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SPECIAL ARTICLE

New concepts regarding cerebral vasospasm: glial-centric mechanisms

Nouveaux concepts concernant le vasospasme cérébral: des mécanismes centrés sur la glie

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Abstract

Purpose *Poor outcome in patients with cerebral vasospasm following subarachnoid hemorrhage remains a serious clinical problem. The current management with focus on the cerebrovascular constriction accounts for the use of "triple-H" therapy (hypertension, hypervolemia, and hemodilution) to enhance cerebral blood flow through constricted vessels. Recent work suggests that spreading depression (a stereotypical response of cerebral cortical tissue to noxious stimuli with subsequent oligemic blood flow) occurs in patients with cerebral vasospasm. A narrative review was conducted to examine the relationship between spreading depression and subarachnoid hemorrhage and to identify the anesthetic effects on the propagation of spreading depression.*

Principal findings *Following review of the literature, an underlying mechanism is advanced that cerebral vasospasm is not primarily a problem of the cerebral vasculature but a consequence of glial cell dysfunction following spreading depression – a glial-centric cause for vasospasm. Such a mechanism for vasospasm becomes manifest when spreading depression waves transition to peri-infarct depolarization waves – with protracted ischemic blood flow in compromised tissue. The extracellular microenvironment with high potassium and low nitric oxide tension can account for conducting vessel narrowing.*

Conclusions *The implication for clinical management is discussed supposing glial cell dysfunction is an underlying mechanism responsible for the vascular spasm.*

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Résumé

Objectif *Les mauvais pronostics chez les patients manifestant un vasospasme cérébral à la suite d'une hémorragie sous-arachnoïdienne demeurent un problème clinique majeur. La prise en charge actuelle se concentre sur la constriction vasculaire cérébrale, ce qui explique le recours au traitement dit des « trois H » (hypertension, hypervolémie et hémodilution) dans le but d'améliorer le débit sanguin cérébral dans les vaisseaux contractés. Des recherches récentes suggèrent qu'une dépression propagée (une réaction typique du tissu cortical cérébral aux stimuli nociceptifs, laquelle est suivie d'un débit sanguin réduit) survient chez les patients manifestant un vasospasme cérébral. Un compte-rendu narratif a été entrepris afin d'examiner la relation entre la dépression propagée et l'hémorragie sous-arachnoïdienne ainsi que d'identifier les effets des anesthésiques sur la propagation de la dépression propagée.*

Constatations principales *Après avoir passé en revue la littérature sur le sujet, l'hypothèse d'un mécanisme sous-jacent est avancée, selon laquelle le vasospasme cérébral n'est pas un problème principalement lié à la vasculature cérébrale mais plutôt la conséquence d'un dysfonctionnement des cellules gliales après une dépression propagée - en d'autres mots, le vasospasme est causé principalement au niveau glial. Ce mécanisme qui provoque le vasospasme est manifeste lorsque les vagues de dépression propagée se changent en vagues de dépolarisation autour de l'infarctus, soit avec un débit sanguin ischémique prolongé dans les tissus compromis. Le micro-environnement extracellulaire, qui comporte des quantités élevées de potassium et basses d'oxyde nitrique, peut expliquer le rétrécissement des vaisseaux conducteurs.*

Conclusion *Les implications de ces découvertes dans la prise en charge clinique sont discutées en partant de*

l'hypothèse que le dysfonctionnement des cellules gliales est l'un des mécanismes sous-jacents responsables du spasme vasculaire.

Cerebral vasospasm (marked narrowing of conducting arteries and parenchymal arterioles) following subarachnoid hemorrhage (SAH) remains a major cause of morbidity and mortality.[1-4] Vasospasm may account for up to one-third of infarctions or deaths following a cerebral bleed – estimated to affect up to 1.2 million patients worldwide per annum.[5] Radiologically, from 60-70% of patients with SAH manifest with vasospasm, which is detectable for up to two weeks following the ictus. Up to one-half of these patients will experience clinical signs of cerebral ischemia. The onset is commonly within three to 12 days after the initial hemorrhage.

Historical mechanisms

Historically, vasospasm following SAH has been deemed to be a problem of the cerebral vasculature (Figure 1). Blood in the subarachnoid space bathing cerebral vessels in some manner causes vasoconstriction. Various mediators of constriction have been advanced: irritation from hemoglobin or breakdown products of hemoglobin, including bilirubin oxidation products (BOXes) and other reactive oxygen species; binding of nitric oxide (NO) by hemoglobin; production of endothelin-1 by damaged endothelium; generation of 20-hydroxyeicosatetraeonic acid (20-HETE) from arachidonic acid; infiltration of the vessel wall by inflammatory cells resulting in vessel narrowing; and manipulation of cerebral vessels during surgical intervention to clip the ruptured aneurysm.[5-8]

The premise of "triple-H" therapy (hypertension, hypervolemia, and hemodilution), which remains a cornerstone of management of intractable cerebral vasospasm, is that ischemia will be relieved by overpowering vessel vasoconstriction by a greater perfusion pressure.[2,9,10] Indeed, this combination therapy can be therapeutic in a significant proportion of patients but often at a cost, especially in the elderly with the potential or reality of myocardial ischemia, pulmonary edema, or renal compromise.

A new mechanism

Recent reviews of cerebral vasospasm provide newer insights to the underlying mechanism of vasospasm. An exciting concept is that vasospasm is related to cortical spreading depression (SD).[6,11-21] In Table 1, there is a synopsis of the current relevant literature based on a search in PubMed with the following strategy, "spreading depression" OR "cortical spreading depression" AND "subarachnoid hemorrhage". Nine of the 13 papers highlighted were published within the past two years. Over 60 years ago, Leão first described spreading depression in experimental animals as a wave of electroencephalogram (EEG) silence moving slowly across the cortical surface (typically at 2-4 $mm \cdot min^{-1}$).[22,23] For the interested reader, a comprehensive review of spreading depression is given by G.G. Somjen.[24] Much work in the 1970s and 80s identified the marked alterations in neuroglial ion fluxes that occurred with SD (extracellular potassium rapidly increasing to 40-50 $meq \cdot L^{-1}$ resulting in EEG silence with

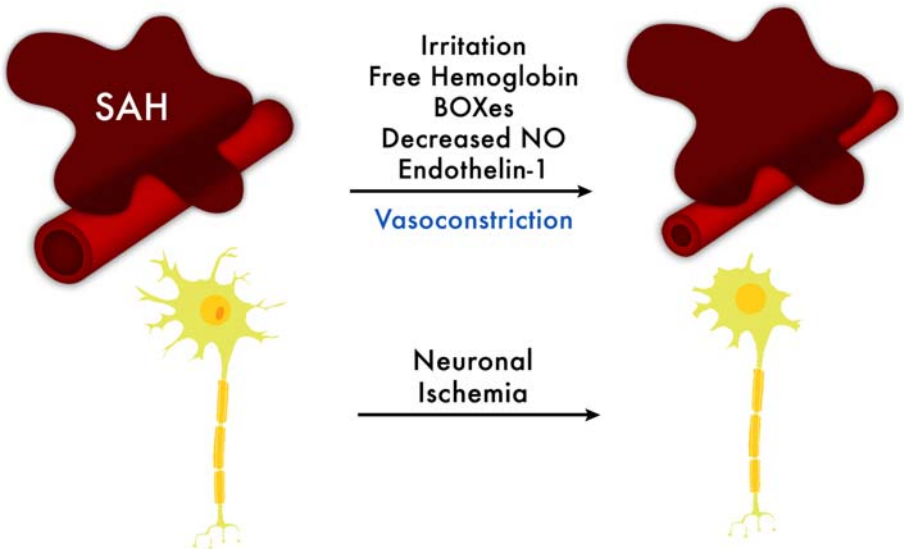

Fig. 1 A stylized diagram of the historical conception of subarachnoid blood leading to cerebral vasoconstriction. Local bleeding leads to heme breakdown products resulting in cerebral vasoconstriction with ischemic damage to adjacent neurons

Table 1 Spreading Depression and Subarachnoid Hemorrhage

STUDY	SPECIES	NUMBER STUDIED	AGENTS USED	REMARKS	ANCILLARY COMMENTARY
Sakowitz *et al.* 2009 (Ref. 11)	human	2	ketamine ($2 - 3\ mg \cdot kg^{-1} \cdot hr^{-1}$)	Case 1 severe head injury with subdural hemorrhage	uncertain if neuro protection afforded
				53 SDs by EcoG over 40 hr. No SDs after ketamine	
				Case 2 SAH and IVH	
				9 SDs by ECoG over 27 hr. No SDs after ketamine	
Izenberg *et al.* 2009 (Ref. 14)	human	4	observational	Four patients with stereotypical migraine auras referred for crescendo TIAs	awareness of this presentation to prevent mistreatment
				All patients found to have SAH after imaging	
Dreier *et al.* 2009 (Ref. 12)	human	13	observational	ECoG and regional blood flow recorded in patients with SAH.	vascular signature noted - low freq vascular fluctuations
				417 SDs noted in these patients	
Pluta *et al.* 2009 (Ref. 6)	human	N/A	review article	State of the art thoughts on cerebral vasospasm	stresses need for new thought processes
				SD is discussed as potentially important mechanism related to vasospasm	
Pearl and Macdonald 2008 (Ref. 15)	human	N/A	review article	Discusses advances in treatment of cerebral vasospasm	poor results with clazosentan discussed
				SD raised as a possible mechanism re vasospasm	
Petzold *et al.* 2008 (Ref. 16)	rat	8	thiopental	In rats and also rat and human brain slices blocking NO lowered SD threshold and induced spreading ischemia	basal NO determined SD threshold
	slices	14			reduced NO promoted ischemia
Macdonald *et al.* 2007 (Ref. 13)	human	N/A	review article	Review of current management including poor results with clazosentan highlighted	SD suggested as cause of vasospasm with high probability
Hansen-Schwartz *et al.* 2007 (Ref. 17)	human	N/A	opinion piece	Discussion of thought processes re vasospasm over past 50 years. Possible relationship of SD with poor outcome discussed	New thought processes for vasospasm needed
Strong *et al.* 2007 (Ref. 18)	human	N/A	current opinion	SD and the more injurious peri-infarct depolarizations re traumatic or ischemic brain injury discussed including SAH	Improved care for glucose and temperature highlighted
Petzold *et al.* 2005 (Ref. 19)	rat	10	MK-801	In presence of high extracellular potassium NMDA antagonist could not prevent SD	situation with ischemic penumbra or SAH
	brain slices	12			
Petzold *et al.* 2003 (Ref. 20)	rat	60	thiopental	In presence of oxyhemoglobin and endothelin-1 SD converted to spreading ischemia	Experimental situation similar to SAH conditions clinically

Table 1 continued

STUDY	SPECIES	NUMBER STUDIED	AGENTS USED	REMARKS	ANCILLARY COMMENTARY
van den Bergh *et al.* 2002 (Ref. 21)	rat	52	fentanyl/midazolam/fluanisone	Experimental SAH resulted in SD waves. Duration attenuated with magnesium (90 $mg \cdot kg^{-1}$)	diffusion weighted lesion size reduced
Dreier *et al.* 1998 (Ref. 47)	rat	77	thiopental	superfusion of cortex with hemoglobin and increased potassium resulted in spreading ischemia effect also seen when NOS inhibitor added	marked drop in CBF seen in this model

ECoG = electrocorticogram; SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; TIA = transient ischemic attack; SD = spreading depression; NO = nitric oxide; CBF = cerebral blood flow; MK-801 = dizocilpine

concomitant decrease in extracellular sodium, chloride, and calcium with a net decrease in extracellular volume at the wave front with movement of water into cells). There is marked hyperemia with the spreading wavefront, followed by a modest long-lasting regional oligemia after passage.[24] Nedergaard and Hansen[25] found no evidence of ischemic pathology in the cortex of rats with a normally perfused cortex. A considerable body of work has equated SD as the underlying mechanism of classical migraine (see review by Gorji).[26] Now a series of studies have demonstrated that multiple SD waves can occur in patients following SAH.[12,27]

Following middle cerebral artery occlusion (MCAO) in the baboon, Branston *et al.*[28] identified transient increases in extracellular potassium with voltage alterations similar to those seen with SD in the ischemic penumbra. Strong and Dardis[29] provided further elucidation in cats. Such penumbral disturbances became known as peri-infarct depolarizations (PIDs). These PIDs differ from SDs in that they are spontaneous, of greater ion flux duration, and associated with protracted periods of ischemic blood flow. Progression to terminal depolarization can occur with repeated PIDs unless substrate delivery can be enhanced. It is suggested that PIDs increase the size of the umbral region of ischemia unless controlled. A very comprehensive overview of these events entitled *Depolarization phenomena in traumatic and ischemic brain injury* is provided by Strong and Dardis.[29]

Resolution of the extracellular potassium load following SD is primarily a function of astrocytes.[30] The astrocyte behaves as a nearly perfect potassium electrode with local changes in membrane potential difference reflective of local potassium concentration.[31] Astrocytic spatial buffering of local changes in potassium enables neuronal transmembrane potential to be re-established for subsequent discharge. The spatial buffering is accomplished through the astrocytes behaving as a synctium. Recent evidence indicates that this function is, in part, accomplished via connections through cellular hemichannels and gap junctions.[32] Ischemia has been shown to open gap junction hemichannels in neurons providing a mechanism for the marked fluxes seen in ions.[33] Intracellular recordings indicate that the neuronal transmembrane potential (V_m) can reach zero millivolts (mV) with SD. This is different from that seen with neuronal discharge where V_m reaches +20 mV. It has been suggested that simultaneous opening of several or all membrane conductances occur with SD (energy dependent, voltage-gated, ionophoretic, and hemichannel).[29]

One of the hallmarks of SD is that a protracted period of decreased cerebral blood flow is seen following the event.[34] Multiple SD waves can enhance this effect.[35] The effect is greatly enhanced with the onset of peri-infarct

depolarizations.[18] Recurrent SD or PID waves result in local glutamate toxicity due to decreased clearance of glutamate load secondary to inadequate spatial buffering by astrocytes. Spreading depression increases the expression of inflammatory cytokines, such as interleukins (IL-1β) and tumour necrosis factor-α.[36] In this context, microglia – the macrophages of the brain - release multiple cytotoxins further impairing astrocyte function.[32] In contrast, microglia have also been shown to block the spread of local damage in the brain by process outgrowth that is chloride channel dependent.[37] In the face of multiple SD or PID waves, it is uncertain if local damage control, as above, could become more generalized. The microglial cytotoxins attract inflammatory cells that contribute to the well-documented increase in inflammation of the cerebral vessels suffering from vasospasm. When SD is initiated experimentally, neuronal injury occurs with evidence of oxidative stress in the presence of astrocyte energy failure.[38] Spreading depression results in reactive oxygen species (ROS) production, in and of itself, independent of subarachnoid blood[39,40] and also initiates expression of immediate early genes, such as c-fos and jun-B.[41]

Woertgen *et al.*[42] have shown the relationship between intraoperative clipping of cerebral aneurysms and the risk of cerebral vasospasm. In patients with temporary clipping of feeding vessels, the incidence of cerebral vasospasm was much higher than if a temporary clip was not required (34% *vs* 20%). As well, temporary clipping duration was correlated with the development of vasospasm. Prevention of cerebral hypoxia in the ipsilateral hemisphere during temporary clipping of the feeding vessel to the aneurysm appears paramount and may be an inciting mechanism for SD during surgery. Also, the rare but documented occurrence of cerebral vasospasm following successful clipping of an unruptured aneurysm can be explained by the SD model of cerebral vasospasm.[43] Twenty-five years ago, Dr. Gardner-Medwin and the author suggested the importance of recurrent SD as a potential source of injury and poor outcome in neurosurgical patients.[44] As well, these authors have studied the effect of hypocapnia (a standard of care during neurosurgical procedures to control intraoperative brain volume) on prolonged resolution of the extracellular potassium load if SD should occur.[45]

Newer potential mechanisms for vessel narrowing

Recent work provides a mechanism linking the presence of PIDs and the large vessel narrowing that is seen with established cerebral vasospasm.[46] Cerebral ischemia and subsequent infarction with PIDs have been proposed as the underlying mechanism of widespread cortical infarction seen diffusely at autopsy following lethal SAH. Spreading ischemia or PID can be induced in rats with a topical application of oxyhemoglobin (as a NO scavenger) in the presence of elevated potassium concentration.[47] *In vitro* experiments demonstrate that superfusing isolated middle cerebral arteries with an ionic cocktail with a composition similar to that seen following PIDs results in vessel constriction in the presence of NO synthase inhibition. The change in diameter from baseline conditions approached 50% narrowing.[46] The predominant vasoconstrictor in the cocktail was the elevated concentration of potassium. Herein lies a mechanism relating the parenchymal alterations that are seen with PID with SAH and large conducting vessel constriction.

Glial-centric model of vasospasm

Collectively, the above analysis suggests that the lesion leading to cerebral vasospasm following subarachnoid bleeding is not principally an alteration in the cerebral vessel, as historically thought, but is a consequence of glial cell dysfunction – both astrocyte and microglia following SD transitioning to PID (Figure 2). Noxious stimuli (represented by blood and its breakdown products) initiate the SD or PID waves. The astrocyte is unique in providing a support function to neurons. Each astrocyte foot process on a cerebral vessel provides a critical linkage between neuron and vessel. Astrocytes behaving as a synctium are critical to spatially buffer extracellular potassium (re-establishing the transmembrane potential to permit neuronal function) and to spatially buffer glutamate (a neurotransmitter that can quickly become neurotoxic).[32] Astrocytes control local vasomotor tone via direct contact with the cerebral vasculature. Recent work indicates that elevated intracellular calcium in astrocytic endfeet, a recognized consequence of neuroglial ion fluxes seen with SD, results in local cerebral vasoconstriction following production of 20-HETE in vascular smooth muscle in an environment of low concentrations of NO.[48] As noted above, this exact scenario exists with SAH with high levels of 20-HETE and consumption of NO from heme breakdown products.[49] The spatial buffering of the astrocyte with generated intracellular calcium waves[50] is a clue as to why vasospasm can become generalized, even in the face of local cisternal blood following rupture of a cerebral vessel. The above alterations in astrocyte signalling and microenvironment changes provide a mechanism to understand the origin of marked local oligemia with PID. The author, together with Gardner-Medwin, have shown the effects of diminished substrate supply to the recovery of SD waves by initiating hypocapnia either with or without mild changes in perfusion pressure.[51] Also, the author highlighted the mechanisms of extracellular acidosis by SD and its

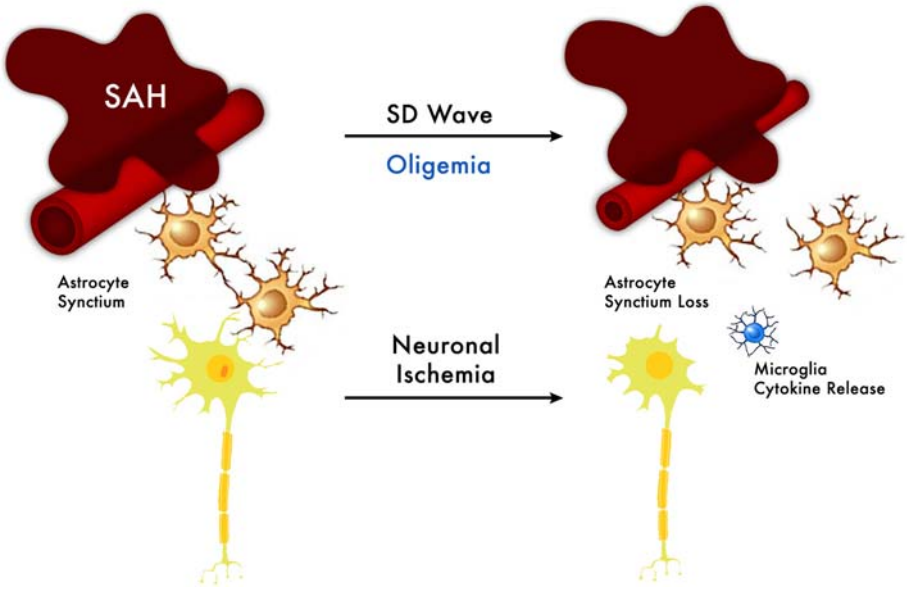

Fig. 2 A stylized diagram of the glial-centric model of cerebral vasospasm following the formation of spreading depression (SD) waves. Blood in the subarachnoid space generates multiple SD waves that cause glial cell dysfunction following glutamate accumulation with hemichannel disruption. Local glutamate toxicity results in the release of inflammatory cytokines from microglia. Spreading depression waves result in increased intracellular calcium concentrations in astrocytic endfeet generating 20-HETE with smooth muscle contraction in the cerebral vessel, which leads to vasoconstriction and neuronal ischemic damage

similarities to cerebral ischemia.[52] Extracellular acidosis can lead to permanent closure of hemichannels leading to local astrocyte dysfunction.[53,54] Non-vesicular glutamate release can be modulated by alterations in pH.[55] With glutamate toxicity, microglia become activated and release cytotoxins via hemichannels.[56]

Consequences of the glial-centric model of cerebral vasospasm

The described mechanisms to account for cerebral vasospasm based on glial cells rather than endothelial cells provide insight into our lack of progress in the treatment of vasospasm. Despite numerous improvements in neurosurgery, neuroanesthesia, critical care, and interventional radiology, the harsh reality is that advances in the management of cerebral vasospasm have been, at best, incremental. Cerebral angioplasty is a recognized advance in the management of cerebral vasospasm, but this is a mechanical intervention not furthering our understanding of the inciting mechanisms. Various vasodilators and anti-inflammatory agents have been tried with very limited success. Nimodipine is the only vasodilator that is widely used.[57] Real hope was placed on the introduction of clazosentan (a specific endothelin-1 antagonist), but despite evidence of attenuation of vessel spasm, outcome was not improved and a number of complications may have contributed to the lack of success, including pulmonary complications and systemic hypotension.[15] Such disappointment with an agent expected to be very successful strongly suggests that a true understanding of what vasospasm comprises remains elusive. A glial-centric theory that accounts for cerebral vasospasm bears a resemblance to a recently published thesis that astrocyte dysfunction is pivotal to Wernicke's encephalopathy with thiamine deficiency.[58]

Potential consequences of a glial-centric model of vasospasm

If a glial-centric model of cerebral vasospasm is correct, a number of our standard therapies are problematic. Anesthetic agents may be especially important in this context. Table 2 highlights the retrieved studies examining the impact of anesthetic agents on spreading depression. This is a synopsis of the current relevant literature based on a search in PubMed with the following strategy, "spreading depression" OR "cortical spreading depression" AND "anesthetic agents". Seventy-eight papers were identified, and the 15 that were documented involve a comparison of various anesthetic agents or deal with an anesthetic agent compared with awake controls on SD propagation and were published in the last 20 years.[59-73] The majority of these studies compared volatile agents primarily with α-chloralose. Halothane consistently attenuates SD waves. Less information is available for isoflurane and sevoflurane. No data are available for desflurane. Ketamine, a known N-methyl D-aspartate (NMDA) receptor antagonist, is a potent attenuator of SD waves. Fixed agents, such as thiopental, pentobarbitone, diazepam, α-chloralose, and equithesin are markedly less efficacious. It is worth noting that propofol has not been studied but would be expected to be similar to the other fixed agents. In light of the data from Table 2, the following commentary is advanced:

Table 2 Anesthetic effects on spreading depression

STUDY	SPECIES	NUMBER STUDIED	AGENTS USED	REMARKS	ANCILLARY COMMENTARY
Kudo *et al.* 2008 (Ref. 59)	rat	77	Isoflurane ± N_2O ± 100% O_2	Urethane highest rate for SD, similar to pentobarbital	
			Urethane ± N_2O ± 100% O_2	N_2O decreased SD with isoflurane or urethane	
			α-chloralose	Decreased propagation speed and duration with N_2O	
				No effect with 100% O_2	
Sonn and Mayevsky, 2006 (Ref. 60)	rat	13	Awake, equithesin	Anesthesia decreased frequency, slowed recovery, decreased energy production	With true controls
Horiguchi *et al.* 2005 (Ref. 61)	rat	72	Increased inspired concentrations halothane	No effect on initiation of SD but decreased O_2 demand and energy production decreased with increased halothane 0.5, 1.0, 2.0% inspired	preconditioning, effect on infarct, volume with 1.0% halothane
			Adenosine receptor blockade		
Kitahara *et al.* 2001 (Ref. 62)	rat	110	halothane, isoflurane, sevoflurane and pentobarbital	decreased SD frequency with 0.5, 1.0, 2.0% inspired for each vapour, sevoflurane least effective; pentobarb similar to 0.5% volatile agent	agents had effect, on neuronal depol, no effect on SD init, c-fos expression, or signal transduction
Kaube *et al.* 2000 (Ref. 63)	human	11	ketamine (intranasal)	hemispheric migraine - improvement in five patients; total of 14 attacks	aura resolved
				initial improvement in three patients	only two patients with improved headache
				six patients no improvement in 11 attacks	
Kruger *et al.*	rat	51	ketamine 100 μg to slice	decreased duration and integral of DC shift	AMPA receptor
1999 (Ref. 64)	neocortical slices				blockade - no effect
Saito *et al.* 1997 (Ref. 65)	cat	15	halothane 0.75% in 70% N_2O	greater penumbral blood flow with halothane decreased transient depolarizations	halothane deemed protective
			α-cloralose (60 $mg \cdot kg^{-1}$)	decreased infarct volume with MCAO	
Piper and Lambert 1996 (Ref. 66)	cat	26	halothane 1.0 - 2.0%	no SD with halothane, 3/7 with isoflurane	volatile agent sparing may account for no SD seen with neurosx
			isoflurane 1.5 - 2.5%	100% incidence with α-chloralose	
			α-cloralose (60 $mg \cdot kg^{-1}$)	additive protection with N_2O	
Saito *et al.* 1995 (Ref. 67)	cat	28	halothane 0.75% in 70% N_2O	inhibition with halothane 0/11 SD	KCl injection into cortex
			α-cloralose (60 $mg \cdot kg^{-1}$) in N_2O	4/9 with α-chloralose	
Rashidy-Pour *et al.* 1995 (Ref. 68)	rat	31	ketamine 50 $mg \cdot kg^{-1}$	tolerance developed to repeated doses of ketamine	conformational change to NMDA receptor over time
			MK-801	absent suppression of SD by 5th injection	
Martin *et al.* 1994 (Ref. 69)	rat	24	halothane, isoflurane and ketamine	inhibition of SD with ketamine; no dose related effect with volatile agents	high doses volatile agents slowed propagation

Table 2 continued

STUDY	SPECIES	NUMBER STUDIED	AGENTS USED	REMARKS	ANCILLARY COMMENTARY
Verhaegan *et al.* 1992 (Ref. 70)	rat	20	ketamine, halothane and isoflurane	SD with background halothane, completely eliminated with ketamine	propagation modulation with glycine receptor antagonism at NMDA receptor site
Guedes and Barreto 1992 (Ref. 71)	rat	14	urethane/halothane thionembutal	decreased propagation with both anesthetic approaches compared to awake animals	control animals awake
Amemori and Bures 1990 (Ref. 72)	rat	15	ketamine	repeated injections of ketamine - initial blockade of SD absent by fifth injection	use dependence of NMDA-gated channels
Marrannes *et al.* 1988 (Ref. 73)	rat	64	ketamine, MK-801, PCP, 2-APH	NMDA antagonists completely eliminated SD, 80 mg·kg^{-1} ketamine IP	no effect with diazepam

NMDA = N-methyl D-aspartate; MCAO = middle cerebral artery occlusion; IP = intraperitoneal; PCP = phencyclidine; 2-APH = DL-2-amino-7-phosphonoheptanoate; MK-801 = dizocilpine; AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

The use of propofol (a common approach to sedation in the intensive care unit) may well be contraindicated in the management of sedation for patients with severe vasospasm. Evidence that propofol attenuates hemichannel communication is potentially of considerable importance.[74] Thus, by its actions on hemichannels, propofol can prevent spatial buffering of potassium and glutamate and enhance the risk of SD or the risk of multiple SD waves or PIDs. Volatile agents and, most specifically, isoflurane have a significantly smaller effect on gap junction function than that seen with propofol. Isoflurane is a cerebral vasodilator, whereas propofol is a cerebral vasoconstrictor based on reduction in metabolic demand. In the context of fully monitored patients with severe vasospasm, use of a cerebral vasodilator can be rationally entertained. By using a volatile agent for sedation, it is possible that less vigorous "triple-H" therapy would be required with extra-organ complications attenuated. As volatile agents decrease the risk of generating SD waves, the mere change of the approach to sedation could improve outcome following severe vasospasm. The use of volatile agents in an intensive care setting is logistically problematic, but approaches have been developed, including the introduction of a volatile anesthetic reflection filter that is adaptable to conventional intensive care ventilators – the so-called AnaConDa (anesthetic conserving device).[75] Another risk of using propofol for sedation in the neurocritical care setting is the propofol infusion syndrome – potential for metabolic, cardiac, renal, and hepatic dysfunction and rhabdomyolysis with high doses and/or prolonged infusion of the agent. Recent work suggests that patients with neurologic disorders may be at greater risk – a 35% incidence of the infusion syndrome in patients managed with refractory epilepsy[76] *vs* a 3.7% incidence in general intensive care unit patients.[77]

Ketamine should be studied for sedation in patients with severe vasospasm. Recent work has again confirmed the potential utility of this NMDA antagonist in diminishing the frequency of SD.[11] In the observational study by Dreier *et al.*,[12] ketamine was used as a rescue agent in the presence of documented SD or PID waves in monitored patients. Prophylactic administration should be considered in patients at risk. Another agent known to attenuate SD incidence is octanol.[36] This agent has been used in lower animals but not clinically.

The agent chosen to augment perfusion pressure in "triple-H" therapy bears investigation in relation to this glial-centric model. Phenylephrine or other α-agonists may not be the optimal choice to augment perfusion pressure, as α-receptor binding increases astrocyte calcium, causes contraction of cerebrovascular smooth muscle, and activates vascular pericytes[78] that cause local vasoconstriction.[48] Dopamine has recently been shown to attenuate cerebral

vasospasm in an *in-vitro* model,[79] and further study into its effects on astrocyte calcium flux may be warranted.

Conclusions

Clearly, much bench-top investigation and clinical work would be required to support or refute the claims advanced here regarding a glial-centric origin of cerebral vasospasm. Focusing on the prevention of spreading depression waves or peri-infarct depolarizations to limit glial cell dysfunction would be a sea change in the clinical management of SAH and cerebral vasospasm. This perspective provides further evidence of the importance of astrocytes to the neurovascular interface.

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Conflicts of interest None declared.

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