

## Special Issue: Brain Aging

# Spreading Depolarization in the Ischemic Brain: Does Aging Have an Impact?

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Recurrent waves of spreading depolarization (SD) spontaneously occur minutes after the onset of focal ischemia in the brain and keep generating for a number of days to follow. It has become widely accepted that ischemia-related SDs are part of the pathophysiology of cerebrovascular diseases and predict worse outcome. SDs may exacerbate ischemic injury via related atypical hemodynamic responses. The incidence of ischemic stroke is known to increase markedly with age; yet, very few studies investigated whether age alters SD evolution and whether a potential age-specific pattern of SD would contribute to the age-related intensification of infarct development. Experimental data demonstrate that aging has a marked impact on SD evolution and corresponding changes in cerebral blood flow. We hypothesize that an age-specific pattern of the SD-associated hemodynamic response must be involved in augmenting the expansion of ischemic brain damage in the elderly patients and that structural and functional (mal)adaptation of the cerebrovascular system with aging serves as a potential basis for compromised vascular reactivity and subsequent tissue damage. The concept put forward is expected to stimulate further investigation to achieve a comprehensive overview of the implication of SD in injury progression in the aged brain.

**Key Words:** Aging—Cerebral blood flow—Cerebral ischemia—Spreading depolarization—Stroke.

Received March 13, 2014; Accepted March 31, 2014

Decision Editor: Rafael de Cabo, PhD

BRAIN injury as a result of stroke can have devastating effects on the patients' quality of life and imposes a heavy burden on the health care system. The resultant neurological deficit obviously depends not only upon the severity and nature of the initial injury but also upon secondary and progressive deleterious events, such as spreading depolarization (SD). Research on SD considerably accelerated in the last decade, in part because SD has been directly and consistently shown to occur in the injured human brain (1,2). SD has been recognized as a potent pathogenic phenomenon that contributes to the progression of ischemic brain injury, and it has become increasingly clear that the occurrence of SD predicts worse clinical outcome from neurological casualties (3,4). Based on accumulating evidence, monitoring SD has been proposed as a potential tool to help design the optimal intervention and therapeutic strategy in neurological intensive care (1).

Clinical investigation of SD is limited due to ethical issues, the unpredictability of SD events, and the restricted range of methods that can be applied in a clinical setting. Accordingly, it is highly relevant to explore the neurodegenerative mechanisms of SD and cerebrovascular pathology in animal models. The early phase of ischemia may be

of special interest because the early SD events that evolve shortly after the onset of an ischemic insult typically escape detection in patients due to the lag between injury onset and admission to a health care unit or the start of data acquisition. Thus, complementary data obtained from clinical and experimental studies will promote our understanding of the pathogenic role SD plays in cerebrovascular diseases. Accordingly, the current review presents experimental and clinical findings side-by-side for the direct comparison, integration, and translation of results.

The incidence of ischemic stroke is known to increase markedly with age; yet, experimental studies examining the role of SD in lesion progression are conventionally carried out with young adult laboratory animals. The reasons for this are likely convenience related: young animals are easy to obtain, tolerate surgical intervention reasonably, mortality rates are low, and fewer animals are required to produce data that are relatively uniform with acceptable variation within experimental groups. Yet, the suitability of young animal models for stroke has been the target of recent debate within the scientific community because it has become widely acknowledged that observations made in young animals may not be directly translated to

human cerebrovascular disease states (5). This applies for SD research as well, where appropriate, aged animal models are needed to elucidate the exact contribution of SD to injury progression in elderly stroke patients.

With the present review, we wish to raise awareness that the age-related alteration of SD evolution may be a symptom or possibly a factor contributing to the escalation of ischemic brain injury in the elderly patients. Because data concerning the impact of age on the pattern of SD is sparse, the topic addressed here may encourage investigators to focus on features of SD evolution typical of the aging brain. This, then, may offer relevant information to better understand the etiology and pathomechanisms of cerebrovascular diseases in elderly patients.

### SPREADING DEPOLARIZATION EVOLVES IN THE ISCHEMIC BRAIN: PATHOGENIC POTENTIAL

Cortical SD is a wave of intense, synchronized depolarization of a critical mass of neurons and glia cells, which propagates across the cerebral cortex at a rate of 2–6 mm/min (6,7). SD can be experimentally initiated in the otherwise physiologically intact cortex by the topical application of high-concentration potassium, local electrical stimulation, or focal mechanical insult (7). High concentration in extracellular potassium and glutamate also mediate the feedforward depolarization event as it propagates across gray matter (7). Regarded originally an experimental curiosity, spontaneously generating SD has proven to be a potent pathogenic phenomenon in neurological diseases such as migraine with aura, subarachnoid hemorrhage, traumatic brain injury, and ischemic stroke (1,8).

Recurrent waves of SD spontaneously occur minutes after the onset of focal ischemia in the rat brain (9,10), whereas single SD events typically evolve within the first hour after global forebrain insults (11). A primary population of SDs typically emerges in the first 2 hours after the induction of focal ischemia, and a secondary SD cluster can generate with a peak frequency approximately 12 hours later (12). In the gyrencephalic cat brain, SDs were recorded to occur up to 14 hours (end point of experiments) after the onset of ischemia (13). Finally, clinical studies identified SDs up till 9 days after the surgical intervention for the alleviation of the primary injury (3,14). The experimental and clinical data together demonstrate that injury-related SDs first occur shortly after the primary ischemic insult and keep generating for a number of days to follow.

SD has long been suspected to aggravate ischemic injury. Indeed, the coincidence of SD evolution and infarct maturation was demonstrated by a linear correlation between the total number or cumulative duration of recurrent SDs and the infarct volume, established after middle cerebral artery occlusion in rats (15,16). In subarachnoid hemorrhage patients, delayed ischemic neurological deficit corresponded with a sequence of recurrent SDs (3). Further, the

prolonged duration of SDs was related to the maturation of cortical lesions after traumatic brain injury (4). The relationship between SD occurrence and injury progression appears causal because KCl-induced SDs invading the penumbra from remote sites increased infarct volumes in experimental stroke (17,18). Moreover, an experimental imaging study revealed that the site of SD elicitation gradually migrated from near the primary ischemic core to increasingly distant areas in the parietal cortex over a 4-hour monitoring period after middle cerebral artery occlusion in the rat (19). If SDs are triggered at the rim of an infarct, this observation indicates, indirectly, the growth of the infarcted area, probably by the conversion of penumbra to infarct. At tissue level, ischemia-induced SDs coincide with dendritic beading and loss of spines indicative of synaptic disintegration (20), and prolonged astroglial swelling leading to disturbed tissue homeostasis (21). In summary, experimental results show that SDs are involved in the progression of ischemic damage during the subacute phase of injury (22), whereas groundbreaking clinical studies have gathered evidence that clusters of prolonged SDs play a key role in delayed injuries and predict worse clinical outcome (3,4).

SDs are thought to initiate in the core or at the border of the ischemic focus in focal ischemia and propagate across tissue not yet infarcted (23–25). In global ischemic models, in which the definition of ischemic core becomes redundant, the site of SD elicitation is suspected to fall in regions most susceptible for the ischemic insult, or undergoing the gravest perfusion deficit due to relatively low microvascular density or uneven perfusion (11). Accordingly, the determination of a flow threshold for SD elicitation is a relevant approach to identify conditions favorable for SD onset. The flow threshold was estimated as the lower range of the brain's autoregulatory capacity in global ischemia (11) or defined accurately as being around 40 ml/g/min in focal ischemia (26). Yet, the ultimate, direct cause of SD elicitation is the critical, elevated concentration of extracellular  $K^+$  and/or glutamate (7), both of which accumulate in the ischemic brain due to increased release from neural elements and altered clearance by astrocytes (27,28).

The duration of SD (ie, the time measured at half amplitude between depolarization and repolarization) extends with the increasing severity of ischemia (1). Thus, at least three types of SD can be differentiated based on duration: (i) short transient SD, which persists from 20 seconds up to a few minutes; (ii) intermediate or prolonged SD, which may last as long as an ischemic flow reduction and be followed by repolarization synchronous with the recovery of local cerebral blood flow (CBF); and (iii) terminal SD, which is not followed by the restoration of resting membrane potential at any time later (1). The prolonged duration of SD indicates the insufficiency of membrane ion pumps to repolarize neurons (1) and is proposed to represent increasingly more severe injury to the brain tissue (4). Researchers agree that the cellular mechanisms corresponding with prolonged

SD include sustained intracellular calcium overload in neurons (20,29). Intracellular calcium accumulation synchronous with glutamate release and N-methyl-D-aspartate receptor activation during SD would resemble excitotoxic events. Yet, no definitive consensus has been reached as to whether SD-related intracellular calcium load is dependent on N-methyl-D-aspartate receptor activation though the most recent results support this concept (20,29,30).

SDs are currently believed to exacerbate ischemic brain injury via related atypical hemodynamic responses (Figure 1). In the rat, the physiological pattern of SD-associated CBF changes is composed of an initial, brief drop of CBF; a marked, transient hyperemia; and a sustained hypoperfusion also known as spreading oligemia (31,32). These three subsequent phases of the SD-related CBF response are assumed to be the result of a sequence and combination of separate vasoregulatory mechanisms (32,33). In man, the pattern of the SD-related CBF response has been acquired only in disease states, but comprehensive analysis and comparison of the CBF response in the rat and patients revealed a good correspondence (34). Hence, the characteristics of the CBF response in the rat are assumed to be applicable for man, and data obtained from rat models are regarded highly relevant for human disease states. Similar to physiological neuronal activation, the evolving functional hyperemia induced by SD supplies the brain tissue with energy substrates to be used by ion exchange pumps for the restoration of resting membrane potential.

The SD-related CBF response shows diverse kinetics in animal models of cerebral ischemia: (i) the hyperemic element may be suppressed; (ii) the initial CBF drop and the spreading oligemia phase of the response may become undetectable, leaving only an obvious hyperemic component visible on the CBF recording; (iii) all three elements of the CBF response may remain obscure; or (iv) the CBF response may develop as hypoemia rather than hyperemia with a particular SD (11,35–39). The reversed CBF response has become known as spreading ischemia and is considered as a result of inverse neurovascular coupling (1). A wide spectrum of ischemic SD-related CBF responses were acquired in patients ranging from dominating hyperemia to prolonged cortical spreading ischemia with intermediate forms characterized by biphasic (hypoemic–hyperemic) responses (40,41).

The vasoregulatory mechanisms that modulate the pattern of CBF responses during ischemia are complex. The normal hemodynamic response to SD is achieved by a fine balance between constrictive and dilator vasoregulatory mechanisms (33). Ischemia alters the baseline tone of arteries: shortly after the occlusion of a cerebral vessel, vasodilation evolves distal to the site of occlusion as an autoregulatory response to maintain CBF against decreasing perfusion pressure. This leads to maximal vasodilation and exhausts microvascular reserve capacity. Days after the primary injury, vasospasm may develop, which is implicated in delayed cerebral

ischemia after subarachnoid hemorrhage (42). In addition to the shift in baseline vascular tone, ischemia also causes endothelial cell dysfunction (43), thereby compromising specific elements of vascular reactivity. A combination of adjusted baseline tone and impaired vascular reactivity during ischemia may set the scene for dominating vasoconstriction, which may account for hampered hyperemia, or spreading ischemia with SD. Vasoconstriction may prevail because local vasoconstrictive mediation becomes accentuated or because counteracting vasodilators that would normally balance out vasoconstriction are not available. Experimental evidence for both options have been gathered. As such, vasoconstrictive mediation in response to electrical field stimulation was shown in brain slices derived from rats with experimental subarachnoid hemorrhage. The vasoconstrictor stimulus was identified as perivascular  $K^+$  concentration increased above the dilation/constriction threshold (20 mM). The excessive extracellular  $K^+$  accumulated as the result of efflux from astrocytes via large-conductance  $Ca^{2+}$ -activated  $K^+$  channels (44). On the other hand, as an example for the role of counteracting vasodilators, the presence of nitric oxide (NO) mediated vasodilation of the isolated middle cerebral artery in the face of elevated extracellular  $K^+$  concentration typical of SD, whereas vasoconstriction developed in the absence of NO (45). A corresponding in vivo study identified NO scavenging (eg, by hemoglobin) as the mechanism limiting NO availability and thereby creating vasoconstrictive CBF response to SD (36). Disabled vasodilation may also uncover the effect of vasoconstrictive prostanooids, which were proposed to mitigate the SD-related vasodilation in the intact brain (46).

The pattern of CBF response associated with a particular SD is not conserved through the course of SD propagation but can change as the same SD travels across areas with varying severity of ischemia. For example, CBF response was hypoemic in the vicinity of the ischemic core but transformed into hyperemia with the increasing distance from the core in animal models of cerebral ischemia and in patients with malignant stroke (37,38,41). These results imply that the metabolic consequences of an SD must be most harmful when the site of SD elicitation is in close proximity to the ischemic core.

The hyperemic types of CBF responses coupled with ischemic SDs may not be necessarily harmful, but under specific conditions, they are suggested not to satisfy the metabolic demand of the tissue and aggravate metabolic supply–demand mismatch (Bere et al., unpublished data, 2014) (Figure 1). The injurious nature of the CBF response may lie in deficient vascular reactivity following SD occurrence: vasodilation that typically evolves in response to hypercapnia, acidosis, and increasing  $K^+$  concentration is severely impaired for hours after the passage of an SD (47–49). In an ischemic environment, such prolonged vasomotor dysfunction may prevent the evolution of proper vasodilation to arising stimuli and thereby become deleterious for the survival of nervous tissue that is already challenged.

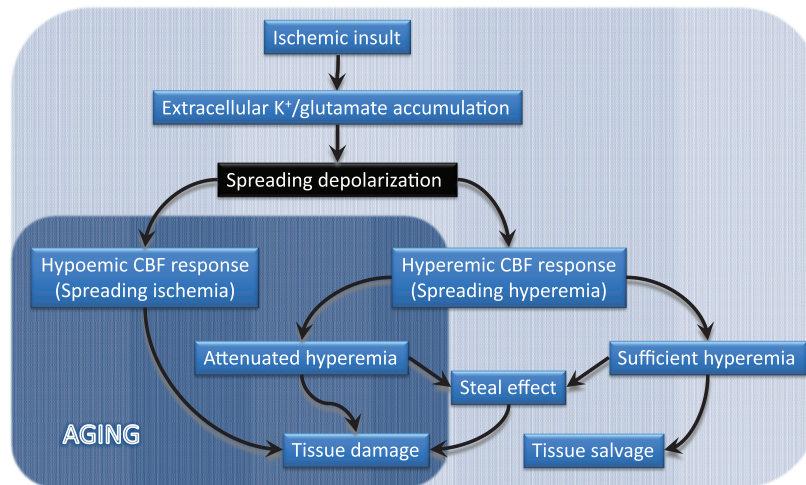


Figure 1. Conceptual cascade of events that lead to various types of hemodynamic response and tissue outcome associated with spreading depolarization. Note that aging sets the scene for the higher incidence of adverse cerebral blood flow (CBF) patterns.

In addition, hyperemic CBF responses may impose cerebrovascular steal in the ischemic region (Figure 1): the hyperemic response may mobilize arterial blood destined to supply more severely hypoperfused territories, thereby further depriving those territories of oxidative substrates (50). This process would cause injury remote to the site of the hyperemic response itself.

Finally, spreading ischemia is the most harmful type of CBF response as it is proposed to maintain a vicious cycle of sustained neuronal depolarization, persistent release of vasoconstrictors, and fatal tissue adenosine triphosphate depletion (1). This concept is supported by the observation that the extent of cortical area with deep perfusion deficit increased with each successive SD in the rat brain (Clark et al., accepted for publication, 2014) (25). Ultimately, SDs with such CBF responses inevitably cause damage to the tissue (37). The above cascade of events is particularly relevant for the maturation of brain infarcts at the expense of the penumbra in ischemic injury (22).

Experimental and clinical observations thus demonstrate convincingly that spontaneous SDs regularly occur in ischemia and are often coupled with atypical hemodynamic responses, which impose irrevocable damage to the ischemic nervous tissue.

#### AGE ALTERS THE TYPICAL FEATURES OF SPREADING DEPOLARIZATION: IMPLICATIONS FOR ISCHEMIC BRAIN INJURY

Even though stroke may occur in any phase of life, aging emerges as the most important independent risk factor for the incidence and prevalence of ischemic stroke (51,52). Aging also significantly predicts poor patient outcomes (52). 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.

As an obvious approach to reveal the influence of aging of stroke pathophysiology, the infarct volume after experimental cerebral vessel occlusion was estimated and compared in young adult (2–4 months) and aging (9–24 months) rodents (52). Aged females consistently had worse stroke outcomes than their young counterparts, whereas studies utilizing male animals remained inconclusive in this respect (52). Still, older mice invariably exhibited more severe neurological impairments and significantly higher mortality rates irrespective of infarct volume (53). Infarct development and neuronal degeneration early after transient middle cerebral artery occlusion were accelerated in old rats compared with their young counterparts (54), and the conversion of penumbra into infarction increased with advancing age in patients (55). SD facilitates early infarct development and the conversion of the penumbra to infarct, but very few studies exist that investigated (i) whether age alters SD evolution and (ii) whether a potential age-specific pattern of SD would contribute to—or at least coincide with—the age-related intensification of infarct development. Such studies would be timely because clinical SD research has, now, achieved the reliable identification of SD events and associated hemodynamic variations in patients.

We have found in rat models that the advancement of age reduces the frequency of  $K^+$ -induced recurrent SDs and increases the latency between subsequent SD events (56). In addition, the rate of SD propagation decreased with increasing age, and SDs failed to propagate longer distances frequently in the aged compared with the young rat brain (57). The susceptibility of the brain to SD may be determined by several features of the gray matter's biochemistry and cytoarchitecture (eg, volume of the interstitial space and maturation of neurotransmitter systems) that undergo adaptational changes during aging (7).



Similar to  $K^+$ -induced SDs, the number of spontaneous SDs during transient focal ischemia was lower in aged rats (Clark et al., accepted for publication, 2014). A clinical study that identified SDs after acute brain injury also reported a higher incidence of SD in young compared with older patients (58). Taken together, the aging brain appears to be less susceptible for SD elicitation. Nevertheless, the ratio of prolonged SDs of all SDs recorded in the ischemic penumbra was found considerably higher in old than in young rats (54% and 7%, respectively), and the cortical surface involved in the propagation of prolonged SDs tripled in old rats with respect to their young counterparts (Clark et al., accepted for publication, 2015). All things considered, the threshold to trigger SDs is higher in the aging brain, but once elicited during ischemia, SDs are persistent and their long duration may indicate metabolic crisis. This may accelerate infarct maturation or extend the volume of infarct in the aging brain.

The deleterious effect of SD is widely attributed to the associated CBF response, the pattern of which may also alter with advancing age. As such, the magnitude of the distinct elements of the CBF response was found to decrease in rats and in a transgenic mouse model of human cerebral amyloid angiopathy with normal aging (56,59). In addition, the hyperemic component in rats developed at a significantly lower rate with age (56), and spreading ischemia—in contrast with spreading hyperemia—appeared in the ischemic penumbra with a significantly higher incidence in old compared with young rats, which coincided with the prevalence of prolonged SDs (Clark et al., accepted for publication, 2014). These results infer that attenuated or reversed SD-coupled CBF response is more probable in the aging brain. Because spreading ischemia appears to have a higher incidence in the aged ischemic brain (Clark et al., accepted for publication, 2014) and the perfusion deficit after the onset of ischemia was shown to worsen in a step-wise fashion with each successive spreading ischemic episode (37), the aging ischemic brain is suggested to be at an increased risk for SD-related injury.

Aging, interacting with pathophysiological events, has a paramount impact on the microvasculature, including exacerbated endothelial damage and blood–brain barrier disruption (60,61). The SD-related CBF response weakens or more frequently inverts in the ischemic penumbra with aging, possibly because aging reorganizes the microvascular architecture unfavorably or renders the cerebral vasoregulatory mechanisms less efficient or compromised (Figure 2). It is a prevailing hypothesis supported by experimental and clinical evidence that the arrangement of native collaterals (ie, vessels that exist before an ischemic insult) or effective cerebrovascular remodeling following ischemic injury may define the fate of the penumbra (62,63). Consequently, inadequate collateral CBF must be an important determinant of infarct growth (64). Indeed, insufficient collateral reserve was shown to contribute to adverse tissue outcome

observed in elderly patients of ischemic stroke (65). Further, experimental data demonstrated that the number and diameter of native collaterals connecting the middle and anterior cerebral artery trees were significantly lower in aged compared with young mice (66). In addition, collateral remodeling after middle cerebral artery occlusion was impaired in the aging ischemic mouse brain, resulting in increased infarct volume (66). SD would normally initiate vasodilation and mobilize reserve blood for the hyperemic response to develop. The rarefaction of collaterals in the penumbra intensified by aging as described earlier may serve as a potential underlying structural basis for attenuated hyperemic CBF responses to SDs (Figure 2).

Aging inflicts functional impairment of the cerebral vasculature as well, which may play a role in the deterioration of the SD-related flow response in the aging ischemic brain. For example, the magnitude of functional hyperemia evoked by whisker stimulation was markedly attenuated in aging mice, and the CBF increase induced by the topical application of the vasodilators acetylcholine or bradykinin also weakened (67). Further, the reduced vascular reactivity to acetazolamide challenge after internal carotid artery occlusion was more obvious in aged than in young mice (68). These functional alterations were associated with vascular and neuronal oxidative stress because scavengers of reactive oxygen species prevented the attenuation of the CBF response (67). The above results on cerebrovascular reactivity suggest that compromised vasodilation caused by oxidative stress may also be involved in the reduced magnitude of the SD-coupled hyperemia in the aging brain (Figure 2).

Focusing on spreading ischemia, an elegant *in vitro* study demonstrated that at elevated extracellular  $K^+$  concentration typical of SD, the presence of NO mediated vasodilation of the isolated middle cerebral artery, whereas vasoconstriction developed in the absence of NO (45). Based on these results, the bioavailability of NO appears to be a decisive

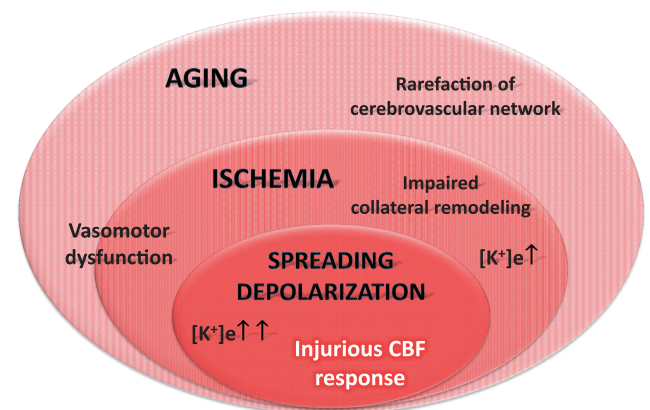


Figure 2. Aging and ischemia impose structural and functional alterations in the cerebrovascular network. The additive impact of these processes is suggested to contribute to the evolution of injurious cerebral blood flow (CBF) responses coupled to spreading depolarization.

condition for the shift to spreading ischemia in the face of an extracellular ionic milieu typical of SD. There is no conclusive evidence that NO synthase expression is hampered in the aging brain (69,70), but increased free radical production restricts NO availability in old rats, which causes dysfunctional NO-based vasodilation (70,71). This age-related pathophysiological process, in combination with elevated extracellular  $K^+$  concentration in the ischemic penumbra, offers an explanation for the higher incidence of spreading ischemia in aged rats.

Besides the contribution of vascular elements of the neurovascular unit to the modulation of the SD-related CBF response, the role of astrocytes in the process deserves consideration. Astrocytes depolarize with SD and are heavily involved in  $K^+$  buffering during SD (7). Moreover, astrocytes control local CBF, via selective increase of  $Ca^{2+}$  concentration in astrocytic endfeet and related efflux of  $K^+$  through various types of  $K^+$  channels (28,72,73). Oscillatory elevation of intracellular  $Ca^{2+}$  in astrocytes was suggested to be a response to glutamate (74), which is released at high concentration during SD and ischemia. Increased glutamate receptor stimulation may contribute to the elevating magnitude of spontaneous astrocytic  $Ca^{2+}$  oscillations, which was proposed to lead to  $K^+$ -dependent inverse neurovascular coupling in response to electrical field stimulation observed after subarachnoid hemorrhage (44). The aging process alters astrocyte function unfavorably and accelerates injury-induced astrocyte reactivity (75). This may conceivably impact on the astrocyte-based vasoregulation and contribute to compromised CBF responses to SD in the aging, ischemic brain.

In summary, the structural and functional changes of the cerebrovascular network that occur during aging are postulated to predispose the microvasculature to atypical CBF responses with SD. This, in turn, is suggested to pose a higher risk for the incidence of SD-related injury in the aging brain.

#### ARE AGE-RELATED CHANGES IN SD EVOLUTION RELEVANT FOR OTHER NEUROLOGICAL DISEASE STATES?

Migraine is a common neurovascular disorder. Migraine often occurs for the first time between 15 and 24 years of age, is most common in the 35 to 40 age group, and is known to decrease in frequency and severity with advancing age (76). About a quarter of all migraines is associated with aura that appears shortly before or during the progression of a migraine headache. It has been long contemplated that SD is involved in the pathophysiology of migraine with aura (8,31). More specifically, the aura is thought to be initiated by the elicitation of SD in the visual cortex, the propagation of which coincides with the expansion of the visual symptoms (scintillation-scotoma) (77). Moreover, the propagation of the long-lasting oligemic component of the CBF response to SD can be identified by single photon emission tomography

in patients with migraine with aura (78). According to the theory, the ventral spreading of SD causes activation of pain-sensitive fibers and related development of headache (31).

The experimental evidence collected here demonstrates that the aging but otherwise intact brain becomes less susceptible for SD elicitation and propagation (56,57). This appears to coincide with the clinical data that migraine headaches become less frequent and severe with advancing age and often cease after the age of 50–60 years. The evaluation of this thought-provoking relationship is highly complicated by the fact that genetic factors and hormonal fluctuations are known to influence the development of both migraine and SD (79–81). Still, the careful, comprehensive examination of the relationship between SD, aging, and migraine with aura would help dissecting processes involved in the evolution of migraine, with the ultimate goal to design effective therapy.

#### CONCLUSION

The summary of the available experimental data demonstrates that aging has a marked impact on SD evolution and corresponding changes in CBF. The presented overview of the field of research has led to the hypothesis that an age-specific pattern of the SD-associated CBF response must be involved in augmenting the expansion of ischemic brain damage in the elderly patients. We propose that structural and functional (mal)adaptation of the cerebrovascular system with aging serves as a potential basis for compromised vascular reactivity and subsequent tissue damage. The process may be relevant for the extension of brain infarcts in the subacute and delayed phases after a primary episode of stroke. The concept put forward mainly relies on initial data derived from experimental SD research, and may stimulate further investigation to achieve a comprehensive overview of the implication of SD in injury progression in the aged brain.

#### FUNDING

This study was supported by grants from the Hungarian Scientific Research Fund (OTKA 81266) and the Hungarian National Development Agency (TÁMOP-4.2.2A-11/1/KONV-2012-0052).

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