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Review

Pathological mechanisms underlying aneurysmal subarachnoid haemorrhage and vasospasm

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ABSTRACT

Aneurysmal subarachnoid haemorrhage is a cerebrovascular disease associated with an overall mortality as high as 50%. Delayed ischaemic neurologic deficits are a major contributor to this statistic, as well as the significant morbidity associated with the disease. Studies examining the pathophysiologic events causing these devastating changes in cerebral blood flow have identified several mechanisms which are thought to contribute to the development of delayed ischaemic neurological deficits, perhaps the most damaging of which are increased intracranial pressure and cerebral vasospasm. In addition, the presence of blood in the subarachnoid space can trigger a myriad of reactions resulting in increased capillary permeability, breakdown of the blood–brain barrier, and inflammation in surrounding neural tissue that adds to the devastating effects of haemorrhage. A detailed understanding of the post-haemorrhagic cellular and molecular changes that contribute to the development of cerebral ischaemia and vasospasm is imperative to the formulation of treatment and prevention options for subarachnoid haemorrhage patients. Despite a large body of research within this field, a complete understanding of rupture and vasospasm remains elusive. This study reviews the role of vasoactive substances, such as endothelin-1, as well as the histochemistry and molecular pathology of post-haemorrhage inflammation in the development of vasospasm and cerebral ischaemia.

1. Introduction

Aneurysmal rupture and its associated sequelae can be devastating events, carrying with them a high rate of morbidity and mortality. Described as a weakening and abnormal dilation of the vascular wall, unruptured cerebral aneurysms are estimated to occur in roughly 3.6–6.0% of the population over the age of 30 [1,2]. While aneurysms may remain asymptomatic for a lifetime, subarachnoid haemorrhage (SAH) can cause lasting damage. SAH itself has an overall mortality of roughly 40–50%, and ruptured aneurysms account for approximately one-quarter of cerebrovascular deaths [2–4]. While the precise mechanism of rupture remains a topic of great research, several theories have been put forth as potential triggers, the most widely accepted of which focuses on the role of hypertension and haemodynamic stresses [5,6].

Risk factors for aneurysm formation and for rupture are similar, for example cigarette smoking, hypertension, heavy alcohol consumption, cocaine, and family history. With regards to cigarette smoking, the association with intracranial aneurysms and SAH is well established. Cigarette smoking has been demonstrated to raise the relative risk of SAH to between 1.9 and 5.2 and some studies have demonstrated dose dependent risks [3,7,8]. Heavy alcohol consumption has also been shown to be an independent risk factor for spontaneous aneurysmal SAH, potentially through its effects on blood pressure and altering haemodynamic factors [7]. Cocaine and its metabolites increase the risk and severity of aneurysms and SAH through its vasoconstrictor properties, which act via nervous stimulation of the vascular smooth muscle, and the profound hypertensive conditions they cause [9].

Beyond the acute effects of SAH, several delayed pathologies can manifest and cause further damage to patients, perhaps the most devastating of which is cerebral vasospasm and resultant delayed ischaemic neurologic deficits (DIND). The incidence of angiographic vasospasm has been reported to range from 70–90% between 3–14 days from ictus [10,11]. Furthermore, up to 50% of these patients with vasospasm are reported to experience DIND [12]. Current therapy aimed at limiting the duration and severity

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of vasospasm in these patients is multifaceted. Historically, the workhorse of medical vasospasm treatment has been "Triple H" therapy, a combination of hypertension, hypervolaemia, and haemodilution, despite conflicting evidence in the neurosurgical literature [13–15]. Current management of patients with SAH and suspected or known vasospasm includes maintaining euvolaemia and allowing autoregulation of blood pressure. Other accepted therapeutic options include calcium channel blockers, endothelin receptor antagonists, sympatholytics, and intra-arterial papaverine. In addition, there are a number of less accepted but theoretically useful methods to prevent vasospasm, which include magnesium, statins, and nitrates [16–18].

Despite the fact that many of the general mechanisms that cause the rupture of cerebral aneurysms are known, the intricacies behind each factor have not been explained in detail. The importance of determining how haemodynamic factors, vascular and extracellular matrix (ECM) remodeling, and genetics interact could help shed light on preventing the pathogenesis of cerebral aneurysms and SAH pharmacologically or through alterations in lifestyle. Additionally, further knowledge about this specific pathology could help prevent the devastation of SAH. The present study represents one of the first compilations of current literature surveying the pathological mechanisms of aneurysmal SAH and cerebral vasospasm.

2. Rupture of cerebral aneurysms and SAH

At the peak of growth of an aneurysm, just prior to rupture, the only tissue of the vessel wall maintaining its integrity is the injured intima and adventitia. The internal elastic lamina is absent or fragmented and little, if any, smooth muscle remains in the media [19]. Prior to aneurysmal pathogenesis, the smooth muscle layers of the arterial wall were primarily responsible for resisting the pulse pressure created by blood flow. The remaining connective tissue is now responsible for resisting arterial blood pressure and the strength of the wall is related to the strength of the remaining collagen network and its orientation.

As in the aneurysm development, haemodynamic forces play a critical role in causing the rupture [6]. The Law of Laplace is the physiological principle governing how vessels withstand intravascular pressures and dictating the point of rupture. This law states that the tension in the wall of the vessel is equal to the transmural pressure times the radius of the vessel and applies to very thin walled vessels, such as those found in the cerebral circulation. As the aneurysm dilates, the tension in the wall increases and because the wall is continually degraded and weakened, it is unable to withstand the tension generated under normal physiological intraluminal pressure, in particular the hypertensive conditions associated with aneurysm development or the acute pressure increases caused by behaviors such as smoking or cocaine. The blood flow in the out-pocketing of a typical saccular aneurysm changes in such a fashion that intraluminal pressure, and most importantly transmural pressure, is altered and the vessel is more likely to burst.

Depending on the rate and extent to which ECM remodeling is occurring, the aneurysm will continue to dilate and bulge from the parent vessel. SAH occurs when the wall of the vessel becomes too fragile to resist the forces created by arterial hydrostatic pulse pressure and blood leaks into the subarachnoid connective tissue. Often, aneurysms rupture near the midpoint of the dome within the body where pressure is greatest [20].

Structural differences that exist between ruptured and unruptured cerebral aneurysms are endothelial damage and replacement of normal ECM components with hyaline-like compounds [21]. This traumatic event is often accompanied by acute ischaemic injury less than 48 hours after the initial haemorrhage as well as pathophysiological changes in cerebral blood flow (CBF) and perfusion pressure and intracranial pressure (ICP), as well as brain oedema and epilepsy [22].

3. CBF and ischemia

After aneurysmal SAH, there are primary and secondary problems that arise in CBF that can cause ischaemia. Primary ischaemia or haemorrhagic ischemia occurs within 1 to 3 days of the bleed and is caused by the loss of tissue perfusion. Secondary or delayed ischaemia occurs when CBF is inadequate to meet metabolic demand of cerebral tissue and is caused by other resultant pathophysiological mechanisms. Only when CBF is unable to meet the metabolic demands of the brain parenchyma will ischemia and potential cerebral infarction occur. Reduction of CBF following SAH is one of the most devastating consequences, creating problems with tissue oxygenation and resultant ischaemic attacks, causing high morbidity and mortality [23].

There are a few pathological changes that are considered to result in delayed decreases in CBF after SAH, including cerebral oedema, hydrocephalus, and vasospasm [24]. Increased ICP is one mechanism through which CBF is reduced. An initial rise in ICP occurs when blood enters the subarachnoid space and is the cause of the sudden severe headache experienced. Also, the delayed onset of cerebral oedema and hydrocephalus, which also raise ICP, can cause compression of neural tissue and perfusing arteries, decreasing blood flow to the brain via increased resistance for penetrating arterioles, subarachnoid resistance arteries, as well as the extracranial feeding arteries that enter at various foramina in the skull. Also, CBF can be altered by decreasing and narrowing the autoregulatory capabilities of the cerebral arteries. This effect occurs through the oxidative stress caused by haemorrhage which can create further damage to endothelial cells, producing dysfunction that prevents the appropriate flow and pressure induced responses. In particular, the reduction in flow-induced dilation, mediated by endothelial release of nitric oxide (NO), is important because it prevents the vasodilatory response necessary to increase cerebral perfusion. NO availability is decreased by endothelial damage and through the biochemical mechanisms generating peroxynitrite which deplete substrates necessary for NO production.

Another way in which cerebral perfusion can be affected after SAH occurs is through impaired capillary perfusion. Studies have demonstrated that morphological changes to intraparenchymal capillaries occur 1 to 2 days post-hemorrhage, including decreases in the area of tissue perfused, reduction in capillary volume and surface density, and increases in intercapillary distance [25]. These changes in the cerebral capillary network decrease CBF by reducing the number of perfusion pathways; increasing the overall resistance to circulation. Interestingly, these changes in the cerebral capillaries are counter-intuitive to the expected response of this vascular bed, which would be to increase capillary number in response to the hypoxia that occurs after SAH.

4. Vasospasm

Vasospasm is characterised by extended constriction of the large extraparenchymal arteries throughout the cerebral circulation. Despite the mysterious causes of vasospasm, it has been extensively researched and is one of the more common causes of reduced CBF [26]. The dangers of vasospasm are further potentiated by the effects on cerebral autoregulation. Under normal physiological conditions, autoregulation serves to maintain constant CBF during fluctuations in cerebral perfusion pressure. During SAH and vasospasm, the range of pressures that elicits these