Menyhart et al., 2017b). Taken together, we postulate that irrespective of the age-related electrophysiological threshold of SD elicitation (which has proven to be higher at old age), a sudden, large drop of cortical perfusion (i.e. blood flow plunging below 20%) will inevitably bring on SDs in the old brain, as well as in the young. We also believe that even though it is more difficult to trigger SDs in the aging brain, once SD is elicited during ischemia, it is persistent at old age, and its long duration may indicate metabolic crisis (Farkas and Bari, 2014).

The experimental research conducted so far has thus provided compelling evidence for the impact of age on the susceptibility of the cerebral gray matter to SD (Fig. 1), yet clinical studies are sparse in this regard, probably due to the inherent limitation of having to consider a high number of risk factors other than age. Still, SDs were reported to occur at higher incidence in young compared to older patients who suffered acute brain injury (Fabricius et al., 2006), which observation is in harmony with the experimental results.

In order to understand what cellular pathways may be altered to account for the higher resistance of the old nervous tissue against SD, the determining factors of SD occurrence will be examined next.

3. Mechanisms behind SD susceptibility

It has been inferred above that various parameters can be taken to express SD susceptibility, such as (i) the latency of SD occurrence with respect to the stimulus, (ii) the frequency of recurrent SD events, (iii) the rate of SD propagation, (iv) the distance SD covers over its course of propagation, or (v) the duration of ECoG depression. Some of these parameters concern SD initiation (i.e. latency with respect to igniting stimulus), others essentially characterize propagation (i.e. rate and distance covered, duration of ECoG depression), or represent a mixture of both initiation and propagation (i.e. frequency of recurrent SDs). The capability of the nervous tissue to recover from SD may be a relevant factor to consider as well, since delayed repolarization may postpone the occurrence of subsequent SD events, and is expected to reduce SD frequency. The network of astrocytes is thought to contribute to this process. In addition, the buffering capacity of astrocytes may also modulate the delay necessary to reach the neurochemical threshold of SD elicitation. Understanding what mechanisms drive SD initiation, propagation, and repolarization is a first step to appreciate how aging may impact on SD susceptibility.

3.1. SD elicitation

In the healthy mammalian brain, extracellular K^+ concentration is kept close to 3–4 mM, independent of fluctuations in blood serum levels (Somjen, 1979), but local changes in extracellular K^+ levels do occur following neuronal activity. In the injured brain, the concentration of K^+ (10–15 mM) sufficient to induce SD is presumably determined by the balance between K^+ efflux and the efficacy of K^+ clearance (Spong et al., 2016). In the context of spontaneous SD occurrence under hypoxia or ischemia, an initial outward K^+ current – which is also reflected by the slow depolarization preceding SD (Hansen, 1977; Hansen and Zeuthen, 1981) – may be, in part, a key trigger. This progressive accumulation of extracellular K^+ is thought to build up due to the reduced availability of ATP, which opens ATP-sensitive K^+ channels to hyperpolarize neurons via K^+ efflux (Sun and Hu, 2010), and, more importantly, reduces the efficiency of neuronal Na^+/K^+-ATPase and thus K^+ reuptake (Hajek et al., 1996). In addition, extracellular levels of K^+ typical of the ischemic penumbra were shown also to decrease Na^+/K^+-ATPase activity by 50% (Major et al., 2017), therefore K^+ itself may amplify its extracellular accumulation. The central role of Na^+/K^+-ATPase in SD initiation is clearly supported by the fact that tissue exposure to ouabain, a Na^+/K^+-ATPase inhibitor, readily produces SD (Balestrino et al., 1999). Ultimately, the excess K^+ in the extracellular space amounts to a depolarizing stimulus that, by the gradual shift in membrane potential, opens voltage-gated Na^+ channels to give way to Na^+ influx. The experimental elicitation of SD with high concentration KCl or electrical stimulation takes advantage of the artificial elevation of extracellular K^+ as well.

When a critical threshold of K^+ levels is reached, the self-propagating SD cycle takes off and invades neighboring tissue (Grafstein, 1956). However, the critical threshold of K^+ concentration appears to be subject to other, variable conditions such as the degree of metabolic impairment or the maturation of the brain, and a set threshold value that would be uniformly valid cannot be determined. To illustrate the variability of SD threshold from the perspective of aging, the extracellular concentration of K^+ sufficient for the spontaneous occurrence of SD due to asphyxia in adult rats (i.e. > 24 weeks old) ranged around 10–12 mM, but was over 20 mM in 12-week-old rats, and could be as high as 30 mM in 4-day-old pups (Hansen, 1977).

In migraine with aura, the progressive accumulation of K^+ to high concentration as it takes place in injured tissue is unlikely, therefore an increased sensitivity or hyperexcitability of neurons may stand in the center of SD elicitation (Vinogradova, 2018). In addition, hyperexcitablity may be relevant for ischemia-related SD, as well, since theoretically such a condition may predict SD occurrence at a lower threshold. Neuronal excitability is partly regulated by neuronal voltage-dependent Na^+ (Nav), K^+ (Kv), and Ca^{2+} (Cav) channels (Misonou, 2010). Structural variations, modulation by second messengers and genetic dysfunction of these channels might influence the SD threshold, the latter being implicated, for example, in familial hemiplegic migraine (FHM) type 1 (FHM1) and 3 (FHM3) (Dichgans et al., 2005; van den Maagdenberg et al., 2004). As such, FHM3 has been linked to a mutation of the α1 subunit of Nav 1.1 (encoded by the SNCA1A gene), which elicits neuronal hyperexcitability and might decrease SD threshold (Dichgans et al., 2005). Neuronal hyperexcitability, on the other hand, is prevented by the activation of Kv1 type delayed-rectifier K^+ channels (Hille, 1992). Interestingly, the selective pharmacological blockade of cerebellar Kv 1.1 and Kv1.2 channels – highly expressed in the cerebellar cortex and Purkinje-cells – was shown to decrease significantly the threshold of spreading acidification and depression in the cerebellar cortex, a phenomenon sharing similarities with SD (Chen et al., 2005). Another type of Kv channel to suppress neuronal excitability is the Kv7.2 (KCNQ2) ion channel (Wulff and Zhorov, 2008). Kv7.2 agonism was found to decrease the frequency of KCl-induced SDs in a dose-dependent manner, probably by promoting membrane hyperpolarization (Wu et al., 2003). Finally, a dominant-negative mutation in the TWIK-related spinal cord K^+ (TRESK) channel caused hyperexcitability in trigeminal neurons (Liu et al., 2013), and was linked to migraine with aura (Enyedi et al., 2012), but the contribution of TRESK channels to SD elicitation has not been demonstrated yet.

Neuronal excitability may be modulated by Cav channels as well. FHM1 is characterized by a mutation in the CACNA1A gene encoding the P/Q type Ca^{2+} channel (van den Maagdenberg et al., 2004), increasing its opening probability. In mice, the gain of function mutation was shown to lower electrical SD threshold *in vivo* in two different variants, S218L and R192Q, both of which were previously shown to be present in FHM patients. The decreased threshold of SD together with increased neuronal excitability is probably mediated by the higher opening probability of the channels at presynaptic terminals (Tottene et al., 2009).

Taken together, these experimental data suggest, that voltage-gated cation channels that tune neuronal excitability contribute to setting the threshold of SD elicitation.

3.2. SD evolution and propagation

Irrespective of whether SD is elicited experimentally or occurs spontaneously, the rapid and marked increase of extracellular K^+ is a powerful trigger, which depolarizes a critical volume of tissue of about 1 mm^3 (Matsuura and Bureš, 1971; Tang et al., 2014). The mass cellular

depolarization leads then to a near-complete breakdown of neuronal transmembrane potential (Somjen, 2001). More specifically, at any point of the tissue involved in SD, the influx of Na^+ leads the depolarization, causing a reduction of extracellular Na^+ concentration from 140 to 150 to 50–70 mM, accompanied by a sudden extracellular surge of K^+ from 3 to 4 to 30–60 Mm, a concurrent decrease of extracellular Ca^{2+} levels from 1 to 1.5 to 0.2–0.8 mM and that of Cl^- from 130 to 74 mM (Hansen and Zeuthen, 1981; Pietrobon and Moskowitz, 2014). Intracellular ion concentrations obviously change in the opposite direction.

The channels mediating K^+ efflux during depolarization are still to be explored, but it is reasonable to suggest that Kv channels must be involved, because the wide spectrum K^+ channel blocker tetraethylammonium (a drug that acts on inward rectifying and delayed outward rectifying K^+ channels) (Cook, 1990); and 4-aminopyridine (a blocker of inward rectifier and A-type K^+ channels) partially limited K^+ efflux with SD (Aitken et al., 1991; Somjen, 2001). Recent evidence indicates that large-conductance Ca^{2+}-activated K^+ (BK) channels contribute to the K^+ surge with SD (Menyhart et al., 2018), and ATP-sensitive K^+ channels that open under metabolic stress could also be involved (Somjen, 2001). Finally, it is suspected that during hypoxia/ischemia, massive nonselective $Na^+(Ca^{2+})/K^+$ conductances take place with SD, via a yet unidentified channel (Czeh et al., 1992, 1993; Gagolewicz, 2017).

Ca^{2+} influx with SD may take place through P/Q type Cav channels, which was tested by the application of gabapentine, an anticonvulsant agent, with P/Q type Ca^{2+} channel inhibitory potential. Gabapentin infusion effectively suppressed SD susceptibility in the intact rat cortex (Hoffmann et al., 2010). Likewise, the topical application of the P/Q type Cav channel blocker ω-agatoxin was also found to remarkably reduce the frequency of repetitive SDs (Richter et al., 2002).

In addition to the ion dislocations, interstitial glutamate concentration also increases from 3–3.5 to 10–11 μM with SD induced by KCl in normal rat cortex (Hinzman et al., 2015), or well over 100 μM in the striatum during anoxia (Satoh et al., 1999). The accumulation of glutamate may manifest via various pathways. Considering SD triggered experimentally in well-nourished tissue, the first results obtained with mutant P/Q type Cav mice suggested that Ca^{2+} influx with SD through these channels liberates glutamate and contributes to SD evolution (Ayata et al., 2000; Pietrobon and Moskowitz, 2014). Glutamate release with SD later was shown to be linked to presynaptic N-methyl-D-aspartate (NMDA) receptor-dependent vesicular exocytosis (Zhou et al., 2013). Further, SD has been found to open neuronal pannexin-1 channels (Karatas et al., 2013) that may also mediate the release of glutamate to some extent (Cervetto et al., 2013; Di Cesare Mannelli et al., 2015). Conversely, the pharmacologic inhibition of the P2X7-pannexin-1_{pore} complex suppressed SD, which was suggested to alleviate the release of K^+, glutamate and pro-inflammatory cytokines (Chen et al., 2017). Glutamate may also originate from astrocytes through pathological processes, including the possibility that increased extracellular K^+ concentration reverses excitatory amino acid transporters (EAATs) (Harada et al., 2015; Malarkey and Parpura, 2008; Nicholls and Attwell, 1990).

Once glutamate builds up to high concentrations, it may overstimulate NMDA receptors, thereby deepening the depolarization, and contributing to SD propagation by the further accumulation of K^+ and glutamate (Harreveld, 1959). Although the NMDA receptor is considered the primary glutamate receptor involved in SD facilitation, some recent studies indicate the role of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors (Costa et al., 2013) and extrasynaptic NMDA receptors (Hardingham and Bading, 2010) as well. Furthermore, recent investigations have suggested the specific involvement of NMDA receptor subtypes NR2A and NR2B in SD susceptibility (Shatillo et al., 2015; Wang et al., 2012). The involvement of the NMDA receptor in the sustenance of SD is underscored by influential clinical studies disclosing that the administration of ketamine, an NMDA receptor antagonist to patients of acute brain injury inhibits SD occurrence effectively (Carlson et al., 2018; Sakowitz et al., 2009). Finally, the volatile anesthetics isoflurane and N_2O, which also dampen NMDA receptor-based excitatory neurotransmission, were shown to suppress SD susceptibility in rats (Kudo et al., 2008). It must be noted, however, that SD evolving in response to anoxia/ischemia cannot be blocked by NMDA receptor antagonism, suggesting the negligible involvement of NMDA receptors in SD propagation under severe metabolic stress (Pietrobon and Moskowitz, 2014).

The volume of the extracellular space also adjusts the concentration of substances present in the extracellular fluid. Water passively follows the fluxes of Na^+ and especially Cl^- via Cl^--coupled transporters (Steffensen et al., 2015) to cause swelling of dendrites (termed "dendritic beading") and astrocytes (Risher et al., 2012), with a concomitant shrinkage of the extracellular space. This may increase the concentrations of extracellular K^+ and glutamate even further (Hansen and Olsen, 1980; Phillips and Nicholson, 1979).

All these results testify that once SD has been elicited, the levels of K^+ and glutamate, which facilitate SD, progressively rise. The propagation of SD, therefore, is thought to be self-sustained, advocated by the volume transmission of high concentration K^+ and glutamate generated by SD itself.

3.3. Recovery from SD

SD is a transient event – although its duration depends on the actual tissue metabolic conditions. The repolarization phase of SD, or recovery of the tissue from SD is mediated by neuronal Na^+/K^+-ATPase to serve K^+ reuptake (Major et al., 2017). Importantly, surplus K^+ is also removed effectively by astrocytes, utilizing various mechanisms including, for instance, astrocytic Na^+/K^+-ATPase, and K^+ siphoning via Kir 4.1 inwardly rectifying K^+ channels or water flux mediated through aquaporin-4 channels (Leis et al., 2005). Similar to K^+ clearance, glutamate buffering is an equally important factor in SD evolution. Glutamate clearance is mainly mediated by excitatory amino acid transporters 1 and 2 (EAAT1 and EAAT2), which are ion- and voltage-dependent, predisposing glutamate reuptake highly susceptible to changes in the ionic composition of the cellular environment and transmembrane potential. For example, EAAT2 is not only co-localized with Na^+/K^+-ATPase, but is also highly dependent on the ion gradient it generates (Cholet et al., 2002). Among EAAT subtypes, the glial specific EAAT2 appears to be responsible for more than 90% of glutamate reuptake in the forebrain (Rimmele and Rosenberg, 2016). The effective involvement of astrocytic buffering in SD management was proven by deleting aquaporin-4 channels, or hindering glutamate clearance. As such, the genetic knock-out of aquaporin-4 channels in mice decreased the rate of the K^+ surge and K^+ reuptake with SD, in association with a slower rate of SD propagation, and lower SD frequency (Yao et al., 2015). On the other hand, EAAT2-mediated glutamate clearance hampered in the absence of the α2 subunit of the astrocytic Na^+/K^+ ATPase was associated with the facilitation of SD initiation (Capuani et al., 2016). Moreover, mice carrying the genetic knock-in of an astrocytic Na^+/K^+ ATPase α2 subunit loss-of-function mutation – as it occurs in FHM2 patients – were prone to decreased SD threshold and increased rate of SD propagation (Leo et al., 2011). Conversely, ceftriaxone, one of the β-lactam antibiotics, stimulated the expression of EAAT2 in astrocytes and concurrently raised SD threshold in FHM2 mutant mice, while inhibition of EAAT2 in wild type mice lowered SD threshold (Capuani et al., 2016). These results collectively suggest that EAAT2 – in tight coupling with Na^+/K^+ ATPase – is essential for glutamate clearance by astrocytes with SD.

The capacity of astrocytes to remove excessive K^+ and glutamate might be enhanced by spatial dispersion via the astrocyte syncytium, shown to be effective during physiological neuronal activation (Kofuji and Newman, 2004; Pannasch and Rouach, 2013). Astrocytes (among other cell types) are linked by gap-junctions formed by two

hemichannels, which consist of pore forming proteins termed connexins. Gap junctions are permeable to small molecules, ions and second messengers, and serve as the structural basis for gliotransmission (Rovegno and Saez, 2018). Gap junctions might be assembled of different connexin isoforms, which determines the role and expression pattern of the pore, placing connexins in the position of indicating intercellular communication. The exact role of connexins in SD initiation and propagation has yet to be explored (Rovegno and Saez, 2018), but the hypothesis may be formulated that the inter-astrocytic movement or redistribution of ions and messengers may facilitate ion or glutamate removal, and thus reduce SD susceptibility. In contrast with this view, exposure to non-specific connexin inhibitors (halothane, octanol and heptanol) blocked SD initiation in the isolated chicken retina (Nedergaard et al., 1995), suggesting that connexin-based channels may enable the intercellular diffusion of ions, and support the propagation of SD. However, much of the work that focused on the involvement of connexins in SD evolution must be interpreted with caution, because the non-selective inhibition of connexins probably impaired inter-neuronal in addition to astrocyte network communication. Also, apart from gap junctions, connexins form unpaired hemichannels, which are large and non-specific pores at the intra- and extracellular interface. Their contribution is often not discriminated at data interpretation (Rovegno and Saez, 2018).

Among the numerous connexin isoforms, connexin-43 has emerged as a constituent of astrocyte gap junctions. Focusing on the glial syncytium alone, the genetic inactivation of connexin-43 selective for astrocytes markedly reduced astrocyte network communication, and increased the rate of SD propagation in the hippocampus of adult mice (Theis et al., 2003). This refined approach does support the hypothesis posited above, confirming the ability of intact astrocyte network function to keep SD in check.

A recent study also revealed that tonabersat, a migraine prophylactic drug that inhibits SD (Goadsby et al., 2009) does not only modulate neuron-satellite glia signaling in the trigeminal ganglion by acting on connexin-26 (Damodaram et al., 2009), but also blocks connexin-43 hemichannels in isolated human cerebral microvascular endothelial cells during simulated ischemia (Kim et al., 2017). The collective evidence that a connexin-43 hemichannel blocker drug inhibits SD may be contradictory to the finding that connexin-43 deletion in astrocytes facilitates SD, but again, the disparity of model systems (i.e. intact mouse brain vs. endothelial cell culture under simulated ischemia; gap junction vs. hemichannel) may render the satisfactory integration of the existing data challenging.

4. The impact of aging on the mechanisms involved in SD evolution

4.1. The impact of aging on SD elicitation

The aging brain appears to be increasingly resistant to SD initiation, as indicated by the higher threshold of experimental SD elicitation (Hertelendy et al., 2017; Maslarova et al., 2011; Menyhart et al., 2015). Less is known about the generation of spontaneous SDs, so – aware of the limitations – we infer here that data obtained with experimental SD initiation – whether in the intact or the ischemic gray matter – also applies for spontaneous SDs. The reasons behind the increased threshold of SD elicitation at old age may be manifold. It is conceivable that the stimulus applied is dissipated in the tissue before SD is ignited. Some evidence suggest that the excitability of the aged nervous tissue is lower, because the age-specific increase in the production of reactive oxygen species modifies the operation of the redox-sensitive K^+ channels (Sesti, 2016) (Fig. 2B). This process may modulate the oligomer formation, permeation and gating properties of Kv channels and BK channels (Sesti, 2016), but it remains to be explored whether these changes manifest at the level of SD evolution. Age may also hamper the recruitment of the minimum tissue volume required for SD initiation. Indeed, the wave front of SD in the old cerebral cortex appears to be narrower than in the young, as seen in imaging studies, and possibly reflected by the shorter transient ECoG depression typical of SD (Farkas et al., 2011; Hertelendy et al., 2017; Makra, 2018).

4.2. The impact of aging on SD evolution and propagation

In addition to the age-related modification of Kv and BK channel function mentioned above (Sesti, 2016), P/Q type Cav channels implicated in SD evolution were shown to be affected by aging, as well. Protein levels of P/Q type Cav channels in synaptosomes extracted from the cerebral cortex significantly decreased at preserved synaptic density

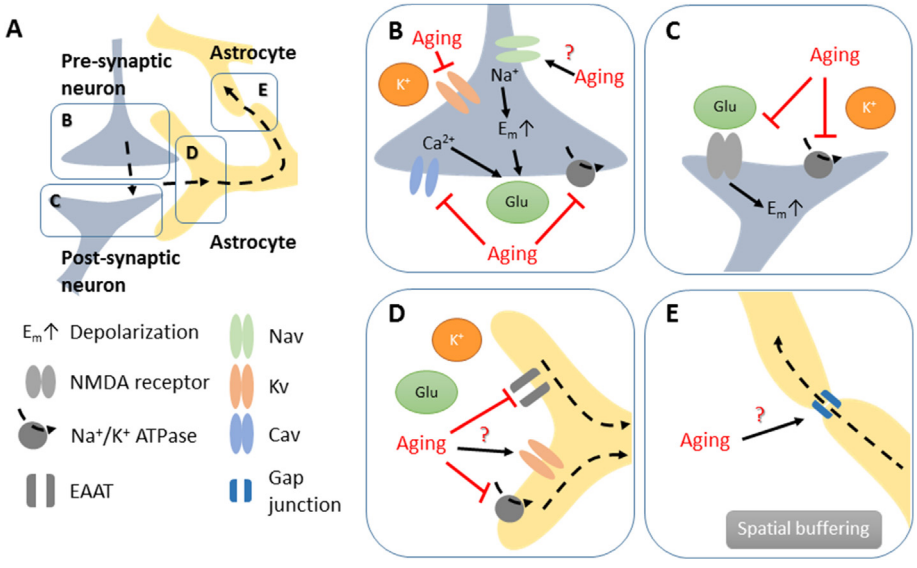

Fig. 2. Conceivable targets of aging, implicated in the susceptibility of the nervous tissue to spreading depolarization (SD). A, Schematic illustration of the cellular elements hosting ion channels and transporters that are involved in SD evolution. B, Age-related dysfunction of the Na^+/K^+ ATPase may contribute to K^+ accumulation in the interstitial space to trigger SD. While little is certain about the impact of aging on voltage-gated Na^+ channels (Nav), the augmented production of reactive oxygen species with aging may alter voltage-gated K^+ channel (Kv) function to reduce the excitability of the nervous tissue (Sesti et al., 2016). Finally, aging may suppress the expression of P/Q type voltage-gated Ca^{2+} channels (Cav) (Iwamoto et al., 2004) that may increase SD threshold. C, The age-related downregulation of NMDA receptor subunits implicated in SD (Kumar et al., 2015; Shatillo et al., 2015; Wang et al., 2012) may impair NMDA-based glutamate (Glu) signaling and SD propagation. Potassium reuptake may be also hampered by the activity of the Na^+/K^+ ATPase decreased in the aging brain (Benzi et al., 1994; Chakraborty et al., 2003; Cohadon and Desbordes, 1986; de Lores Arnaiz and Ordieres, 2014; Kocak et al., 2002). D, Clearance mechanisms linked to astrocytes, such as Na^+/K^+ ATPase activity, the expression of excitatory amino acid transporters (EAAT) and K^+ syphoning through Kir4.1 channels may become ineffective or lower in the aging brain, leaving higher concentration of K^+ and glutamate in the extracellular space, and thereby delaying repolarization. E, The spatial buffering capacity of astrocytes complementing clearance mechanisms may also be altered by age, although direct evidence in support of the suggestion is still to be acquired. Note, that the concept put forward here is not meant to be comprehensive, and may provoke further thoughts.

in old rats compared to adults (Iwamoto et al., 2004). Since the pharmacological inhibition of P/Q type Cav channels was shown to suppress SD occurrence (Richter et al., 2002; Hoffmann et al., 2010), the decreased expression of the channel protein at old age may also impede SD evolution (Fig. 2B).

The ionic movements underlying SD are also accompanied by the release of glutamate, which sustains SD by binding to and activating NMDA receptors. The decay of NMDA receptor-based signaling with aging has been repeatedly demonstrated in the context of suboptimal synaptic neurotransmission and failing cognitive performance (Kumar, 2015). It is plausible that NMDA receptor-based signaling is compromised due to oxidative stress mounting to levels relevant for functional deterioration in the aged brain. Declining NMDA receptor function was, for example, linked to the oxidation of Ca^{2+}/calmodulin-dependent protein kinase II (Bodhinathan et al., 2010). Among a number of potential mechanisms that may affect NMDA receptors in aging, the expression of distinct NMDA receptor subunits was found to be subject to age-related changes, as well (Kumar, 2015). Importantly, mRNA and protein expression of the modulatory NR2A and the NR2B subunits, both implicated in SD evolution (Shatillo et al., 2015; Wang et al., 2012), appeared to be downregulated in the aged brain (Kumar, 2015; Magnusson et al., 2010; Zhao et al., 2009). In summary, the age-related dysfunction of NMDA receptors may restrict SD evolution (Fig. 2C).

4.3. The impact of aging on the recovery from SD

The proper function of neuronal and astrocytic Na^+/K^+ ATPase, and K^+ and glutamate clearance mechanisms of astrocytes significantly contribute to the cessation of SD (Leis et al., 2005; Major et al., 2017), which is hampered in the old ischemic brain with respect to the young (Clark et al., 2014; Menyhart et al., 2015).

Most studies conducted in this regard agree that the activity of the Na^+/K^+-ATPase decreases in the aging brain (Benzi et al., 1994; Chakraborty et al., 2003; Cohadon and Desbordes, 1986; de Lores Arnaiz and Ordieres, 2014; Kocak et al., 2002). Crude miscrosomal preparations must have provided evidence for the combined weakening of neuronal and astrocytic Na^+/K^+-ATPase activity, because this approach is not expected to discriminate between cell types (Kocak et al., 2002). On the other hand, investigations using synaptosomes demonstrated the age-related decline in neuronal Na^+/K^+-ATPase activity, selectively (Benzi et al., 1994; Chakraborty et al., 2003). Moreover, enzyme activity decreasing with age has been linked to oxidative stress, which is enhanced in the aged brain (Chakraborty et al., 2003). It is noteworthy that Na^+/K^+-ATPase hyperactivity in response to ischemia is less obvious in the aging than in the adult brain (Villa et al., 2002), in agreement with the slower recovery from SD reported in old rats suffering from cerebral ischemia (Clark et al., 2014; Menyhart et al., 2015).

Apparently, astrocytes in the aged brain display morphological alterations as well as functional adaptation (Verkhratsky et al., 2016), and show characteristics of senescence-associated secretory phenotype (Salminen et al., 2011). Intuitively, age-related loss of function should include the reduction of the efficacy of astrocyte transport mechanisms, but there is only few and indirect or conflicting evidence to be lined up. As such, both transcript and protein levels of the Kir4.1 channel and the EAAT2 glutamate transporter were shown to be gradually downregulated in the pericontusional cortical region over 3 days after experimental TBI in mice, which proved to be more pronounced in the old group of animals with respect to adults (Gupta and Prasad, 2013). Yet, in the uninjured cortex of the same mice, aging itself increased Kir4.1 and aquaporin-4 transcript and protein levels, interpreted as an adaptive response to maintain K^+ and water homeostasis (Gupta and Kanungo, 2013). Further, aquaporin-4 channels participating in astrocytic K^+ uptake appeared to be less polarized (i.e. more dispersed) in astrocyte end feet in old mice (Kress et al., 2014). The expression of glial fibrillary acidic protein (GFAP) increases with age (Salminen et al., 2011), and the expression of EAAT2 has been found to decrease with increasing GFAP content, at least in brain samples of Alzheimer's disease patients (Simpson et al., 2010). It is also intriguing that the amplitude of Ca^{2+} signaling in astrocytes in response to the activation of their NMDA receptors was found markedly decreased at old age in protoplasmic cells isolated from the rodent cortex (Lalo et al., 2011), which may indicate that aging astrocytes are less responsive to glutamate. Altogether, these data are suggestive that transport and signaling by astrocytes are altered in the old brain (Fig. 2D and E). Yet it remains to be investigated to what degree astrocyte aging contributes to the recovery from SD, delayed in the old cerebral gray matter, especially under ischemic conditions.

Finally, astrocyte network function that relies on gap junctional contacts between adjacent cells may be subject to aging. Even though the level of the most typical astrocytic gap junction protein connexin-43 seems to be maintained into old age in the rodent brain and retina, the number, size and connexin composition of astrocytic gap junction plaques may change (Cotrina et al., 2001; Mansour et al., 2013). Whether these subtle but detectable alterations in gap junction structure contribute to any (mal)adaptation of astrocyte network communication with aging is yet to be examined.

5. Additional factors that modulate SD susceptibility: relevance for brain injury

5.1. Metabolic status of the tissue

The metabolic status of the tissue has already been alluded to in the previous chapters as an important factor to modulate SD evolution, but its distinct aspects have not been discussed so far. The supply of glucose and oxygen are crucial for the proper working of energy-dependent ion pumps, and thus the effective maintenance of resting membrane potential. The first indication that the restricted availability of energy substrates facilitates, while surplus glucose impedes SD was delivered by creating systemic hypo- and hyperglycemia in rats. Hypoglycemia shortened, while hyperglycemia postponed the onset delay of SD in response to hypoxia initiation (Hansen, 1978). Later, hyperglycemia was also shown to elevate the electric threshold of SD elicitation, and to reduce the frequency of high K^+-induced recurrent SDs in normally-perfused tissue (Hoffmann et al., 2013). Hypoglycemia, on the other hand, did not alter SD susceptibility, but prolonged the cumulative duration of recurrent SDs elicited in the otherwise intact cortex (Hoffmann et al., 2013). Interestingly, suppression of glycogen, lactate or glucose utilization in the cerebral cortex of mice reduce SD elicitation threshold, suggesting a significant role for astrocyte-neuron lactate shuttle during SD (Kilic et al., 2018). In conclusion, the unlimited supply of circulating plasma glucose may restrict the repeated occurrence of SD in the intact and ischemic cerebral cortex.

While hyperglycemia thus appeared to suppress SD, hyperoxia did not affect the duration of SD, neither did hypoxia in anesthetized, normotensive rats (Sukhotinsky et al., 2010). Yet, in a model of focal cerebral ischemia, episodic hypoxia or sensory stimulation causing neural activation was associated with the elicitation of spontaneous SDs in the somatosensory cortex (von Bornstadt et al., 2015). The mechanisms suggested to be involved include a worsening mismatch between increasing O_2 demand against a reduced O_2 supply in ischemic penumbra tissue (von Bornstadt et al., 2015).

Anaerobic metabolism in ischemic tissue produces lactic acidosis (Katsura et al., 1991), which is considerably augmented by SDs emerging (Menyhart et al., 2017b; Selman et al., 2004). It has been long appreciated that mild tissue acidosis suppresses SD, because pH 6.67–6.97, achieved by HCl or NaOH application, the elevation of pCO_2 or withdrawal of bicarbonate in the medium of brain slice preparations inhibited SD initiation and reduced the velocity of SD propagation (Tombaugh and Somjen, 1996; Tong and Chesler, 2000). Low pH may restrict SD evolution via NMDA receptor inhibition (Tang et al., 1990)

or by the adjustment of the conductance and gating properties of Kv, Nav, and Cav channels (Tombaugh and Somjen, 1996). Recent analysis has refined the view that acidosis impedes SD by presenting that lower tissue pH predicted smaller SD amplitude in the normally perfused cerebral cortex only, while the positive correlation between tissue pH and SD amplitude was lost under ischemia in anesthetized rats (Menyhart et al., 2017a). In the ischemic tissue, the SD suppressing effect of tissue acidosis was proposed to be obscured by glutamate and K^+, present at high concentration.

5.2. Neuroinflammation

Neuroinflammation has been recognized as a central pathogenic component of cerebral ischemia. Microglia, the resident immune cells of the brain are heavily implicated in mediating the inflammatory response. SD is known to activate microglia (Shibata and Suzuki, 2017), and evidence has also been accumulating recently that activated microglia may, in turn, promote SD generation. Of note, the selective elimination of microglia was found to elevate SD threshold in brain slices (Pusic et al., 2014), and to reduce the incidence of spontaneous SDs in mice subjected to focal cerebral ischemia (Szalay et al., 2016). Particularly, the M1 polarization of microglia may contribute to SD initiation (Pusic et al., 2014). Activated microglia are the source of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα) and interleukin-1β (IL-1β), which may mediate the microglia-related potentiation of SD. Experimental data addressing the role of TNFα in SD susceptibility remain, however, inconclusive. Exposing brain slices to TNFα for 3 days prior to SD elicitation decreased the threshold of SD (Grinberg et al., 2013), yet the acute, topical administration of TNFα on the cortical surface of anesthetized rodents reduced SD amplitude, probably by augmenting GABA release via the activation of TNFα receptor type-2 (Richter et al., 2014). The action of IL-1β in a similar experimental setting was found dose dependent, as only the lower dose used attenuated SD amplitude (Richter et al., 2017). Microglia-derived cytokines may, therefore, modulate SD susceptibility in various, complex ways, which deserve further examination.

5.3. Nitric oxide

Acute cerebral ischemia gives rise to nitric oxide (NO) production, partially in response to the release of pro-inflammatory cytokines (Willmot et al., 2005; Murphy and Gibson, 2007). While NO produced by the neuronal and inducible isoforms of nitric oxide synthase (nNOS and iNOS, respectively) were shown to be neurotoxic (Huang et al., 1994; Zhao et al., 2000), NO from endothelial source (eNOS) may be protective against injury (Huang et al., 1996). From the perspective of SD susceptibility, the non-selective pharmacological blockade of NOS lowered SD threshold (Petzold et al., 2008), while the selective inhibition of nNOS did not significantly alter SD initiation (Petzold et al., 2008; Urenjak and Obrenovitch, 2000). Complementary experiments relying on the use of eNOS or nNOS knock-out mice revealed that particularly eNOS-derived NO upheld the physiological threshold of SD elicitation. The availability of NO from an endothelial source may, therefore, fine-tune the susceptibility of injured tissue to SD.

All these data attest that the network of pathways that are capable of the modulation of SD susceptibility intersect and are rather complex. Obviously, a therapeutical approach to lessen SD occurrence in patients may be most effective if a number of SD suppressing approaches were to be combined and tailored to the unique conditions of specific groups of patients.

6. Conclusions

The last fifteen years witnessed a rapid advance in our understanding of the pathophysiologic role SD plays in migraine with aura (Goadsby et al., 2017), and particularly in the progression of secondary lesions in acute brain injury (Dreier et al., 2017; Hartings et al., 2017). Recurrent SDs evolving from minutes up to weeks following the primary insult have been recognized to contribute to the growth of secondary injury of ischemic nature, and worsen clinical outcome of neurological conditions.

Even though aging may reduce the susceptibility of the nervous tissue to SD (Clark et al., 2014; Farkas et al., 2011; Hertelendy et al., 2017; Maslarova et al., 2011; Menyhart et al., 2015), the consequences of SD recurrence in the old brain have proven to be graver (Farkas and Bari, 2014). For example, tissue acidosis implicated in ischemic neurodegeneration is associated with SD, and is disproportionately more pronounced in the old brain than in the young (Menyhart et al., 2017a, 2017b). The cerebral blood flow response to SD may turn into deleterious spreading ischemia in the injured tissue (Dreier, 2011), which is more probable in the aged cerebral cortex than in the young (Clark et al., 2014; Menyhart et al., 2015). In fact, SDs coupled with spreading ischemia appear to cause an overall reduction of cerebral blood flow in the old brain, over a period when partial flow compensation should take place (Clark et al., 2014; Menyhart et al., 2015). Finally, prolonged SD indicative of scarcer metabolic resources of the tissue covers larger tissue volume in the old as compared with the young cerebral cortex in experimental focal ischemia (Clark et al., 2014). All these results underscore the augmented pathogenic potential of SD in the aging brain.

The suppression of recurrent SDs or counteracting SD associated spreading ischemia is a realistic approach for neuroprotection, and is expected to be beneficial for injury outcome after SAH, malignant ischemic stroke or TBI. A number of experimental studies conducted to this end have presented evidence that NMDA receptor blockade (Sanchez-Porras et al., 2015; Reinhart and Shuttleworth, 2018), or the inhibition of P/Q type Ca^{2+} channels potentially reduces SD susceptibility (Hoffmann et al., 2010). On the other hand, L-type voltage-gated Ca^{2+} channel antagonism was shown to reverse spreading ischemia to hyperemia (Dreier et al., 1998), and lessen the weight of early hypoperfusion in the full cerebral blood flow response to SD (Menyhart et al., 2018). The first clinical trials to prevent repeated SD occurrence by the application of ketamine are promising (Carlson et al., 2018; Sakowitz et al., 2009). Taken that recurrent SDs may pose an increased burden in the aging injured brain, the benefit of therapeutic approaches to restrict SD generation and propagation may be particularly relevant for elderly patients.

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Conflicts of interest

The Authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2018.10.010.

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