The circle of Willis revisited: Forebrain dehydration sensing facilitated by the anterior communicating artery

How hemodynamic properties facilitate more efficient dehydration sensing in amniotes

Matija Fenrich | Karlo Habjanovic | Josip Kajan | Marija Heffer

Laboratory of Neurobiology, Faculty of Medicine, J. J. Strossmayer University of Osijek, Osijek, Croatia

Correspondence
Matija Fenrich, Laboratory of Neurobiology, Faculty of Medicine, J. J. Strossmayer University of Osijek, Osijek, Croatia.
Email: mfenrich@mefos.hr

Funding information
Medicinski Fakultet, Sveučilište u Zagrebu

Abstract
We hypothesize that threat of dehydration provided selection pressure for the evolutionary emergence and persistence of the anterior communicating artery (ACoA – the inter-arterial connection that completes the Circle of Willis) in early amniotes.

The ACoA is a hemodynamically insignificant artery, but, as we argue in this paper, its privileged position outside the blood-brain barrier gives it a crucial sensing function for the osmolarity of the blood against the background of the rest of the brain, which efficiently protects itself from dehydration. Till now, the questions of why the ACoA evolved, and what its physiological function is, have remained unsatisfactorily answered. The traditional view—that the ACoA serves as a collateral source of vascularization in case of arterial stenosis—is anthropocentric, and not in accordance with principles of natural selection that apply more generally. Diseases underlying arterial stenosis are associated with aging and the human lifestyle, so this cannot explain why the ACoA formed hundreds of millions of years ago and persisted in amniotes to this day.

The peculiar hemodynamic properties of the ACoA could be selected traits that allowed for more efficient forebrain detection of dehydration and complex behavioral responses to water loss, a major advantage in the survival of early amniotes. This hypothesis also explains insufficient hydration often seen in elderly humans.

KEYWORDS
arterial circle of Willis, circumventricular organs, dehydration, evolution, hypertension

INTRODUCTION
The vertebrate brain is vascularized by two arterial systems. The anterior system, also called the carotid system, derives from the internal carotid arteries (ICA) and irrigates the forebrain. The posterior system, called the vertebral system, derives from the vertebral arteries and mainly irrigates the brainstem.[1] The circle of Willis (CoW) is an anatomical name for arteries found at the base of the brain in amniotes (i.e., reptiles, birds and mammals), which are assembled in a roughly circular configuration (Figure 1).[2,3] All the arteries of the CoW are embryonically derived from the carotid system.[4,5] The basic vascular plan of the vertebrate brain is highly conserved among species, but this
FIGURE 1  Schematic depiction of the main arteries associated with the circle of Willis (CoW). Left panel: a simplified vascular plan of the CoW. All the arteries of the CoW are derived from two terminal intracranial divisions of the internal carotid artery. Anterior divisions give rise to a pair of anterior cerebral arteries (ACA), a pair of middle cerebral arteries (MCA) and a single anterior communicating artery (ACoA). Posterior divisions give rise to caudal cerebral arteries that fuse to form a single basilar artery (BA), whereas the unfused segment remains as posterior communicating artery (PCoA). Lateral branches of the posterior divisions give rise to a pair of posterior cerebral arteries (PCA). Right panel: an overview of the homologous arteries at the basal forebrain in non-amniote vertebrates (which do not have the CoW), and in amniote vertebrates (which do have the CoW)

is often obscured by inconsistent anatomical nomenclature. For that reason, homologous vessels in this paper will be referred to by names accepted in human anatomy.

The forebrain of all vertebrates is supplied by a pair of ICAs that, after entering the cranium and arriving at the base of the brain, branch into their anterior and posterior division. These divisions give rise to the anterior and posterior cerebral arteries, respectively. Although many textbooks consider the CoW an anastomosis between the carotid and vertebral arterial systems, this is only true in birds and mammals. Thus, this cannot be considered a defining characteristic of the CoW.

Traditionally, the CoW is considered a compensatory system that ensures collateral blood supply in case of arterial stenosis or occlusion. However, considering the timing and circumstances in which the CoW evolved, this explanation is not satisfactory. Atherosclerotic stenosis is primarily associated with the human lifestyle, and it occurs after the reproductive age of an individual. Therefore, it could neither have been a source of selection pressure in early amniotes, nor could it explain the persistence of the CoW for hundreds of millions of years to this day.

The original evolutionary pressure that led to the emergence of the CoW and its physiological function remain largely uncertain. Vrselja et al. hypothesized that the CoW might serve as a system for attenuation of forces associated with intra-arterial pressure waves during an increase in systolic blood pressure. They proposed that the communicating arteries of the CoW passively dissipate the energy of the reflected pressure waves, thus, protecting the brain from the potential damage.

This hypothesis is, however, not substantiated by our contemporary understanding of cerebrovascular hemodynamics and the evolution of the CoW. Namely, the authors proposed that the stress to the cerebral microcirculation is a consequence of a sudden change in the blood flow conditions, that is, a significant rise in the resistance in the distal arterial tree. However, due to branching, the total resistance and pressure in the distal arteries is actually lower relative to the resistance in the larger proximal arteries. The shifting of increased intravascular resistance from distal towards the more proximal cerebral arteries, which occurs during increased physical activity, is not evidence of energy dissipation in the CoW, but a consequence of blood flow
arterial stiffness). Because such conditions are also predispositions that cause a significant decrease in arterial compliance (i.e., development.

From a physiological standpoint, the brain is already well protected from the potential stress exerted by pressure waves. Significant compliance of the extracranial portion of the ICA and reflex vasconstriction mediated by sympathetic innervation efficiently buffer the systolic surges of blood pressure in the cerebral vasculature. Similarly, the baroreceptors in the brainstem monitor the blood pressure in the posterior cerebral circulation, and are also suggested to contribute to the reflex sympathetic vasconstrictor response. Experiments with animals that underwent unilateral ablation of the cranial sympathetic fibers and subsequently developed diffuse cortical lesions in the ipsilateral hemisphere have directly demonstrated that intact cerebrovascular sympathetic innervation is crucial for protecting the integrity of cerebral microcirculation. These experiments have also indirectly shown that the protective function of the CoW, even if present, is not sufficient to prevent damage. Since evolutionary emergence of the sympathetic vasomotor innervation to the cerebral arteries predates the divergence of amniotes and, thus, the emergence of the CoW itself, we believe that the hypothesized pressure-dissipating function of the CoW is unlikely to be the source of selection pressure for its development.

Pressure waves might threaten the brain only under pathologic conditions that cause a significant decrease in arterial compliance (i.e., arterial stiffness). Because such conditions are also predominantly associated with human lifestyle and aging, we believe that this too would present an unlikely source of evolutionary pressure for the emergence and persistence of the CoW in non-human amniotes.

In spite of a lack of understanding of the physiological function of the CoW, the circumstances underlying the evolutionary emergence of its posterior communicating arteries (PCoA) are well known and will be briefly reviewed in this article. However, the circumstances that led to the development of the anterior communicating artery (ACoA) and its role are poorly understood. The ACoA does not significantly contribute to brain vascularization, but for some reason, it persisted in different taxa for hundreds of millions of years of evolution. In addition, absence of the ACoA seems to be among the rarest CoW variations in humans. Therefore, the aim of this article is to propose an answer to why natural selection favored the persistence of this small, hemodynamically insignificant artery. Essentially, the resolution of the question relates to special features of the ACoA that, in contrast to roles in hemodynamics, rather must have evolved to have body fluid sensing functions. Furthermore, this resolution explains physiological manifestations of aging-related carotid artery stenosis—in particular the decrease in the drive to drink water, often seen in elderly people. To elaborate our hypothesis comprehensively, we first have to review the evolutionary history of the arteries that form the CoW.

ARTERIES OF THE CIRCLE OF WILLIS HAVE EMERGED INDEPENDENTLY AND ASYNCHRONOUSLY

All the arteries of the CoW develop through angiogenesis from the ICA. Embryonically, the resulting vasculature in all vertebrates can be classified as either anterior or posterior. The anterior division of the ICA supplies the rostral forebrain, while the posterior division supplies the caudal brain structures. This basic organization of the cerebral arteries is already present in fish taxa, implying that this structural plan predates the tetrapod land invasion in the mid to late Devonian.

Partial midline fusion of the posterior branches was the first significant morphological variation of this basic structural plan. Even though this variation can be sporadically found in some fish species, it became a rule in amphibious tetrapods. This fusion resulted in the formation of the basilar artery at the level of the pons, whereas the more proximal segments remained unfused and are homologous to the PCoAs. It is important to emphasize that the CoW does not exist in amphibians, it only appears with the formation of the ACoA in amniotes (Figure 2).

The large temporal gap between the emergence of the first homologues of the PCoAs and the emergence of the ACoA brings into question the unity of the CoW as an anatomical structure. The anterior and posterior segments of the CoW have evolved separately, at different times, in different environments. The probable reason that the CoW has been described as a single structure is that, to the human mind, it looks like a single structure. This, however, is evidently not substantiated either by phylogeny or embryology. The most recent morphological change in the evolutionary history of the CoW was the fusion of the basilar artery with the vertebral arteries, forming the vertebo-basilar arterial system in birds and mammals. Since the reptilian basilar artery is not fused with the vertebral arteries, it is possible that this morphological change could be a result of convergent evolution (Figure 2). The vertebo-basilar fusion developed concurrently with the enlargement of the dorsal cortex, which provided the selection pressure for evolution of increased capacity in the carotid system. In avian posterior circulation, the original rostrocaudal blood flow remains conserved, while in mammals the blood flow changes to the opposite direction. Because the vertebral arteries predominantly supply the caudal brain, the mammalian proximal segments of the posterior cerebral divisions of the ICA became hypoplastic or aplastic, and are anatomically described as the PCoAs. This change from a predominantly carotid supply to the posterior cerebral circulation to a predominantly vertebral supply is conserved in fetal development, where the switch of the blood flow direction correlates with the growth of the posterior cerebrum, and this phenomenon is also responsible for the frequent anatomical variations of the PCoAs in humans.

On the other hand, the circumstances in which the ACoA emerged are not completely clear. Embryonically, it is derived from a transiently present meshwork of small pial arteries (surrounded by
cerebrospinal fluid, and not yet penetrating into the brain proper) located between the two anterior cerebral arteries (ACA).

Considering that blood flow through the ACoA under physiologic conditions is negligible, and that it doesn’t affect the hemodynamics of the CoW, its role in brain vascularization is hard to explain. However, this small, insignificant artery has evolved and persisted in living amniotes, hence implying some other, yet unknown, function.

The first signs of a solution to this conundrum arose from microanatomical studies, which showed that the ACoA gives rise to a few small perforating branches that enter the brain to supply the sensory circumventricular organs. The terminals of these perforating arteries have fenestrated endothelium and lack a functional blood-brain barrier. Curiously, the sensory organs supplied by the ACoA are key structures in the forebrain regulation of hydromineral balance, a function that did not exist in pre-amniote vertebrates. To solve the riddle of why the ACoA appeared in early amniotes and persisted to this day, one must take into account the ecological and evolutionary circumstances that existed at the time. In the following sections, we will review the development of the forebrain regulation of hydromineral homeostasis, and then propose a hypothesis that the constant threat of dehydration represented the selection pressure for the development and persistence of the ACoA.

### Risk of dehydration was a source of strong selection pressure in early amniotes

One of the key adaptations in vertebrates is the ability to counteract fluctuations in osmolarity of body fluids. For that reason, a complex peptidergic signaling system (using peptide-based endocrine transmitters) emerged very early in their evolutionary history—namely—the renin-angiotensin-aldosterone system (RAAS). In short, the RAAS is activated when hypovolemia causes a reduction in kidney blood flow, which triggers the conversion of prorenin to renin in the kidneys. Renin, in turn, converts angiotensigen to angiotensin I, and angiotensin-converting-enzyme proteolytically cleaves angiotensin I into angiotensin II (ANG-II). Being transported by blood, ANG-II exerts its effects on many organs and tissues, resulting in a systemic response that increases the perfusion of tissues and counteracts water loss. In parallel to that, the area postrema, a circumventricular organ in the dorsal brainstem, has evolved to detect hypernatremia (abnormally high blood sodium concentration). Its osmotically sensitive neurons stimulate the cardiorespiratory center, the sympathetic neurons in the brainstem, and synthesis and release of antidiuretic hormone (ADH), or its homologs, from the hypothalamus. In addition to that, it has been proposed that the area postrema might harbor central baroreceptors that react to changes in cerebral blood pressure by...
modulating the sympathetic output. The interaction between the RAAS and the brainstem sensors is mediated by a positive feedback loop consisting of (1) an increase in the sympathetic output by the area postrema, which causes vasconstriction in the kidney and subsequent RAAS activation, and (2) by the RAAS, whose effector peptide ANG-II activates the neurons in the area postrema. In aquatic non-amniote vertebrates, that is, fish, this causes reflex swallowing by relaxing the esophageal musculature. Stereotactic application of ANG-II to the area postrema in terrestrial vertebrates also causes reflex swallowing, but this obviously does not help rehydrate the organism. While the RAAS-mediated mechanisms are primarily directed towards prevention of the further loss of water, the central sensors are directly involved in water replenishment.

The land invasion of early tetrapods some 370 million years ago (mya) brought new challenges in terms of regulation of hydromineral balance. Early tetrapods lived in shallow waters and occasionally ventured onto land to take advantage of a new ecological niche. These sporadic excursions onto land drove the selection for a series of new traits, a review of which would be out of the scope of this article.

Several tens of millions of years later, early amphibious tetrapods and their immediate evolutionary descendants, that is, Amphibia and Reptilomorpha, eventually became the first land vertebrates. However, the life cycle of amphibious tetrapods remained bound to aquatic habitats. Their eggs and larvae develop in water until the end of metamorphosis. Furthermore, even adult amphibians are highly dependent on aquatic habitats, because they rehydrate through transdermal absorption using specialized ventral skin. Thus, early and current amphibians were, and still are, semiaquatic organisms.

The next significant step in land vertebrate evolution was the divergence of the first amniotes 318 mya. They are named after the amniotic sac and fluid, which granted them the ability to lay eggs and hatch progeny outside water. This, for the first time, made the life cycle of land vertebrates independent of aquatic habitats. Their eggs and larvae develop in water until the end of metamorphosis. Furthermore, even adult amphibians are highly dependent on aquatic habitats, because they rehydrate through transdermal absorption using specialized ventral skin. Thus, early and current amphibians were, and still are, semiaquatic organisms.

The OVLT and SFO are specialized neuro-endothelial structures, which, together with the area postrema, are collectively termed sensory circumventricular organs (CVO). These structures are privileged locations where the brain comes into direct contact with blood. The blood-brain barrier normally prevents that, so the sensory CVO have undergone selection for several traits that facilitate their exposure to blood solvents, such as fenestrated arteries, permeable tight junctions, a lack of blood-brain barrier and specialized endothelial cells called tanycytes. The origin and evolution of many of these structures is still mostly unknown, but it seems that the secretory CVO, that is, neurohypophysis and epiphysis, are ontogenically older and more conserved than the sensory CVO. It has also been proposed that the forebrain sensory CVO might embryonically arise from the floor plate. In addition to dehydration sensing, the forebrain sensory CVO are also implicated in thermoregulation, a function that is tightly connected to hydromineral homeostasis.

Information about blood composition arrives to the OVLT and SFO through two perforating arteries, the supraoptical and subfornical branches of the ACoA (Figure 4A), which either arise directly from the ACoA, or from the subcallosal branch of the ACoA. Let us emphasize that the ACoA originally emerged in amniotes, so other vertebrates do not have a homologous artery. True “physiologic” or hypertonic dehydration is associated with a relative increase in sodium concentration due to a reduction in circulatory volume. Neurons in the OVLT and SFO directly react to ANG-II, while the glial cells, that is, astrocytes, are the sodium sensors. Astrocytes in the OVLT and SFO express special Na+K+ ATPases. Thus, once they open, the intracellular increase in sodium stimulates Na+K+ -ATPases causing ATP depletion, which in turn stimulates energy metabolism. An increase in metabolic activity precipitates anaerobic conditions within astrocytes, resulting in lactate and epoxeyicosatrienoic acid (EETA) production in the SFO and in the OVLT, respectively.

The astrocytes and neurons in the OVLT and SFO express yet another type of osmosensitive receptors, called Transient Receptor Potential Vanilloid 1 (TRPV1). These receptors’ ability to sense extracellular hypertonicity seems to be temperature-dependent and facilitated by presence of protons, which may also be a type of signal transduction associated with products of anaerobic metabolism in astrocytes. Lactate and EETA function as gliotransmitters that stimulate nearby neurons, whose activity mediates disinhibition of the neural circuits involved in regulation of salt and water intake, activation of cortical areas involved in conscious perception of thirst, activation of paraventricular hypothalamic nuclei, medial preoptic and suprapoctic nuclei, stimulation of the sympathetic nervous system, and release of neuropeptides from the posterior pituitary (oxytocin and ADH in mammals, vasotocin in reptiles, and mesotocin in avians) (Figure 4B). Unlike sensors in the brainstem, that is, the area postrema, sensors in the forebrain provided a way to react to dehydration with complex affective, cognitive and behavioral patterns, such as water seeking, volitional drinking, decision making, and not just with neuroendocrine and autonomic responses. Coupling of the aforementioned higher-order forebrain functions with central dehydration sensing evolved concomitantly with the development of the cerebral

**FOREBRAIN DEHYDRATION SENSING RELIES ON ANAEROBIC METABOLISM IN SPECIALIZED ASTROCYTES**

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| Features | FISH | AMPHIBIANS | REPTILES | BIRDS | AMNIOTES | MAMMALS |
|----------|------|------------|----------|-------|----------|--------|
| Anatomical overview | ![Image] | ![Image] | ![Image] | ![Image] | ![Image] | ![Image] |
| ACoA | × | × | × | ✓ | ✓ | ✓ | (vestigial) |
| PCoA and fused basilar artery | × | ✓ | ✓ | ✓ | ✓ | ✓ | (vestigial) |
| Vertebro-basilar fusion | × | × | × | ✓ | ✓ | ✓ | (vestigial) |
| Forebrain sodium sensing | × | × | ? | ✓ | ✓ | ✓ | ? |
| Brainstem sodium sensing | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Central regulation of osmolarity | Reflex swallowing | Cutaneous absorption | Drinking of salt water | Drinking of fresh water | Dietary intake or metabolic water (fat oxidation) | Metabolic water (fat oxidation) |
| Dominant hydration strategy | ![Image] | ![Image] | ![Image] | ![Image] | ![Image] | ![Image] |

* Chelidae (turtles) and Hydrophiinae (sea snakes)  
** Pinnipeds (sea lions, fur seals, true seals, walrus)  
*** Cetaceans (whales, dolphins, porpoises) and sirenians (manatees, dugong)

**FIGURE 3** Overview of anatomical and physiological features related to CoW morphology and central regulation of osmolarity in vertebrates. Fish and amphibians rely on sensing of hypernatremia by the area postrema in the brainstem. The ACoA and forebrain dehydration sensing were documented in reptiles, birds and mammals. Some marine reptiles seem to lack the ACoA. Non-amniote vertebrates do not have the ACoA. Amphibious mammals likely retain the same CoW configuration as terrestrial mammals. Marine mammals developed an alternative cerebral vascularization source (rete mirabile system), and may exhibit only vestigial remnants of the original CoW. Dominant hydration strategies are also summarized. Schematic illustrations are based on textual descriptions in the referenced publications.

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**ACoA DOES NOT CONTRIBUTE TO CEREBRAL CIRCULATION UNDER PHYSIOLOGICAL CONDITIONS**

The ACoA is a small artery, around 1–3 mm in diameter. Typically, it connects two parallel ACAs, which supply the rostral forebrain. Numerical studies based on in vivo measurements show that the ACoA does not contribute to cerebral blood circulation under physiological conditions. Its absence does not affect the hemodynamic parameters in the CoW, neither in inflowing nor outflowing arteries. Furthermore, in the ACoA there is practically no blood flow from one ACA to the other. Due to the asymmetry of the arterial tree, pressure waves arrive at the ACoA at different times in the cardiac cycle; however, this phase difference is not large enough to permit physiologically significant net flow. Despite blood flow through the ACoA being negligible, during systole, there are pressure wave collisions and possibly some very discrete crossflow phenomena. It has
FIGURE 4  Sensory circumventricular organs (CVO) in the forebrain. (A) Parasagittal section through a human brain with locations of the forebrain sensory CVO. The organum vasculosum laminae terminalis (OVLT) is located in the terminal lamina of the third ventricle. The organum subfornicale (SFO) is located inferior to the rostral aspect of the body of fornix, near the interventricular foramen of Monro. The OVLT is vascularized by the supraoptic branch of the anterior communicating artery (ACoA), and the SFO by the subfornical branch of the ACoA. Both branches sometimes arise from a common subcallosal branch of the ACoA. (B) Schematic illustration of the local neural circuitry involved in sodium sensing in the OVLT and SFO. Astrocytes expressing NaX and TRPV1 are in close contact with the fenestrated vascular endothelium. NaX and TRPV1 channels in the astrocytes react to hypernatremia. NaX activation triggers the anaerobic metabolism and production of gliotransmitters, that is, lactate and epoxyeicosatrienoic acid (EETA). These gliotransmitters activate the GABA-ergic interneurons, whose activity leads to disinhibition of principal neurons. TRPV1 signaling leads to presynaptic modulation of neural activity. This results in activation of a series of centrally-mediated homeostatic mechanisms aimed at correcting the dehydration, such as release of the anti-diuretic hormone (ADH), oxytocin, increased sympathetic output, thirst, drinking, water seeking and so on.

been suggested that these conditions might contribute to the formation of aneurism.[78] Considering the negligible contribution of the ACoA to brain vascularization, and the fact that it is prone to the development of cerebrovascular pathologies, it is perplexing that natural selection favored the persistence of this blood vessel for more than 300 millions of years.

The ACoA’s potential in brain blood supply comes into effect only under pathologic conditions. Due to atherosclerotic stenosis of the ICA, blood flow in the left and right carotid circulation becomes more asymmetric, leading to an increase in phase and pressure difference, which establishes the blood flow through the ACoA towards the side of the stenosis.[12,28,29] Atherosclerotic stenosis is a slow progressing pathologic process which theoretically gives blood vessels enough time to adapt to an increased flow and remodel accordingly.[24,79–81] Endothelial mechanoreceptors transduce the perceived increase in blood flow into intracellular signaling.[80,82,83] This triggers reorganization of adhesion proteins in the basement membrane.[80] The ACoA does not normally accommodate significant blood flow,[12–15] so this flow increase would lead to flow-induced intramural stress, endothelial dys-function and aneurysm formation.[84,85] Taking into account that the ACoA is hemodynamically insignificant under physiologic conditions, and that atherosclerosis is primarily a disease associated with aging and the human lifestyle,[26,27] this compensatory function could not be a source of selection pressure for emergence and persistence of the ACoA in non-human amniotes.

Considering the peculiar hemodynamic properties of the ACoA, it might seem rather surprising that its perforating branches supply structures as important as the forebrain sensory CVO. However, in the next section, we will argue that exactly these special properties directly support their sensoric function.

ACoA IS A SPECIAL VASCULAR NICHE THAT FACILITATES SENSORIC FUNCTION OF OVLT AND SFO

Physiologic loss of water is characterized by a reduction in extracellular fluid, leading to a relative increase in sodium concentration.[40] It is also
associated with reduced tissue perfusion, which results in switching to anaerobic metabolism in the peripheral tissues.\[^{86}\] However, the brain has very limited capacity for anaerobic metabolism, and it is, therefore, a privileged organ during dehydration.\[^{87}\] Blood flow centralization, neurovascular coupling and cerebral autoregulation maintain adequate blood supply, avoiding and postponing anaerobic metabolism in the brain.\[^{87-89}\] For these reasons, it might seem illogical that amniotes evolved to have sensors for dehydration in such a privileged milieu, where the effects of dehydration are mitigated the most. However, having these sensors adjacent to the neurons involved in the relevant effector homeostatic mechanisms is rather beneficial to the functioning of this network.

Considering that the specialized astrocytes detect dehydration by coupling hypernatremia with intracellular signaling dependent on anaerobic metabolism, the privileged status of the brain during dehydration could hinder their function. We assume that cerebral autoregulation (which modifies vascular resistance and maintains adequate brain tissue perfusion) and neurovascular coupling (which redistributes the blood flow to areas of the brain that are metabolically more active) could delay the response of astrocytes to dehydration by preventing the switch to anaerobic metabolism.\[^{87}\] Therefore, the SFO and the OVLT must have undergone selection for additional traits to bypass this obstacle. We argue that the blood supply to the sensory CVO is less privileged than elsewhere in the brain. Indicative of this is that the components of the blood-brain barrier are crucial for efficient cerebral autoregulation and neurovascular coupling\[^{17,90,91}\] yet the perforating branches of the ACoA lack a blood-brain barrier.\[^{33-35}\] This suggests that the CVO could be less protected from hyoperfusion than the rest of the brain.

Furthermore, negligible blood flow in the ACoA\[^{14,15}\] might indicate less efficient oxygenation of the area supplied by its branches relative to other sites in the brain.\[^{92}\] Considering that intracellular signalization in the OVLT and SFO is based on anaerobic metabolism, we suggest that the less efficient oxygenation might be another adaptation that facilitates faster detection of hypernatremia. While the rest of the brain remains adequately perfused for a longer time compared to the peripheral tissues under dehydration,\[^{18}\] the OVLT and SFO could be special niches in which anaerobic conditions are established far sooner than elsewhere in the brain. Additionally, the turbulent flow in the ACoA, in spite of being discrete,\[^{78}\] could ease diffusion of the blood solvents throughout its branches,\[^{93}\] which would certainly be beneficial to the function of the sensors.

Therefore, we propose that the ACoA might have originally emerged as a simple anatomical variation that eventually became favored over the ACA as a source of blood supply to the OVLT and SFO. We argue that the reasons for this were its hemodynamic properties, which might have been associated with a better sensory function of the OVLT and SFO, and thus, a faster behavioral response to loss of water. An early reaction to imminent dehydration was of vital importance for the stem amniotes, and could have presented a strong enough source of evolutionary pressure to select for and maintain the ACoA in the population. Unlike the RAAS, whose function is to acutely counteract hyoperfusion and to stop further loss of water, forebrain detection and regulation of hydromineral balance primarily activates the neural circuits involved in affection and motivation, that is, water seeking and drinking, ensuring long-term correction of hydromineral disturbances.\[^{34,38,40}\] In light of that, despite being physiologically insignificant in brain vascularization, the ACoA could present an important adaptation to terrestrial life.

Taking into account that several morphologic variations of the ACoA were described in humans,\[^{94}\] and that atherosclerotic stenosis of the ICA can trigger flow increase in the ACoA and possibly precipitate flow-induced vessel remodeling,\[^{28,80,81}\] we suggest that certain anatomical configurations and/or altered hemodynamic conditions of the ACoA could lead to suboptimal functioning of the forebrain sensory CVO.

### ALTERED HEMODYNAMIC CONDITIONS IN ACoA COULD PLAY A ROLE IN HYDROMINERAL DISTURBANCES AND NEUROGENIC HYPERTENSION

Forebrain sensory CVO directly modulate the activity of neural circuits and nuclei involved in hydromineral homeostasis and sympathetic activation,\[^{39,73}\] suggesting that their dysfunction could manifest through disrupted activity of the aforementioned circuitry. Development and rupture of an aneurysm and chronic progressive atherosclerotic stenosis of the ICA would cause changes in the hemodynamic conditions in the ACoA. These conditions are didactic examples of a pathologically increased flow through the ACoA (atherosclerotic stenosis of the ICA) and pathologically decreased flow through the ACoA branches (rupture of an ACoA aneurysm).

Since the branches of the ACoA originate from the superior and posterior arterial surface,\[^{33,64}\] we predict that an aneurism rupture would cause different sensory CVO dysfunctions based on the location of the aneurism, that is, whether the branches were affected or not. In patients with a ruptured aneurism with preserved perforating branches, that is, aneurism of the anterior or inferior arterial wall, an acute transitory decrease in the perfusion of the sensory CVO would occur, resulting in anaerobic metabolism in astrocytes, paraventricular hypothalamus disinhibition with inappropriate ADH secretion, and higher sympathetic activity with consequent hypertension. Inappropriate ADH secretion could be subacutely maintained as long as the sensory CVO are hypoperfused, leading to dilutional hyponatremia. In the long term, this could probably be compensated by the RAAS.

Alternatively, if the perforating branches of the ACoA are damaged during the aneurism rupture, that is, aneurism of the anterior or superior arterial wall, permanent devascularisation and loss of sensors could occur. Acutely, this would manifest as sensor activation due to hypoperfusion and anaerobic metabolism in the astrocytes, but subacutely, due to loss of sensors, basal inhibition of ADH secretion would take over. In such patients, adipsic hypernatremia (excessive blood sodium in the absence of drive to drink) and central diabetes insipidus might develop. Both of these aneurism-rupture outcomes have been
clinically reported\textsuperscript{[95–98]} but it was unclear why some patients developed hyponatremia, while others developed hypernatremia and central diabetes insipidus. As far as we know, the present paper is the first to give a theoretical framework that could explain these paradoxical clinical observations. The importance of these clinical reports is that they directly support the idea that altered hemodynamic conditions in the ACoA result in hydromineral disturbances.

As opposed to an aneurism rupture, unilateral atherosclerotic stenosis of the ICA leads to an increase in blood flow through the ACoA (Figure 5).\textsuperscript{[28]} This increase in blood flow could lead to higher sensory CVO oxygenation.\textsuperscript{[92]} This would imply a higher threshold for detection of hypernatremia due to hindered activation of anaerobic metabolism in the Na\textsubscript{+},K\textsubscript{−}-expressing astrocytes. If the increased blood flow and possible subsequent ACoA remodeling due to atherosclerotic disease leads to impaired forebrain detection and signaling of hypernatremia, we suggest that this would clinically present as higher susceptibility to dehydration, diminished ADH secretion, and higher sympathetic activity due to the stimulatory effects of the hypernatremia on the area postrema.

Atherosclerotic stenosis of the carotid artery is a chronic process that manifests in old age.\textsuperscript{[26,27]} Curiously, older patients have been reported to have a higher susceptibility to dehydration due to insufficient fluid intake and impaired feeling of thirst, which frequently results in electrolyte imbalance.\textsuperscript{[40,99]} Furthermore, an increase in basal sympathetic tone occurs with aging, possibly contributing to essential hypertension.\textsuperscript{[100]} Though in some patients these disorders could be a result of impaired kidney function,\textsuperscript{[99,101]} in others with atherosclerosis they could be caused by sensory CVO dysfunction due to altered hemodynamic conditions in the ACoA.

The hypothesis that an increase in ACoA blood flow could negatively affect the function of the forebrain sensory CVO implies that their dysfunction could lead to or contribute to neurogenic hypertension. Along with atherosclerosis of the ICA, hypertension would additionally damage the vascular endothelium, establishing a vicious cycle.\textsuperscript{[26]}

While aneurysmatic changes and atherosclerosis are mainly associated with old age, younger people with certain anatomical variations of the ACoA could be more prone to SFO and OVLT dysfunction. We suggest that ACoA agenesis would have the greatest impact on the function of the forebrain dehydration sensors. In the absence of the ACoA, the OVLT and SFO are directly vascularized by the ACA.\textsuperscript{[33]} Due to higher blood flow and, thus, better oxygenation capacity of the ACA compared to the ACoA,\textsuperscript{[14]} this anatomical variation could be associated with suboptimal conditions for forebrain detection of dehydration. Individuals who lack the ACoA might be more susceptible to hypernatremia. This would lead to higher basal sympathetic and RAAS activity, which are known components of essential and neurogenic hypertension.\textsuperscript{[101]}

Finally, in vivo experiments with application of intra-arterial filaments or some other means of ICA stenosis/occlusion could be performed to test whether altered hemodynamic conditions in the ACoA could lead to development of hydromineral disturbances and/or neurogenic hypertension. These experiments would, together with evidence summarized in this paper, help to assess the plausibility of our hypothesis and its implications (as summarized in Table 1). A noteworthy limitation is a lack of evidence from molecular and gene expression studies. Genes, proteins and signaling pathways involved in forebrain regulation of hydromineral balance seem to be ancient, and have orthologs among many vertebrate species.\textsuperscript{[38,59,102]}
TABLE 1  Closing summary

| Hypothesis | Natural selection favored the persistence of the ACoA because this artery allowed for more efficient forebrain detection of dehydration |
|------------|----------------------------------------------------------------------------------------------------------------------------------|
| Implications if correct | Hemodynamic properties of the ACoA are selected traits that facilitate OVLT and SFO-mediated dehydration sensing |
| Summary of evidence | Altered hemodynamic conditions in the ACoA are associated with hydromineral disturbances |

Anatomy

- Perforators of the ACoA vascularize the OVLT and SFO\(^{[33–35]}\)
- ACoA does not contribute to brain vascularization under physiologic conditions\(^{[12,13,15,28,29]}\)
- Absence of the ACoA is among the rarest CoW-related findings in human specimens\(^{[30–32]}\)

Embryology

- Phylotypic embryonic stages of the development of the CoW are conserved among vertebrate taxa, and indicate that the ACoA first appeared in primitive amniotes\(^{[4,5]}\)

Molecular biology

- Genes and signaling pathways involved in OVLT and SFO development have their orthologs in many vertebrates\(^{[59]}\)
- Mammalian Na\(_\text{+}\) channel probably originated from a duplicated SCN1A ancestor in tetrapods prior to amniote radiation, and the TRPV1 channel originated in early vertebrates.\(^{[102,103]}\)

Morphological phylogenetics

- ACoA has been documented in amniote species only\(^{[2,5,6]}\)
- Cerebral cortex, a crucial component of forebrain regulation of hydromineral balance, exists only in amniotes\(^{[75,76]}\)

Physiology

- Forebrain regulation of hydromineral balance has only been attested in amniotes\(^{[36,104]}\)
- ACoA branches lack the blood-brain barrier, suggesting less efficient autoregulation and neurovascular coupling, which could facilitate dehydration sensing\(^{[17,33–35,90,91]}\)
- Physiologically insignificant blood flow in the ACoA implies less efficient oxygenation than elsewhere in the brain, which could facilitate dehydration sensing\(^{[14,15,92]}\)

Clinical medicine

- Reports of hydromineral disturbances in patients with ACoA pathologies (hyponatremia, hypernatremia, inappropriate ADH secretion, central diabetes insipidus, hypertension)\(^{[95–98]}\)
- Elderly patients with atherosclerosis are prone to thirst impairment and dehydration\(^{[40,99]}\)

The aim of this article was to propose an answer to why natural selection favored the persistence of a small and hemodynamically insignificant artery such as the ACoA. This table summarizes the proposed hypothesis, its most important implications and evidence presented in this paper. Physiological water loss was a source of evolutionary pressure for traits that allowed for forebrain-mediated responses to dehydration. This was supported by the emergence of a new cerebral artery—the anterior communicating artery, whose special hemodynamic and microvascular features are selected traits that facilitate forebrain dehydration sensing.

**CONCLUSION**

The explanation that the function of the communicating arteries of the CoW is to provide a collateral blood supply in case of arterial stenosis is anthropocentric and incorrect in light of the principles of natural selection. Atherosclerosis, the main cause of ICA stenosis, is typically a disease associated with aging and the human lifestyle, so it cannot explain why the CoW formed more than 300 mya in early amniotes, and persisted among living reptiles, birds and mammals.

The PCoAs are remnants of primitive proximal segments of caudal cerebral arteries, hypoplastically remodeled due to the redirection of the blood supply from the carotid to the vertebro-basilar arterial system. The circumstances that lead to the emergence of the ACoA, however, are not well known. The ACoA neither affects the hemodynamics of the CoW nor does it present a functional anastomosis due to a lack of flow, making it unclear why such a blood vessel would be evolutionarily favored.

We have presented an exhaustive review of the evolutionary history of the ACoA and its tight connection with the development of forebrain regulation of hydromineral homeostasis. We argue that the peculiar hemodynamic properties of the ACoA could be selected traits that allowed for a more efficient and timely response to water loss. Considering that dehydration was a major threat to early amniotes, it could have created strong enough selection pressure for the emergence and persistence of this artery. Because the ACoA is susceptible to remodeling during the course of aging-related diseases, we proposed that altered hemodynamic conditions in the ACoA may cause impairment in the forebrain detection of dehydration (and hence a decline in voluntary water intake), making an individual more prone to hypernatremia and neurogenic hypertension.
This paper provides the first explanation for the emergence and physiological function of the ACoA that is in accordance with the principles of natural selection.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a conflict of interest.

AUTHOR CONTRIBUTIONS

Matija Fenrich devised the conceptual ideas. Matija Fenrich, Karlo Habjanovic, Josip Kajan and Marija Heffer reviewed the literature, and Matija Fenrich drafted the initial manuscript. Matija Fenrich, Karlo Habjanovic, Josip Kajan and Marija Heffer devised the conceptual ideas. Matija Fenrich, Karlo Habjanovic, Josip Kajan and Marija Heffer reviewed the literature, and Matija Fenrich drafted the initial manuscript. Matija Fenrich, Karlo Habjanovic, Josip Kajan and Marija Heffer revised and expanded the manuscript. Matija Fenrich made the figures. All authors approved the final version as submitted.

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