SNI

SURGICAL NEUROLOGY INTERNATIONAL

SNI: Inflammation

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: **Russell Blaylock,** MD Advanced Nutritional Concepts and Theoretical Neurosciences, Flowood, MS, USA

Review Article

The role of inflammation and potential use of sex steroids in intracranial aneurysms and subarachnoid hemorrhage

Jack W. Barrow[1,2], Nefize Turan[1], Pasang Wangmo[1], Anil K. Roy[1], Gustavo Pradilla[1]

[1]Cerebrovascular Research Laboratory, Department of Neurosurgery, Emory University School of Medicine, Atlanta, Georgia, USA, [2]Mercer University School of Medicine, Savannah, Georgia, USA

E-mail: Jack W. Barrow - jackwbarrow@gmail.com; Nefize Turan - nefizet@gmail.com; Pasang Wangmo - pwangmo@emory.edu; Anil K. Roy - anil.kumar.roy@emory.edu; *Gustavo Pradilla - gpradil@emory.edu
*Corresponding author

Received: 20 March 18 Accepted: 15 May 18 Published: 26 July 18

Abstract

Background: Aneurysmal subarachnoid hemorrhage (aSAH) continues to be a devastating neurological condition with a high risk of associated morbidity and mortality. Inflammation has been shown to increase the risk of complications associated with aSAH such as vasospasm and brain injury in animal models and humans. The goal of this review is to discuss the inflammatory mechanisms of aneurysm formation, rupture and vasospasm and explore the role of sex hormones in the inflammatory response to aSAH.

Methods: A literature review was performed using PubMed using the following search terms: “intracranial aneurysm,” “cerebral aneurysm,” “dihydroepiandrosterone sulfate” “estrogen,” “hormone replacement therapy,” “inflammation,” “oral contraceptive,” “progesterone,” “sex steroids,” “sex hormones” “subarachnoid hemorrhage,” “testosterone.” Only studies published in English language were included in the review.

Results: Studies have shown that administration of sex hormones such as progesterone and estrogen at early stages in the inflammatory cascade can lower the risk and magnitude of subsequent complications. The exact mechanism by which these hormones act on the brain, as well as their role in the inflammatory cascade is not fully understood. Moreover, conflicting results have been published on the effect of hormone replacement therapy in humans. This review will scrutinize the variations in these studies to provide a more detailed understanding of sex hormones as potential therapeutic agents for intracranial aneurysms and aSAH.

Conclusion: Inflammation may play a role in the pathogenesis of intracranial aneurysm formation and subarachnoid hemorrhage, and administration of sex hormones as anti-inflammatory agents has been associated with improved

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/sni.sni_88_18

Quick Response Code:

How to cite this article: Barrow JW, Turan N, Wangmo P, Roy AK, Pradilla G. The role of inflammation and potential use of sex steroids in intracranial aneurysms and subarachnoid hemorrhage. Surg Neurol Int 2018;9:150.
http://surgicalneurologyint.com/The-role-of-inflammation-and-potential-use-of-sex-steroids-in-intracranial-aneurysms-and-subarachnoid-hemorrhage/

functional outcome in experimental models. Further studies are needed to determine the therapeutic role of these hormones in the intracranial aneurysms and aSAH.

Key Words: Estrogen, inflammation, intracranial aneurysms, progesterone, sex hormones, subarachnoid hemorrhage

INTRODUCTION

Patients surviving an aneurysmal subarachnoid hemorrhage (aSAH) often develop cerebral vasospasm and delayed ischemic neurological injury.[79] Approximately two-thirds of patients with aSAH develop angiographic vasospasm 3–14 days after rupture of an aneurysm.[79] Following aSAH, inflammatory cells enter the central nervous system (CNS) leading to a decrease in cerebral blood flow (CBF) and endothelial cell death.[79,89] Inflammation, increase in endothelin-1(ET-1), and depletion of nitric oxide (NO) from endothelial dysfunction are associated with the onset of vasospasm.[19,89] Sex differences in the inflammatory and apoptotic response to brain injury induced by SAH have been shown to exist in experimental models,[42] and sex hormones such as estrogen and progesterone have been shown to have beneficial effects on inflammation and edema after SAH.[128,141,146] Treatment with estrogen has been shown to decrease ET-1 and increase NO.[75] Mortality has also been shown to be significantly reduced in progesterone treated SAH animals.[141] Even though the incidence of SAH is generally found to be higher in females, there have been conflicting results on the different gender outcomes associated with aSAH.[6,133] The purpose of this review is to explore the relationship between inflammation and vasospasm in the setting of aSAH, as well as the potential benefits of sex hormones as a therapeutic anti-inflammatory intervention.

Role of inflammation in intracranial aneurysms and subarachnoid hemorrhage

Evidence of inflammation in aneurysm formation and rupture

Factors leading to abnormal vascular remodeling and weakening of the vessel wall are not well understood, but chronic inflammation and infiltration of inflammatory cells has been shown to be an early histologic hallmark for aneurysms.[26] The number of macrophages within the aneurysmal wall increases as intracranial aneurysms (IAs) develop, while macrophage-depleted mice have much lower rates of IA formation compared to controls.[66] Widespread macrophage infiltration with accelerated extracellular matrix degradation was also shown to correlate with increased rates of aneurysmal rupture.[3,66] T-cells, mast cells, and humoral response were also shown to be involved in the formation of IAs.[67,132] Chemokines and cell adhesion molecules such as monocyte chemotactic protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1) play a role in the recruitment of monocytes/macrophages to early sites of aneurysm formation and arterial wall degeneration.[2,121] Along with inflammatory cell infiltration, endothelial dysfunction and induction of proinflammatory cascades such as activation of NF-kB, increased expression of IL-1B, and elevated TNF-alpha have been suggested to play a role in IA development.[4,26] Increased levels of cyclooxygenase within the walls of ruptured and unruptured aneurysms, as well as a reduction in rate of rupture with aspirin administration was also demonstrated.[51-53] In animal studies, loss of mural cells, increased neutrophil accumulation in intraluminal thrombus, adventitial fibrosis, and inflammation were some of the characteristics of progressing and ruptured IAs in rats.[82] In human IA samples, epithelial denudation of the aneurysm wall, apoptosis of mural cells, luminal thrombosis, T-cell, and macrophage infiltration were associated with rupture.[44]

Evidence of inflammatory markers in the systemic circulation and cerebrospinal fluid after subarachnoid hemorrhage

Inflammatory markers increase in the systemic circulation as well as in cerebrospinal fluid (CSF) following SAH and are predictive of poor outcomes.[57,68,71,90] This has led to increased interest in the development of biomarkers to predict outcomes after aSAH [Table 1]. High body temperature and leukocytosis have also been correlated with worse outcomes after aSAH, though no causal relationship was established between intracerebral and peripheral inflammation.[32,126,130] C-reactive protein (CRP) was shown to be increased in several studies, peaking at 73–96 hours, and correlated with worse EBI.[43,76,157] In another study, high-sensitivity CRP (hs-CRP), which is a more precise measure of CRP, was found to be significantly associated with poor outcomes determined by Glasgow Outcome Scale at 3 months.[126] Zhong *et al*. showed that higher levels of IL-6 and IL-10 24 hours after admission is associated with severe EBI, and increased the susceptibility to infections such as pneumonia.[157] The rate of change of IL-6 and erythrocyte sedimentation rate (ESR) levels were also associated with DCI.[87] Red blood cell distribution width (RDW), an emerging inflammatory marker, was also found to be significantly higher in SAH patients and associated with poor outcome.[25] Asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthase and a marker of endothelial dysfunction and inflammation, was also

Table 1: Several inflammatory biomarkers that are found to be increased in the serum and cerebrospinal fluid of SAH patients

Marker	Location	Timing	Function
White blood cell (WBC) count	Serum and cerebrospinal fluid (CSF)	-Days 1, 4, 7, 10, and 14 after SAH in serum[20] -Within 14 days in CSF[123]	-Correlated with delayed cerebral ischemia (DCI) occurrence.[20] -WBC count remain elevated for 14 days in SAH patients. No difference was found in the CSF cell counts in patients with DCI vs those without.[123]
C-reactive protein (CRP)	Serum and CSF	-Days 1, 3, 5, 7, 9, 11, and 13 in serum[60] -Days 0, 1, 2, 3, 5, 7 in CSF[40]	-Significant differences were found between patients that developed vasospasm vs those that did not on days 1, 3 and 5.[60] -Peak value was observed on day 3 in both serum and CSF levels. Higher CRP levels correlated with vasospasm and poor outcome.[40]
High-sensitivity c-reactive protein (hs-CRP)	Serum	Not available[126]	Significant association was found between high hs-CRP levels and poor Glasgow Outcome Scale score.[126]
Erythrocyte sedimentation rate (ESR)	Serum	Up to 15 days[87]	Time-independent association between ESR and DCI was found.[87]
Interleukin-1beta receptor antagonist	Serum and CSF	-First two weeks in both serum and CSF[47]	Development of systemic inflammatory response syndrome post-SAH and organ failure were correlated with significant increase in serum only.[47]
IL-6	Serum and CSF	-Up to 15 days in serum[87] -In less than 48 hours in serum[117] -daily in CSF[72]	-Rate of change in IL-6 was associated with DCI.[87] -IL-6 was elevated in patients with global cerebral edema, SAH early brain edema score $\geq$3 and Hunt and Hess $\geq$4.[117] -IL-6 in CSF was increased in patients with vasospasm. Levels between 530 and 3100 pg/mL were associated with increased likelihood of vasospasm.[72]
IL-8	Serum and CSF	-Serially over 14 days in both serum and CSF[102]	Patients experiencing vasospasm had significantly higher CSF levels of IL-8 on days 5 and 7.[102]
Tumor necrosis factor-α (TNF-α)	Serum and CSF	-Up to 2 weeks in serum[24] -Up to 12 days in serum[8] -Day 2 in CSF and meta-analysis[145]	Elevated TNF-α on days 2 and 3 and global elevation were correlated with poor outcome but not vasospasm.[24] -No association was found between TNF-α and DCI.[8] -Serum levels of TNF-α were increased in relation with vasospasm and correlated with Hunt and Hess grade.[145]

shown be increased starting from day 2 and was highest approximately 9–10 days after SAH.[76,114] Higher levels of macrophage migration inhibitory factor (MIF), soluble CD40 ligand (sCD40L), and platelet-derived growth factor (PDGF)-BB were also correlated with poor outcome.[23,70] aSAH patients may also experience cardiopulmonary complications as part of the systemic reaction.[142] Pulmonary edema that occurs after SAH was associated with cardiac failure in the early phase and inflammatory response in the delayed phase.[99] It is worth noting that thromboelastography maximum amplitude (MA), a marker of platelet activation, was shown to be higher in patients with severe EBI and DCI,[43] and the association between MA and clinical outcome was reported to be stronger than that between traditional biomarkers.[111]

Several studies have investigated various inflammatory mediators in cerebrospinal fluid (CSF) following aSAH, with some conflicting reports.[68,69] Many studies point to the prominent role of tumor necrosis factor-alpha (TNF-α), though other studies have found increased levels of interleukin (IL)-6 and IL-8 but not TNF-α.[36,69,147] One recent study found detectable levels of TNF-α in 30% of patients after SAH, suggesting that the amount and type of inflammation may vary considerably in different patients.[56] In animal models of SAH, blockage of TNF-α has been shown to reduce apoptosis in the hippocampus after SAH.[64] Another inflammatory marker found throughout many studies is endothelin-1 (ET-1), and monocytes isolated from CSF of these patients are capable of producing ET-1.[37,83] As with several other pro-inflammatory molecules, the

expression of ET-1 is highly variable. In one study, mRNA expression of ET-1 levels were found to be present in 46% of the patients with SAH 5 days after the start of symptoms versus none detectable in the CSF of control participants.[37] A study from a different group, however, failed to detect ET-1 after SAH at various time points using radioimmunoassay for big endothelin.[49] The variation found in these inflammatory markers reflects the heterogeneity of complications associated with aSAH.[27,124] The conflicting findings in these studies may stem from the time CSF levels of these markers were measured and the diagnostic method used following SAH or the difference in inflammatory response experienced by each participant.

Evidence for inflammation as a cause of vasospasm after subarachnoid hemorrhage

Several clinical studies have attempted to correlate fever and inflammation in the absence of infection with vasospasm.[81,86,96,98,100,104,115,125,139,144] Pro-inflammatory agents, such as lipopolysaccharide (LPS),[113] have been administered using the intracisternal route to show that vasospasm can occur in the absence of blood. This has demonstrated that the presence of red blood cells (RBCs) or hemoglobin (Hgb) are not necessary for the induction of vasospasm. Among the cellular adhesion molecules, E-selectin has also been shown to correlate well with the patients' response to SAH.[107] E-selectin was found to be in higher concentrations in the CSF of SAH patients who develop moderate or severe vasospasm.[107] In addition, inhibition of E-selectin with an inhibitory antibody was shown to decrease vasospasm in rodent models.[74] Other adhesion molecules have been implicated as well. In one study Mac-1 monoclonal antibodies and anti-LFA-1 antibodies were administered systemically, and were shown to reduce vasospasm in rat,[29] rabbit,[109] and primate[28] SAH models. Similar results have been shown with anti-ICAM1 monoclonal antibodies in a rodent model.[101] Among other pro-inflammatory cytokines, TNF-α levels in patients with lower grade SAH were shown to correlate with severity of vasospasm.[50] This has been further studied as TNF-α inhibitors were shown to attenuate vasospasm in animal models.[15] The levels of other inflammatory cytokines such as IL-1B, IL-6, IL-8, and MCP-1 were also shown be increased in the artery wall, serum, and CSF correlating with vasospasm and severity of SAH.[1,36,45,54,78,93,95,97,140] Signaling pathways have been examined as well in the induction of vasospasm, namely, mitogen-activated protein-kinase (MAPK) and nuclear factor kappa-B (NF-κB).[5] Other studies have suggested that oxidative stress[58] and complement pathway activation[153] could play an important role in the induction of vasospasm as well.

Recent studies have been done to explore a possible genetic predisposition to vasospasm. One promising avenue has been the study of haptoglobin proteins, which are responsible for removal of free hemoglobin from CSF that may be the cause of inflammation. Haptoglobin (Hp) has three known distinct phenotypes in humans – Hp1-1, Hp2-1, and Hp2-2.[14] In humans, the haptoglobin proteins with α-2 subunits are associated with higher rates of vasospasm compared to other haptoglobin types(α1-α1).[13] This is consistent with animal models that demonstrate more severe vasospasm and worst outcome after SAH in genetically altered Hp2-2 rodents.[18]

Changes in NO have also been extensively studied in the induction of vasospasm. Increase in the levels of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase[113] were detected in mice after SAH, and this physiological response to SAH is decreased in pro-inflammatory Hp2-2 transgenic mice compared with Hp1-1 mice.[108,116] This further supports the evidence that Hp2-2 genotypes are associated with a worse outcome in SAH, as these participants would have less NO, which is involved in signaling pathways that lead to vasodilation and cytoprotection.[144] Studies have also suggested that an alteration dubbed "eNOS uncoupling"[150] may lead to production of superoxides instead of NO following SAH.[116]

ET-1, a potent vasoconstrictor, is thought to play a role in the inflammatory response after SAH.[65,84,120] Increase in ET-1 levels in patients with SAH and symptomatic vasospasm has been documented in several studies, and the amount of blood found within the cisterns correlated well with the level of ET-1 in CSF.[65,84,120] However, other studies found no significant elevation of ET-1 after SAH, and similarly, no correlation between ET-1 levels and vasospasm.[49,65] Similarly, administration of anti-ET-1 monoclonal antibodies was effective in decreasing vasospasm in some studies.[30,148,158] A rodent study suggested that transgenic mice overexpressing ET-1 experienced more severe vasospasm and edema.[151] Some studies have attempted the use of clazosentan, a synthetic endothelin receptor antagonist (ETRA), to reduce vasospasm in rodent SAH models, however, the overall morbidity from vasospasm was unchanged.[22]

Several studies have shown a relationship between glutamate, as well as a synthetic analog N-methyl-D-aspartate (NMDA), and vasodilation under physiological conditions.[17,39] These effects appear to result from neuronal NMDA receptor activation subsequent neuronal depolarization, and production of neuronal NO, which diffuse to cerebral arterioles and arteries leading to vasodilation.[17,39] Glutamate receptors were not shown on human and rat microvascular endothelial cells, further suggesting that the effect of glutamate on vasodilation is indirect through diffusion of substances from cells surrounding the cerebral vessels.[92] On the other hand, synaptic glutamate receptor 1 (GluR1) has been shown to be reduced in mice 24 hours after SAH

which also corresponds to peak vasoconstriction in mice.[135] Bell *et al*.[9] have demonstrated reduction in surface glutamate receptor 2 (GluR2) in rats 7 days after SAH in areas proximal to microthombosis and thrombin activated platelets. Such reduction in glutamate receptors possibly contributes to vasoconstriction after SAH. A study utilizing S-4-carboxyphenylglycine (S-4-CPG), a glutamate receptor antagonist, inhibited vasospasm in haptoglobin 2-2 mice after SAH induction.[46] Similarly, combination therapy with a GluN1/GluN2B NMDA receptor and metabotropic glutamate receptor 1 negative allosteric modulator was neuroprotective by attenuating apoptosis and improving functional outcome after SAH.[154] Neutrophil depletion, which has been associated with reversal of vasospasm, caused a shift in the NMDA receptor subunit composition toward a memory sparing phenotype, and enhanced memory after experimental SAH.[110] These findings illustrate the complex relationship between glutamate and NMDA receptors and SAH-induced vasospasm. The mechanisms mediating these interactions need to be further explored and scrutinized to clarify the contribution of these receptors to the pathophysiology of SAH-induced inflammation and brain injury.

The impact of sex hormones on intracranial aneurysms and subarachnoid hemorrhage

Estrogen

Estrogen is the primary female sex hormone responsible for the development and regulation of the female reproductive system, although it has been found to play a role in male physiology as well.[91] Estrogen receptor-alpha (ER-α) and estrogen receptor-beta (ER-β) genes encode estrogen receptors (ER) inside the nuclear membrane. Estrogen alters glutamatergic and GABAergic neuronal activity in many steroid-sensitive brain regions[59] and may stimulate mitogen-activated protein kinase (MAPK) signal transductive pathways to protect cells in a manner similar to as growth factors.[122]

Estrogen is thought to play a role in aneurysm formation. Females have been shown to develop intracranial aneurysms at higher rates than males and, experimental animal studies support the hypothesis that induced estrogen deficiency via bilateral oophorectomy in rats causes an increase in the frequency of aneurysm formation and augment the aneurysm size.[62] Moreover, reversal of this induced deficiency with continuous-release pellets of 17-β estradiol reduces the frequency of aneurysm formation.[63] These effects are attributed to estrogen's protective role on endothelial cell growth and function.[63] ERβ agonist were also shown to reduce the frequency of aneurysm formation in wild type ovariectomized mice but not in ovariectomized ERβ knockout mice suggesting that ERβ receptors found on aneurysm walls are involved in the protective effects of estrogen.[129] Whether estrogen may be used as a pharmacological agent to reduce the chronic inflammation and loss of mural cells in the aneurysm wall must be elucidated in future studies.

Evidence obtained from animal studies suggests that continuous estrogen treatment in SAH-induced rats may decrease the rate and severity of vasospasm by inhibiting endothelin-1 production, increasing iNOS expression, and preserving eNOS expression.[75] Mechanistically, estrogen's attenuation of cerebral vasospasm may be related to its potent vasodilatory action.[33] Estrogen has also been shown to be a potent neuroprotective agent in ischemic stroke,[59] particularly in premenopausal women.[59] In the CNS, estrogen is known to reduce lipid peroxidation,[7,112] protect against oxidative stress,[16] decrease the production of reactive oxygen species,[31] and interrupt the accumulation of intracellular peroxide in an ER-dependent manner.[136] Moreover, a growing number of studies demonstrate that exogenous estradiol reduces tissue damage resulting from experimental ischemic stroke in both sexes. Female reproductive steroids also may ameliorate ischemic injury through promotion of γ-aminobutyric acid type A (GABA (A)) receptor-mediated mechanisms, as well as through suppression of excitatory amino acid toxicity.[59] Estrogen inhibits inflammatory signaling through the inhibition of NF-κB, an important pro-inflammatory pathway activated after SAH.[146] In addition, tamoxifen, a selective estrogen receptor modulator, was found to modulate TLR4/NF-κB signaling pathways and improve the cognitive and behavioral outcome of SAH rats.[128]

Progesterone

Progesterone (PROG) is another sex steroid naturally synthesized by neurons and oligodendrocytes in the CNS. In addition to its hypothalamic receptors involved in the regulation of female reproductive physiology, PROG receptors are constitutively expressed in other parts of the brain including the cerebral cortex, hippocampus, basal ganglia, and cerebellum.[119] The classical progesterone receptor-mediated genomic actions of progesterone occur via activation of nuclear progesterone receptor-A (PR-A) and PR-B.[41,131,152] The nonclassical signaling of progesterone is mediated by membrane progesterone receptors such as mPRα, mPRβ, mPRγ, mPRδ, and mPRε.[41,131,152] On the other hand, allopregnanolone, the metabolite of progesterone, mediates its effects as a potent positive allosteric modulator of GABA (A) receptors in the CNS.[119] PROG and its metabolite allopregnanolone were shown to have strong anti-inflammatory, anti-apoptotic and neuroprotective properties in various neurological injury models including traumatic brain injury (TBI) ischemic stroke, neonatal hypoxic brain injury, diabetic neuropathy, and demyelinating disorders.[34,73,105,118,137,143] A water soluble progesterone analogue, which would facilitate its delivery in emergency conditions, has been recently developed.[138]

Progesterone may play a critical role in altering the pathogenesis of SAH, and has already been proven to be beneficial in few studies of experimental SAH.[152] Chang *et al*.[21] have shown that rats treated with progesterone one hour after SAH induction show reduced vasospasm and greater levels of eNOS compared to controls. Progesterone-mediated increase in eNOS is thought to be related to the Akt signaling pathway, which has also been implicated in estrogen-mediated vasodilation. Progesterone stabilizes the blood–brain barrier (BBB) [149] and significantly reduces the mortality associated with SAH in experimental animals.[141] Progesterone treatment was shown to increase appetite scores of SAH rats, decrease proinflammatory cytokines such as IL-1b, TNF-a, and IL-6 in the intestines, and improve the gut structure.[155,156] Our group has shown that progesterone prevented basilar artery vasospasm, reduced iba-1 expression in the cortex and cerebellum, and restored functional synapses in the hippocampus in mice after SAH.[135] Progesterone has also improved motor performance on rotarod and grip strength testing 6 and 9 days after SAH, respectively.[135] Future studies are necessary to clarify the role of progesterone as a pharmacological agent to reduce chronic inflammation in intracranial aneurysms and to reduce vasospasm and inflammation-induced brain injury seen after SAH.

Testosterone and dihydroepiandosterone sulfate

Testosterone, another gonadal sex steroid, also plays important roles in the CNS, but its direct role in SAH is still unclear.[11] Testosterone is physiologically secreted by the testes and adrenal glands and transported by the sex hormones binding globulins (SHBG) and albumins.[11,61] It acts through activation of androgen receptors (AR)[11] found in multiple neurons throughout the brain.[10] Testosterone may also play a neuroprotective and anti-inflammatory role in the CNS.[85,106] In the setting of SAH, testosterone was shown to inhibit vasospasm in SAH rabbits; however, the exact mechanism is unclear.[48] Future studies are needed to investigate the role of testosterone in aneurysm formation and SAH.

Dihydroepiandrosterone sulfate (DHEAS) is another sex steroid recently associated with favorable outcomes in human SAH.[55] Higher serum levels of DHEAS were correlated with favorable neurological outcomes after SAH. In the same cohort, favorable outcomes were also associated with lower levels of IL-6,[55] although DHEAS levels were only studied in peripheral circulation.[94]

Oral contraceptives and hormone replacement therapy

Several population-based studies have failed to show a strong association between risk of SAH and the use of oral contraceptives.[12,38,88] The results on the influence of hormonal replacement therapy (HRT) on incidence of SAH, on the other hand, are conflicting. Several studies have shown that HRT reduces the risk of SAH in postmenopausal women with odds ratios ranging from 0.6 (0.4–0.8) to 0.47 (0.26–0.86) with the greatest risk reduction in women with a history of smoking.[38,77,88] On the contrary, other studies showed no influence of HRT on the incidence of SAH in women.[35,103]

Translation from bench to bedside and remaining challenges with clinical trials

Though there is promising data alluding to sex hormones as potential therapeutic agents for vasospasm and neuroprotection in aSAH patients, the gap between animal studies and human trials is still large. Concern surrounding the failure of clinical trials evaluating progesterone in TBI in humans despite extensive supporting data in animal models calls for more precise outcome measures and alternative clinical trial methodologies.[80] Potential challenges for failure of randomized clinical trials in SAH are thought to include functional ineffectiveness of the tested therapies, timing and dose of the treatment, inadequate sample size, insensitive or inappropriate outcome measures, the confounding effect of rescue therapies in placebo groups, treatment-associated side effects, and variations in practice across different centers.[80] The lessons learned from the failed phase III randomized clinical trial of progesterone for the treatment of TBI is that careful evaluation of dosage needed to treat the patients is critical and that outcome measures need to be further improved to detect the efficacy of future therapeutic agents.[127] Extensive neurobehavioral testing is also needed to ensure the functional effectiveness of a therapeutic agent before proceeding to a randomized clinical trial.[134]

CONCLUSION

Inflammation in the CNS is a major contributing force behind vasospasm and early brain injury in aSAH patients. Though this link has been made in many animal experiments, human trials with anti-inflammatory agents have not been successful in reducing morbidity and mortality and improving functional outcome. Evaluation of sex hormones as potential therapeutic agents to stabilize intracranial aneurysms and improve functional outcome in aSAH patients is promising as many preliminary animal studies indicate the safety and effectiveness of the sex steroids to cross the BBB. Future studies are warranted to determine the role of sex hormones in treatment of these conditions.

Financial support and sponsorship

Nil.

Disclosure/Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Aihara Y, Kasuya H, Onda H, Hori T, Takeda J. Quantitative analysis of gene expressions related to inflammation in canine spastic artery after subarachnoid hemorrhage. Stroke 2001;32:212-7.
2. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Egashira K, Hashimoto N. Impact of monocyte chemoattractant protein-1 deficiency on cerebral aneurysm formation. Stroke 2009;40:942-51.
3. Aoki T, Kataoka H, Morimoto M, Nozaki K, Hashimoto N. Macrophage-derived matrix metalloproteinase-2 and -9 promote the progression of cerebral aneurysms in rats. Stroke 2007;38:162-9.
4. Aoki T, Kataoka H, Shimamura M, Nakagami H, Wakayama K, Moriwaki T, *et al*. NF-kappaB is a key mediator of cerebral aneurysm formation. Circulation 2007;116:2830-40.
5. Arthur JS, Ley SC. Mitogen-activated protein kinases in innate immunity. Nature reviews. Immunology 2013;13:679-92.
6. Ayala C, Croft JB, Greenlund KJ, Keenan NL, Donehoo RS, Malarcher AM, *et al*. Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995-1998. Stroke 2002;33:1197-201.
7. Ayres S, Abplanalp W, Liu JH, Subbiah MT. Mechanisms involved in the protective effect of estradiol-17beta on lipid peroxidation and DNA damage. Am J Physiol 1998;274:E1002-8.
8. Beeftink MM, Ruigrok YM, Rinkel GJ, van den Bergh WM. Relation of serum TNF-alpha and TNF-alpha genotype with delayed cerebral ischemia and outcome in subarachnoid hemorrhage. Neurocrit Care 2011;15:405-9.
9. Bell JD, Thomas TC, Lass E, Ai J, Wan H, Lifshitz J, *et al*. Platelet-mediated changes to neuronal glutamate receptor expression at sites of microthrombosis following experimental subarachnoid hemorrhage. J Neurosurg 2014;121:1424-31.
10. Belle MD, Lea RW. Androgen receptor immunolocalization in brains of courting and brooding male and female ring doves (Streptopelia risoria). Gen Comp Endocrinol 2001;124:173-87.
11. Białek M, Zaremba P, Borowicz KK, Czuczwar SJ. Neuroprotective role of testosterone in the nervous system. Pol J Pharmacol 2004;56:509-18.
12. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: A population-based case-control study. Stroke 1986;17:831-5.
13. Borsody M, Burke A, Coplin W, Miller-Lotan R, Levy A. Haptoglobin and the development of cerebral artery vasospasm after subarachnoid hemorrhage. Neurology 2006;66:634-40.
14. Bowman BH, Kurosky A. Haptoglobin: The evolutionary product of duplication, unequal crossing over, and point mutation. Adv Hum Genet 1982;12:189-261, 453-184.
15. Bowman G, Dixit S, Bonneau RH, Chinchilli VM, Cockroft KM. Neutralizing antibody against interleukin-6 attenuates posthemorrhagic vasospasm in the rat femoral artery model. Neurosurgery 2004;54:719-25; discussion 725-716.
16. Bruce-Keller AJ, Keeling JL, Keller JN, Huang FF, Camondola S, Mattson MP. Antiinflammatory effects of estrogen on microglial activation. Endocrinology 2000;141:3646-56.
17. Busija DW, Bari F, Domoki F, Louis T. Mechanisms involved in the cerebrovascular dilator effects of N-methyl-d-aspartate in cerebral cortex. Brain Res Rev 2007;56:89-100.
18. Chaichana KL, Levy AP, Miller-Lotan R, Shakur S, Tamargo RJ. Haptoglobin 2-2 genotype determines chronic vasospasm after experimental subarachnoid hemorrhage. Stroke 2007;38:3266-71.
19. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. World Neurosurg 2010;73:22-41.
20. Chamling B, Gross S, Stoffel-Wagner B, Schubert GA, Clusmann H, Coburn M, *et al*. Early Diagnosis of Delayed Cerebral Ischemia: Possible Relevance for Inflammatory Biomarkers in Routine Clinical Practice? World Neurosurg 2017;104:152-7.
21. Chang CM, Su YF, Chang CZ, Chung CL, Tsai YJ, Loh JK, *et al*. Progesterone attenuates experimental subarachnoid hemorrhage-induced vasospasm by upregulation of endothelial nitric oxide synthase via Akt signaling pathway. Biomed Res Int 2014;2014:207616.
22. Chen G, Tariq A, Ai J, Sabri M, Jeon HJ, Tang EJ, *et al*. Different effects of clazosentan on consequences of subarachnoid hemorrhage in rats. Brain Res 2011;1392:132-9.
23. Chen YH, Cheng ZY, Shao LH, Shentu HS, Fu B. Macrophage migration inhibitory factor as a serum prognostic marker in patients with aneurysmal subarachnoid hemorrhage. Clin Chim Acta 2017;473:60-4.
24. Chou SH, Feske SK, Atherton J, Konigsberg RG, De Jager PL, Du R, *et al*. Early elevation of serum tumor necrosis factor-alpha is associated with poor outcome in subarachnoid hemorrhage. J Investig Med 2012;60:1054-8.
25. Chugh C, Nyirjesy SC, Nawalinski KP, Sandsmark DK, Frangos S, Maloney-Wilensky E, *et al*. Red Blood Cell Distribution Width is Associated with Poor Clinical Outcome After Subarachnoid Hemorrhage: A Pilot Study. Neurocrit Care 2015;23:217-24.
26. Chyatte D, Bruno G, Desai S, Todor DR. Inflammation and intracranial aneurysms. Neurosurgery 1999;45:1137-46; discussion 1146-1137.
27. Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: Frequency, predictors, and impact on outcome. Stroke 2002;33:1225-32.
28. Clatterbuck RE, Gailloud P, Ogata L, Gebremariam A, Dietsch GN, Murphy KJ, *et al*. Prevention of cerebral vasospasm by a humanized anti-CD11/CD18 monoclonal antibody administered after experimental subarachnoid hemorrhage in nonhuman primates. J Neurosurg 2003;99:376-82.
29. Clatterbuck RE, Oshiro EM, Hoffman PA, Dietsch GN, Pardoll DM, Tamargo RJ. Inhibition of vasospasm with lymphocyte function-associated antigen-1 monoclonal antibody in a femoral artery model in rats. J Neurosurg 2002;97:676-82.
30. Clozel M, Breu V, Burri K, Cassal JM, Fischli W, Gray GA, *et al*. Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist. Nature 1993;365:759-61.
31. Culmsee C, Vedder H, Ravati A, Junker V, Otto D, Ahlemeyer B, *et al*. Neuroprotection by estrogens in a mouse model of focal cerebral ischemia and in cultured neurons: Evidence for a receptor-independent antioxidative mechanism. J Cereb Blood Flow Metab 1999;19:1263-9.
32. Dhar R, Diringer MN. The burden of the systemic inflammatory response predicts vasospasm and outcome after subarachnoid hemorrhage. Neurocrit Care 2008;8:404-12.
33. Ding D, Starke RM, Dumont AS, Owens GK, Hasan DM, Chalouhi N, *et al*. Therapeutic implications of estrogen for cerebral vasospasm and delayed cerebral ischemia induced by aneurysmal subarachnoid hemorrhage. Biomed Res Int 2014;2014:727428.
34. El-Etr M, Rame M, Boucher C, Ghoumari AM, Kumar N, Liere P, *et al*. Progesterone and nestorone promote myelin regeneration in chronic demyelinating lesions of corpus callosum and cerebral cortex. Glia 2015;63:104-17.
35. Falkeborn M, Persson I, Terént A, Adami HO, Lithell H, Bergström R. Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. Arch Intern Med 1993;153:1201-9.
36. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schütt S, *et al*. Inflammatory cytokines in subarachnoid haemorrhage: association with abnormal blood flow velocities in basal cerebral arteries. J Neurol Neurosurg Psychiatry 2001;70:534-7.
37. Fassbender K, Hodapp B, Rossol S, Bertsch T, Schmeck J, Schütt S, *et al*. Endothelin-1 in subarachnoid hemorrhage: An acute-phase reactant produced by cerebrospinal fluid leukocytes. Stroke 2000;31:2971-5.
38. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, *et al*. Risk factors for subarachnoid hemorrhage: An updated systematic review of epidemiological studies. Stroke 2005;36:2773-80.
39. Fergus A, Lee KS. Regulation of cerebral microvessels by glutamatergic mechanisms. Brain Res 1997;754:35-45.
40. Fountas KN, Tasiou A, Kapsalaki EZ, Paterakis KN, Grigorian AA, Lee GP, *et al*. Serum and cerebrospinal fluid C-reactive protein levels as predictors of vasospasm in aneurysmal subarachnoid hemorrhage. Clinical article. Neurosurg Focus 2009;26:E22.
41. Franco HL, Jeong JW, Tsai SY, Lydon JP, DeMayo FJ.In vivo analysis of progesterone receptor action in the uterus during embryo implantation. Semin Cell Dev Biol 2008;19:178-86.
42. Friedrich V, Bederson JB, Sehba FA. Gender influences the initial impact of subarachnoid hemorrhage: An experimental investigation. PLoS One 2013;8:e80101.
43. Frontera JA, Provencio JJ, Sehba FA, McIntyre TM, Nowacki AS, Gordon E, *et al*. The Role of Platelet Activation and Inflammation in Early Brain Injury Following Subarachnoid Hemorrhage. Neurocrit Care 2017;26:48-57.

44. Frösen J, Piippo A, Paetau A, Kangasniemi M, Niemelä M, Hernesniemi J, *et al*. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: Histological analysis of 24 unruptured and 42 ruptured cases. Stroke 2004;35:2287-93.
45. Gaetani P, Tartara F, Pignatti P, Tancioni F, Rodriguez y Baena R, *et al*. Cisternal CSF levels of cytokines after subarachnoid hemorrhage. Neurol Res 1998;20:337-42.
46. Garzon-Muvdi T1, Pradilla G, Ruzevick JJ, Bender M, Edwards L, Grossman R, *et al*. A glutamate receptor antagonist, S-4-carboxyphenylglycine (S-4-CPG), inhibits vasospasm after subarachnoid hemorrhage in haptoglobin 2-2 mice [corrected]. Neurosurgery 2013;73:719-28; discussion 729.
47. Gruber A, Rössler K, Graninger W, Donner A, Illievich MU, Czech T. Ventricular cerebrospinal fluid and serum concentrations of sTNFR-I, IL-1ra, and IL-6 after aneurysmal subarachnoid hemorrhage. J Neurosurg Anesthesiol 2000;12:297-306.
48. Gürer B, Turkoglu E, Kertmen H, Karavelioglu E, Arikok AT, Sekerci Z. Attenuation of cerebral vasospasm and secondary injury by testosterone following experimental subarachnoid hemorrhage in rabbit. Acta Neurochir 2014;156:2111-20; discussion 2120.
49. Hamann G, Isenberg E, Strittmatter M, Schimrigk K. Absence of elevation of big endothelin in subarachnoid hemorrhage. Stroke 1993;24:383-6.
50. Hanafy KA, Stuart RM, Khandji AG, Connolly ES, Badjatia N, Mayer SA, *et al*. Relationship between brain interstitial fluid tumor necrosis factor-alpha and cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Clin Neurosci 2010;17:853-6.
51. Hasan D, Hashimoto T, Kung D, Macdonald RL, Winn HR, Heistad D. Upregulation of cyclooxygenase-2 (COX-2) and microsomal prostaglandin E2 synthase-1 (mPGES-1) in wall of ruptured human cerebral aneurysms: Preliminary results. Stroke 2012;43:1964-7.
52. Hasan DM, Chalouhi N, Jabbour P, Magnotta VA, Kung DK, Young WL. Imaging aspirin effect on macrophages in the wall of human cerebral aneurysms using ferumoxytol-enhanced MRI: Preliminary results. J Neuroradiol 2013;40:187-91.
53. Hasan DM, Mahaney KB, Brown RD Jr, Meissner I, Piepgras DG, Huston J, *et al*. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. Stroke 2011;42:3156-62.
54. Hendryk S, Jarzab B, Josko J. Increase of the IL-1 beta and IL-6 levels in CSF in patients with vasospasm following aneurysmal SAH. Neuro Endocrinol Lett 2004;25:141-7.
55. Höllig A, Thiel M, Stoffel-Wagner B, Coburn M, Clusmann H. Neuroprotective properties of dehydroepiandrosterone-sulfate and its relationship to interleukin 6 after aneurysmal subarachnoid hemorrhage: A prospective cohort study. Crit Care 2015;19:231.
56. Hopkins SJ, McMahon CJ, Singh N, Galea J, Hoadley M, Scarth S, *et al*. Cerebrospinal fluid and plasma cytokines after subarachnoid haemorrhage: CSF interleukin-6 may be an early marker of infection. J Neuroinflammation 2012;9:255.
57. Horstmann S, Su Y, Koziol J, Meyding-Lamadé U, Nagel S, Wagner S. MMP-2 and MMP-9 levels in peripheral blood after subarachnoid hemorrhage. J Neurol Sci 2006;251:82-6.
58. Hsieh HL, Yang CM. Role of Redox Signaling in Neuroinflammation and Neurodegenerative Diseases. Biomed Res Int 2013;2013:484613.
59. Hurn PD, Macrae IM. Estrogen as a neuroprotectant in stroke. J Cereb Blood Flow Metab 2000;20:631-52.
60. Hwang SH, Park YS, Kwon JT, Nam TK, Hwang SN, Kang H. Significance of C-reactive protein and transcranial Doppler in cerebral vasospasm following aneurysmal subarachnoid hemorrhage. J Korean Neurosurg Soc 2013;54:289-95.
61. Iqbal MJ, Dalton M, Sawers RS. Binding of testosterone and oestradiol to sex hormone binding globulin, human serum albumin and other plasma proteins: Evidence for non-specific binding of oestradiol to sex hormone binding globulin. Clin Sci (Lond) 1983;64:307-14.
62. Jamous MA, Nagahiro S, Kitazato KT, Satomi J, Satoh K. Role of estrogen deficiency in the formation and progression of cerebral aneurysms. Part I: Experimental study of the effect of oophorectomy in rats. J Neurosurg 2005;103:1046-51.
63. Jamous MA, Nagahiro S, Kitazato KT, Tamura T, Kuwayama K, Satoh K. Role of estrogen deficiency in the formation and progression of cerebral aneurysms. Part II: Experimental study of the effects of hormone replacement therapy in rats. J Neurosurg 2005;103:1052-7.
64. Jiang Y, Liu DW, Han XY, Dong YN, Gao J, Du B, *et al*. Neuroprotective effects of anti-tumor necrosis factor-alpha antibody on apoptosis following subarachnoid hemorrhage in a rat model. J Clin Neurosci 2012;19:866-72.
65. Jung CS, Lange B, Zimmermann M, Seifert V. The CSF concentration of ADMA, but not of ET-1, is correlated with the occurrence and severity of cerebral vasospasm after subarachnoid hemorrhage. Neurosci Lett 2012;524:20-4.
66. Kanematsu Y, Kanematsu M, Kurihara C, Tada Y, Tsou TL, van Rooijen N, *et al*. Critical roles of macrophages in the formation of intracranial aneurysm. Stroke 2011;42:173-8.
67. Kataoka H. Molecular mechanisms of the formation and progression of intracranial aneurysms. Neurol Med Chir (Tokyo) 2015;55:214-9.
68. Kaynar MY, Tanriverdi T, Kafadar AM, Kacira T, Uzun H, Aydin S, *et al*. Detection of soluble intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in both cerebrospinal fluid and serum of patients after aneurysmal subarachnoid hemorrhage. J Neurosurg 2004;101:1030-6.
69. Kikuchi T, Okuda Y, Kaito N, Abe T. Cytokine production in cerebrospinal fluid after subarachnoid haemorrhage. Neurol Res 1995;17:106-8.
70. Kubo Y, Koji T, Yoshida J, Ogawa A, Ogasawara K. Predicting neurological deficit severity due to subarachnoid haemorrhage: Soluble CD40 ligand and platelet-derived growth factor-BB. Crit Care Resusc 2016;18:242-6.
71. Kubo Y, Ogasawara K, Kakino S, Kashimura H, Tomitsuka N, Sugawara A, *et al*. Serum inflammatory adhesion molecules and high-sensitivity C-reactive protein correlates with delayed ischemic neurologic deficits after subarachnoid hemorrhage. Surg Neurol 2008;69:592-6; discussion 596.
72. Lenski M, Huge V, Briegel J, Tonn JC, Schichor C, Thon N. Interleukin 6 in the Cerebrospinal Fluid as a Biomarker for Onset of Vasospasm and Ventriculitis After Severe Subarachnoid Hemorrhage. World Neurosurg 2017;99:132-9.
73. Leonelli E, Bianchi R, Cavaletti G, Caruso D, Crippa D, Garcia-Segura LM, *et al*. Progesterone and its derivatives are neuroprotective agents in experimental diabetic neuropathy: A multimodal analysis. Neuroscience 2007;144:1293-304.
74. Lin C, Dumont AS, Calisaneller T, Kwan AL, Hwong SL, Lee KS. Monoclonal antibody against E selectin attenuates subarachnoid hemorrhage-induced cerebral vasospasm. Surg Neurol 2005;64:201-5; discussion 205-206.
75. Lin CL, Shih HC, Dumont AS, Kassell NF, Lieu AS, Su YF, *et al*. The effect of 17beta-estradiol in attenuating experimental subarachnoid hemorrhage-induced cerebral vasospasm. J Neurosurg 2006;104:298-304.
76. Lindgren C, Hultin M, Koskinen LO, Lindvall P, Borota L, Naredi S. ADMA levels and arginine/ADMA ratios reflect severity of disease and extent of inflammation after subarachnoid hemorrhage. Neurocrit Care 2014;21:91-101.
77. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrhage and hormonal factors in women. A population-based case-control study. Ann Intern Med 1994;121:168-73.
78. Lu H, Shi JX, Chen HL, Hang CH, Wang HD, Yin HX. Expression of monocyte chemoattractant protein-1 in the cerebral artery after experimental subarachnoid hemorrhage. Brain Res 2009;1262:73-80.
79. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. Nature reviews. Neurology 2014;10:44-58.
80. Macdonald RL, Jaja B, Cusimano MD, Etminan N, Hanggi D, Hasan D, *et al*. SAHIT Investigators--on the outcome of some subarachnoid hemorrhage clinical trials. Translational stroke research, 2013;4:286-96.
81. Maiuri F, Gallicchio B, Donati P, Carandente M. The blood leukocyte count and its prognostic significance in subarachnoid hemorrhage. J Neurosurg Sci 1987;31:45-8.
82. Marbacher S, Marjamaa J, Bradacova K, von Gunten M, Honkanen P, Abo-Ramadan U, *et al*. Loss of mural cells leads to wall degeneration, aneurysm growth, and eventual rupture in a rat aneurysm model. Stroke 2014;45:248-54.
83. Masaoka H, Suzuki R, Hirata Y, Emori T, Marumo F, Hirakawa K. Raised plasma endothelin in aneurysmal subarachnoid haemorrhage. Lancet 1989;2:1402.
84. Mascia L, Fedorko L, Stewart DJ, Mohamed F, terBrugge K, Ranieri VM, *et al*. Temporal relationship between endothelin-1 concentrations and cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Stroke 2001;32:1185-90.
85. Matsumoto A. Hormonally induced neuronal plasticity in the adult motoneurons. Brain Res Bull 1997;44:539-47.

86. McGirt MJ, Mavropoulos JC, McGirt LY, Alexander MJ, Friedman AH, Laskowitz DT, *et al*. Leukocytosis as an independent risk factor for cerebral vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:1222-6.
87. McMahon CJ, Hopkins S, Vail A, King AT, Smith D, Illingworth KJ, *et al*. Inflammation as a predictor for delayed cerebral ischemia after aneurysmal subarachnoid haemorrhage. J Neurointerv Surg 2013;5:512-7.
88. Mhurchu CN, Anderson C, Jamrozik K, Hankey G, Dunbabin D; Australasian Cooperative Research on Subarachnoid Hemorrhage Study (ACROSS) Group. Hormonal factors and risk of aneurysmal subarachnoid hemorrhage: An international population-based, case-control study. Stroke 2001;32:606-12.
89. Miller BA, Turan N, Chau M, Pradilla G. Inflammation, vasospasm, and brain injury after subarachnoid hemorrhage. Biomed Res Int 2014;2014:384342.
90. Mocco J, Mack WJ, Kim GH, Lozier AP, Laufer I, Kreiter KT, *et al*. Rise in serum soluble intercellular adhesion molecule-1 levels with vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 2002;97:537-41.
91. Moreno P, Beisken S, Harsha B, Muthukrishnan V, Tudose I, Dekker A, *et al*. BiNChE: A web tool and library for chemical enrichment analysis based on the ChEBI ontology. BMC Bioinformatics 2015;16:56.
92. Morley P, Small DL, Murray CL, Mealing GA, Poulter MO, Durkin JP, *et al*. Evidence that functional glutamate receptors are not expressed on rat or human cerebromicrovascular endothelial cells. J Cereb Blood Flow Metab 1998;18:396-406.
93. Muroi C, Seule M, Sikorski C, Dent W, Keller E. Systemic interleukin-6 levels reflect illness course and prognosis of patients with spontaneous nonaneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl 2013;115:77-80.
94. Murthy SB, Naval NS. Dehydroepiandrosterone sulphate: diabolical hormone or epiphenomenon in aneurysmal subarachnoid hemorrhage? Crit Care 2015;19:352.
95. Nam DH, Kim JS, Hong SC, Lee WH, Lee JI, Shin HJ, *et al*. Expression of interleukin-1 beta in lipopolysaccharide stimulated monocytes derived from patients with aneurysmal subarachnoid hemorrhage is correlated with cerebral vasospasm. Neurosci Lett 2001;312:41-4.
96. Neil-Dwyer G, Cruickshank J. The blood leucocyte count and its prognostic significance in subarachnoid haemorrhage. Brain 1974;97:79-86.
97. Ni W, Gu YX, Song DL, Leng B, Li PL, Mao Y. The relationship between IL-6 in CSF and occurrence of vasospasm after subarachnoid hemorrhage. Acta Neurochir Suppl 2011;110(Pt 1):203-8.
98. Niikawa S, Hara S, Ohe N, Miwa Y, Ohkuma A. Correlation between blood parameters and symptomatic vasospasm in subarachnoid hemorrhage patients. Neurol Med Chir 1997;37:881-4; discussion 884-885.
99. Obata Y, Takeda J, Sato Y, Ishikura H, Matsui T, Isotani E. A multicenter prospective cohort study of volume management after subarachnoid hemorrhage: Circulatory characteristics of pulmonary edema after subarachnoid hemorrhage. J Neurosurg 2016;125:254-63.
100. Oliveira-Filho J, Ezzeddine MA, Segal AZ, Buonanno FS, Chang Y, Ogilvy CS, *et al*. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. Neurology 2001;56:1299-304.
101. Oshiro EM1, Hoffman PA, Dietsch GN, Watts MC, Pardoll DM, Tamargo RJ. Inhibition of experimental vasospasm with anti-intercellular adhesion molecule-1 monoclonal antibody in rats. Stroke 1997;28:2031-7; discussion 2037-2038.
102. Osuka K, Suzuki Y, Tanazawa T, Hattori K, Yamamoto N, Takayasu M, *et al*. Interleukin-6 and development of vasospasm after subarachnoid haemorrhage. Acta Neurochir (Wien) 1998;140:943-51.
103. Pedersen AT, Lidegaard O, Kreiner S, Ottesen B. Hormone replacement therapy and risk of non-fatal stroke. Lancet 1997;350:1277-83.
104. Pellettieri L, Nilsson B, Carlsson CA, Nilsson U. Serum immunocomplexes in patients with subarachnoid hemorrhage. Neurosurgery 1986;19:767-71.
105. Peterson BL, Won S, Geddes RI, Sayeed I, Stein DG. Sex-related differences in effects of progesterone following neonatal hypoxic brain injury. Behav Brain Res 2015;286:152-65.
106. Pike CJ. Testosterone attenuates beta-amyloid toxicity in cultured hippocampal neurons. Brain Res 2001;919:160-5.
107. Polin RS, Bavbek M, Shaffrey ME, Billups K, Bogaev CA, Kassell NF, *et al*. Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. J Neurosurg 1998;89:559-67.
108. Pradilla G, Garzon-Muvdi T, Ruzevick JJ, Bender M, Edwards L, Momin EN, *et al*. Systemic L-citrulline prevents cerebral vasospasm in haptoglobin 2-2 transgenic mice after subarachnoid hemorrhage. Neurosurgery 2012;70:747-56; discussion 756-747.
109. Pradilla G, Wang PP, Legnani FG, Ogata L, Dietsch GN, Tamargo RJ. Prevention of vasospasm by anti-CD11/CD18 monoclonal antibody therapy following subarachnoid hemorrhage in rabbits. J Neurosurg 2004;101:88-92.
110. Provencio JJ, Swank V, Lu H, Brunet S, Baltan S, Khapre RV, *et al*. Neutrophil depletion after subarachnoid hemorrhage improves memory via NMDA receptors. Brain Behav Immun 2016;54:233-42.
111. Ramchand P, Nyirjesy S, Frangos S, Doerfler S, Nawalinski K, Quattrone F, *et al*. Thromboelastography Parameter Predicts Outcome After Subarachnoid Hemorrhage: An Exploratory Analysis. World Neurosurg 2016;96:215-21.
112. Rattanajarasroj S, Unchern S. Comparable attenuation of Abeta (25-35)-induced neurotoxicity by quercitrin and 17beta-estradiol in cultured rat hippocampal neurons. Neurochem Res 2010;35:1196-205.
113. Recinos PF, Pradilla G, Thai QA, Perez M, Hdeib AM, Tamargo RJ. Controlled release of lipopolysaccharide in the subarachnoid space of rabbits induces chronic vasospasm in the absence of blood. Surg Neurol 2006;66:463-9; discussion 469.
114. Rodling-Wahlström M, Olivecrona M, Koskinen LO, Naredi S, Hultin M. Subarachnoid haemorrhage induces an inflammatory response followed by a delayed persisting increase in asymmetric dimethylarginine. Scand J Clin Lab Invest 2012;72:484-9.
115. Rousseaux P, Scherpereel B, Bernard MH, Graftieaux JP, Guyot JF. Fever and cerebral vasospasm in ruptured intracranial aneurysms. Surg Neurol 1980;14:459-65.
116. Sabri M, Ai J, Knight B, Tariq A, Jeon H, Shang X, Marsden PA, *et al*. Uncoupling of endothelial nitric oxide synthase after experimental subarachnoid hemorrhage. J Cereb Blood Flow Metab 2011;31:190-9.
117. Savarraj J, Parsha K, Hergenroeder G, Ahn S, Chang TR, Kim DH, *et al*. Early Brain Injury Associated with Systemic Inflammation After Subarachnoid Hemorrhage. Neurocrit Care 2017 [Epub ahead of print].
118. Sayeed I, Stein DG. Progesterone as a neuroprotective factor in traumatic and ischemic brain injury. Prog Brain Res 2009;175:219-37.
119. Schumacher M, Mattern C, Ghoumari A, Oudinet JP, Liere P, Labombarda F4 *et al*. Revisiting the roles of progesterone and allopregnanolone in the nervous system: Resurgence of the progesterone receptors. Prog Neurobiol 2014;113:6-39 .
120. Seifert V, Löffler BM, Zimmermann M, Roux S, Stolke D. Endothelin concentrations in patients with aneurysmal subarachnoid hemorrhage. Correlation with cerebral vasospasm, delayed ischemic neurological deficits, and volume of hematoma. J Neurosurg 1995;82:55-62.
121. Shi C, Awad IA, Jafari N, Lin S, Du P, Hage ZA, *et al*. Genomics of human intracranial aneurysm wall. Stroke 2009;40:1252-61.
122. Singer CA, Figueroa-Masot XA, Batchelor RH, Dorsa DM. The mitogen-activated protein kinase pathway mediates estrogen neuroprotection after glutamate toxicity in primary cortical neurons. J Neurosci 1999;19:2455-63.
123. Singh TD, Maloney P, Rabinstein AA, Hocker S. Significance of routine cerebrospinal fluid analysis in subarachnoid hemorrhage. J Neurosurg Sci 2017;61:117-23.
124. Sozen T, Tsuchiyama R, Hasegawa Y, Suzuki H, Jadhav V, Nishizawa S, *et al*. Immunological response in early brain injury after SAH. Acta Neurochir Suppl 2011;110(Pt 1):57-61.
125. Spallone A, Acqui M, Pastore FS, Guidetti B. Relationship between leukocytosis and ischemic complications following aneurysmal subarachnoid hemorrhage. Surg Neurol 1987;27:253-8.
126. Srinivasan A, Aggarwal A, Gaudihalli S, Mohanty M, Dhandapani M, Singh H, *et al*. Impact of Early Leukocytosis and Elevated High-Sensitivity C-Reactive Protein on Delayed Cerebral Ischemia and Neurologic Outcome After Subarachnoid Hemorrhage. World Neurosurg 2016;90:91-5.
127. Stein DG. Embracing failure: What the Phase III progesterone studies can teach about TBI clinical trials. Brain Injury 2015;29:1259-72.
128. Sun X, Ji C, Hu T, Wang Z, Chen G. Tamoxifen as an effective neuroprotectant against early brain injury and learning deficits induced by subarachnoid hemorrhage: possible involvement of inflammatory signaling. J Neuroinflammation 2013;10:157.
129. Tada Y, Makino H, Furukawa H, Shimada K, Wada K, Liang EI, *et al*. Roles of estrogen in the formation of intracranial aneurysms in ovariectomized female mice. Neurosurgery 2014;75:690-5; discussion 695.

130. Tam AK, Ilodigwe D, Mocco J, Mayer S, Kassell N, Ruefenacht D, *et al*. Impact of systemic inflammatory response syndrome on vasospasm, cerebral infarction, and outcome after subarachnoid hemorrhage: exploratory analysis of CONSCIOUS-1 database. Neurocrit Care 2010;13:182-9.
131. Thomas P, Pang Y. Membrane progesterone receptors: evidence for neuroprotective, neurosteroid signaling and neuroendocrine functions in neuronal cells. Neuroendocrinology 2012;96:162-71.
132. Tulamo R, Frösen J, Junnikkala S, Paetau A, Kangasniemi M, Peláez J, *et al*. Complement system becomes activated by the classical pathway in intracranial aneurysm walls. Lab Invest 2010;90:168-79.
133. Turan N, Heider RA, Zaharieva D, Ahmad FU, Barrow DL, Pradilla G. Sex Differences in the Formation of Intracranial Aneurysms and Incidence and Outcome of Subarachnoid Hemorrhage: Review of Experimental and Human Studies. Transl Stroke Res 2016;7:12-9.
134. Turan N, Miller BA, Heider RA, Nadeem M, Sayeed I, Stein DG, *et al*. Neurobehavioral testing in subarachnoid hemorrhage: A review of methods and current findings in rodents. J Cereb Blood Flow Metab 2017;37:3461-3474.
135. Turan N, Miller BA, Huie JR, Heider RA, Wang J, Wali B, *et al*. Effect of Progesterone on Cerebral Vasospasm and Neurobehavioral Outcomes in a Rodent Model of Subarachnoid Hemorrhage. World Neurosurg 2018;110:e150-e159.
136. Vedder H, Anthes N, Stumm G, Würz C, Behl C, Krieg JC. Estrogen hormones reduce lipid peroxidation in cells and tissues of the central nervous system. J Neurochem 1999;72:2531-8.
137. Wali B, Ishrat T, Stein DG, Sayeed I. Progesterone improves long-term functional and histological outcomes after permanent stroke in older rats. Behav Brain Res 2016;305:46-56.
138. Wali B, Sayeed I, Guthrie DB, Natchus MG, Turan N, Liotta DC, *et al*. Evaluating the neurotherapeutic potential of a water-soluble progesterone analog after traumatic brain injury in rats. Neuropharmacology 2016;109:148-58.
139. Walton JN. The prognosis and management of subarachnoid haemorrhage. Can Med Assoc J 1955;72:165-75.
140. Wang Y, Zhong M, Tan XX, Yang YJ, Chen WJ, Liu W, *et al*. Expression change of interleukin-8 gene in rabbit basilar artery after subarachnoid hemorrhage. Neurosci Bull 2007;23:151-5.
141. Wang Z, Zuo G, Shi XY, Zhang J, Fang Q, Chen G. Progesterone administration modulates cortical TLR4/NF-kappaB signaling pathway after subarachnoid hemorrhage in male rats. Mediators Inflamm 2011;2011:848309.
142. Wartenberg KE, Mayer SA. Medical complications after subarachnoid hemorrhage. Neurosurg Clin N Am 2010;21:325-38.
143. Webster KM, Wright DK, Sun M, Semple BD, Ozturk E, Stein DG, *et al*. Progesterone treatment reduces neuroinflammation, oxidative stress and brain damage and improves long-term outcomes in a rat model of repeated mild traumatic brain injury. J Neuroinflammation 2015;12:238.
144. Weir B, Disney L, Grace M, Roberts P. Daily trends in white blood cell count and temperature after subarachnoid hemorrhage from aneurysm. Neurosurgery 1989;25: 161-5.
145. Wu W, Guan Y, Zhao G, Fu XJ, Guo TZ, Liu YT, *et al*. Elevated IL-6 and TNF-alpha Levels in Cerebrospinal Fluid of Subarachnoid Hemorrhage Patients. Mol Neurobiol 2016;53:3277-85.
146. Wunderle K, Hoeger KM, Wasserman E, Bazarian JJ. Menstrual phase as predictor of outcome after mild traumatic brain injury in women. J Head Trauma Rehabil 2014;29:E1-8.
147. Xie X, Wu X, Cui J, Li H, Yan X. Increase ICAM-1 and LFA-1 expression by cerebrospinal fluid of subarachnoid hemorrhage patients: Involvement of TNF-alpha. Brain Res 2013;1512:89-96.
148. Yamaura I, Tani E, Maeda Y, Minami N, Shindo H. Endothelin-1 of canine basilar artery in vasospasm. J Neurosurg 1992;76:99-105.
149. Yan F, Hu Q, Chen J, Wu C, Gu C, Chen G. Progesterone attenuates early brain injury after subarachnoid hemorrhage in rats. Neurosci Lett 2013;543:163-7.
150. Yang YM, Huang A, Kaley G, Sun D. eNOS uncoupling and endothelial dysfunction in aged vessels. Am J Physiol Heart Circ Physiol 2009;297:H1829-36.
151. Yeung PK, Shen J, Chung SS, Chung SK. Targeted over-expression of endothelin-1 in astrocytes leads to more severe brain damage and vasospasm after subarachnoid hemorrhage. BMC Neurosci 2013;14:131.
152. Young AM, Karri SK, Ogilvy CS. Exploring the use of estrogen & progesterone replacement therapy in subarachnoid hemorrhage. Curr Drug Saf 2012;7:202-6.
153. Zanier ER, Zangari R, Munthe-Fog L, Hein E, Zoerle T, Conte V, *et al*. Ficolin-3-mediated lectin complement pathway activation in patients with subarachnoid hemorrhage. Neurology 2014;82:126-34.
154. Zhang Z, Liu J, Fan C, Mao L, Xie R, Wang S, *et al*. The GluN1/GluN2B NMDA receptor and metabotropic glutamate receptor 1 negative allosteric modulator has enhanced neuroprotection in a rat subarachnoid hemorrhage model. Exp Neurol 2018;301(Pt A):13-25.
155. Zhao XD, Zhou YT. Effects of progesterone on intestinal inflammatory response and mucosa structure alterations following SAH in male rats. J Surg Res 2011a; 171:e47-53.
156. Zhao XD, Zhou YT. Effects of progesterone on intestinal inflammatory response and mucosa structure alterations following SAH in male rats. J Surg Res 2011b; 171:e47-53.
157. Zhong W, Zhang Z, Zhao P, Shen J, Li X, Wang D, Li G, *et al*. The Impact of Initial Systemic Inflammatory Response After Aneurysmal Subarachnoid Hemorrhage. Turk Neurosurg 2017;27:346-52.
158. Zuccarello M, Boccaletti R, Romano A, Rapoport RM. Endothelin B receptor antagonists attenuate subarachnoid hemorrhage-induced cerebral vasospasm. Stroke 1998;29:1924-9.