doi:10.1093/brain/awaa169 BRAIN 2020: 143; 1–3 | e58

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Heterogeneity of the circle of Willis and its implication in hippocampal perfusion

Jose Gutierrez

Department of Neurology, Columbia University, New York, NY, USA

Correspondence to: Jose Gutierrez
710 W 168th St, 6th fl, Suite 639, New York, NY, 10032, USA
E-mail: jg3233@cumc.columbia.edu

We read with interest the paper by Perosa *et al.* (2020) entitled 'Hippocampal vascular reserve associated with cognitive performance and hippocampal volume'. The author reported that a mixed blood supply of the hippocampus by the posterior cerebral artery (PCA) and anterior choroidal artery (AChA) may provide vascular reserve and protect against cognitive impairment. The work is novel and critically important, given the relevance of hippocampal injury in Alzheimer's dementia and other cognitive disorders. It is unclear, however, how the authors accounted for the heterogeneous configuration of the circle of Willis in their methods. There is no mention of the role that another anterior circulation artery, the posterior communicating artery (Pcomm), may play in hippocampal injury in certain circumstances.

Animal models exist that support a role of the Pcomm in causing hippocampal injury. The arterial supply of the hippocampus has general similarities across different species of large mammals, especially as it refers to the PCA and AChA supply. Interestingly, the PCA in cats and sheep is mostly supplied by the carotid arteries with various degrees of basilar artery-derived flow contributions (Goetzen and Sztamska, 1992). In mice, there is an even greater proportion of hippocampal flow derived from the anterior circulation (Özdemir *et al.*, 1999). This predominant anterior circulation blood supply of the hippocampus in smaller mammals is likely the result of smaller frontal lobes compared to humans. The large volume of the human frontal lobes increases the flow demand via the carotids. The progressive shift of the source of PCA supply towards the vertebrobasilar system in humans represents an adaptive hydrodynamic solution to the competing flow demands (Menshawi *et al.*, 2015). Because of the dominant anterior circulation blood supply to the hippocampus in smaller mammals, occlusion of the middle cerebral artery (MCA) causes hippocampal ischaemia in mice with a hypoplastic Pcomm or an incomplete circle of Willis (Kitagawa *et al.*, 1998; Özdemir *et al.*, 1999). Mongolian gerbils are often used to study ischaemic injury to the forebrain and hippocampus because they have a rudimentary basilar-Pcomm connection and often lack anteroposterior anastomoses (Yoshimine and Yanagihara, 1983; Laidley *et al.*, 2005). Consequently, in Mongolian gerbils, occlusion of the Pcomm or bilateral internal carotid arteries (ICAs) causes hippocampal ischaemia (Yoshimine and Yanagihara, 1983), especially in gerbils with an absent or hypoplastic Pcomm (Laidley *et al.*, 2005; Seal *et al.*, 2006; Ahn *et al.*, 2019).

The shift towards a dominant basilar artery supply of the hippocampus via PCA in humans is not universal. In fact, ~20% of the population lacks one or both PCA P1 segment (i.e. a foetal PCA, branch of the ICA) (Van Overbeeke *et al.*, 1991; Gutierrez *et al.*, 2013) and 10% have at least one hypoplastic P1 segment (Gutierrez *et al.*, 2013; Vrselja *et al.*, 2014). In other words, a third of the population has an anterior circulation dominant blood supply to the distal PCA.

A more detailed description of the blood supply to the hippocampus and medial temporal lobe regions reveals a complexity not easily captured by the PCA or the AChA. In humans, the ambien gyrus is supplied by the anterosuperior parahippocampal arteries (also known as uncal arteries), which are branches of the MCA in the anterior aspect, and branches of the ICA, AChA, and PCA in the posterior aspect. The ventrolateral region of the entorhinal cortex (anterior parahippocampal gyrus) is supplied by the anteroinferior parahippocampal arteries, which may originate in either the MCA (specifically as branches from the MCA anterior temporal artery) or the PCA, and less often from the AChA (Huther *et al.*, 1998). The anterior hippocampal formation is supplied by the medial uncal arteries, branches most often of the AChA and less often of the PCA. Occasionally, medial

Advance access publication June 28, 2020

uncal arteries may arise from anastomoses of the anterosuperior parahippocampal arteries. The lateral aspect of the hippocampus and its digitations are supplied by the lateral uncal arteries, branches of the AChA or the PCA, less often as branches of the PCA-derived anterior temporal artery or segmental branches of medial uncal arteries (Huther *et al.*, 1998). The lateral and medial uncal arteries together supply the anterior and medial hippocampus and therefore are also known as anterior and medial hippocampal arteries typically described as branches of the PCA and less commonly of the AChA (Marinković *et al.*, 1992). The areas TF/TH and the caudal part of the parahippocampal gyrus are supplied by the posterior parahippocampal arteries, branches of the PCA (most commonly) or the AChA. The posterior hippocampal arteries supply the posterior aspects of the hippocampus and are derived from the PCA in all cases (Huther *et al.*, 1998). The terminal arterial branches to the hippocampus are also known as straight or fork arteries (branches of the medial or posterior temporal arteries). These arteries penetrate the dentate gyrus, the subiculum and the body and fimbria of the hippocampus (Marinković *et al.*, 1992). The intraparenchymal course of the internal hippocampal arteries is divided in two; the dorsal arteries and their respective subregional branches (CA1, CA2, etc.) that pierce the surface of the dentate gyrus and the sector arteries that run within the medullary septum (Marinković *et al.*, 1992; Huang and Okudera, 1997). More often than not there exist anastomoses between intrahippocampal, parahippocampal, subicular and uncal arteries (Marinković *et al.*, 1992; Huang and Okudera, 1997) effectively communicating the ICA and MCA indirectly to the hippocampal arteries and creating a strong network favouring collateral flow (Goetzen and Sztamska, 1992). The internal hippocampal arteries do not from anastomoses, however, and therefore are terminal arteries (Goetzen and Sztamska, 1992). The average luminal diameter of arteries supplying the medial temporal lobe including the hippocampus ranges from 215–335 μm with up to 800 μm described in some cases (Marinković *et al.*, 1992; Huther *et al.*, 1998). These small arteries are susceptible to siphon-like geometric deformation in the form of knot-loops and vascular glomeruli in the setting of ageing or brain large artery disease (Goetzen and Sztamska, 1992).

The relative neglect of the circle of Willis configuration and the Pcomm is a problem with most of the data discussed in the previous paragraph. Often, the Pcomm is rarely mentioned other than as an anatomical referent. Some authors imply that the PCA (foetal or not) supplies the hippocampus regardless of whether it originates as a branch of the basilar artery or of the carotid artery (Goetzen and Sztamska, 1992; Erdem *et al.*, 1993). We believe that this proposal may be reasonable. For example, presurgical epileptic patients who receive an ICA injection (distal to the origin of the AChA) of amobarbital show amobarbital distribution in the entire hippocampus if they have a foetal PCA (Urbach *et al.*, 1999). Unfortunately, this study did not investigate the degree of amobarbital distribution as a function of inverse reciprocal relationship noted by us between the calibre of the PCA and the Pcomm (Gutierrez *et al.*, 2013). Other data suggest that patients with strokes due to a carotid dissection, who have an ipsilateral foetal PCA, present with medial hippocampal ischaemia (Walha *et al.*, 2013). In a large population-based study, we found that a larger left Pcomm/PCA average luminal diameter related to episodic memory and predicted greater cognitive decline (Gutierrez *et al.*, 2018). In this context, it would stand to reason to hypothesize that in individuals with a foetal PCA or a hypoplastic PCA P1 segment, the ICA provides most of the flow to the P2 and P3 segments of the PCA, from which the hippocampal arteries originate (Erdem *et al.*, 1993). We surmise then that the anatomical, functional, epidemiological and clinical data presented above reveal the need to integrate the anatomy of the circle of Willis in the study of hippocampal blood supply and the proposed model of hippocampal vascular reserve.

With this in mind, it would prudent for Perosa *et al.* (2020) to disclose further details regarding how they integrated the above-described heterogeneity of the circle Willis in their results, and whether their results would remain the same by incorporating the contribution of the ipsilateral Pcomm and/or foetal PCA to the hippocampus blood supply.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Funding

Supported by National Institute on Aging (1R01AG057709 and 1R01AG066162).

Competing interests

The author reports no competing interests.

References

Ahn JH, Song M, Kim H, Lee TK, Park CW, Park YE, et al. Differential regional infarction, neuronal loss and gliosis in the gerbil cerebral hemisphere following 30 min of unilateral common carotid artery occlusion. Metab Brain Dis 2019; 34: 223–33.

Erdem A, Yasargil G, Roth P. Microsurgical anatomy of the hippocampal arteries. J Neurosurg 1993; 79: 256–65.

Goetzen B, Sztamska E. Comparative anatomy of the arterial vascularization of the hippocampus in man and in experimental animals (cat, rabbit and sheep). Neuropatol Pol 1992; 30: 173–84.

Gutierrez J, Kulick E, Park Moon Y, Dong C, Cheung K, Ahmet B, et al. Brain arterial diameters and cognitive performance: Northern Manhattan study. J Int Neuropsychol Soc 2018; 24: 335–46.

Gutierrez J, Sultan S, Bagci A, Rundek T, Alperin N, Elkind MS, et al. Circle of Willis configuration as a determinant of intracranial dolichoectasia. Cerebrovasc Dis 2013; 36: 446–53.

Huang YP, Okudera T. Arterial supply to the hippocampal formation. Neuroimaging Clin N Am 1997; 7: 31–50.

Huther G, Dorfl J, Van der Loos H, Jeanmonod D. Microanatomic and vascular aspects of the temporomesial region. Neurosurgery 1998; 43: 1118–36.

Kitagawa K, Matsumoto M, Yang G, Mabuchi T, Yagita Y, Hori M, et al. Cerebral ischemia after bilateral carotid artery occlusion and intraluminal suture occlusion in mice: evaluation of the patency of the posterior communicating artery. J Cereb Blood Flow Metab 1998; 18: 570–9.

Laidley DT, Colbourne F, Corbett D. Increased behavioral and histological variability arising from changes in cerebrovascular anatomy of the Mongolian gerbil. Curr Neurovasc Res 2005; 2: 401–7.

Marinković S, Milisavljević M, Puškaš L. Microvascular anatomy of the hippocampal formation. Surg Neurol 1992; 37: 339–49.

Menshawi K, Mohr JP, Gutierrez J. A functional perspective on the embryology and anatomy of the cerebral blood supply. J Stroke 2015; 17: 144–58.

Özdemir YG, Bolay H, Erdem E, Dalkara T. Occlusion of the MCA by an intraluminal filament may cause disturbances in the hippocampal blood flow due to anomalies of circle of Willis and filament thickness. Brain Res 1999; 822: 260–4.

Perosa V, Priester A, Ziegler G, Cardenas-Blanco A, Dobisch L, Spallazzi M, et al. Hippocampal vascular reserve associated with cognitive performance and hippocampal volume. Brain 2020; 143: 622–34.

Seal JB, Buchh BN, Marks JD. New variability in cerebrovascular anatomy determines severity of hippocampal injury following forebrain ischemia in the Mongolian gerbil. Brain Res 2006; 1073-1074: 451–9.

Urbach H, Kurthen M, Klemm E, Grunwald T, Van Roost D, Linke DB, et al. Amobarbital effects on the posterior hippocampus during the intracarotid amobarbital test. Neurology 1999; 52: 1596–602.

Van Overbeeke JJ, Hillen B, Tulleken CA. A comparative study of the circle of Willis in fetal and adult life. The configuration of the posterior bifurcation of the posterior communicating artery. J Anat 1991; 176: 45–54.

Vrselja Z, Brkic H, Mrdenovic S, Radic R, Curic G. Function of circle of Willis. J Cereb Blood Flow Metab 2014; 34: 578–84.

Walha K, Ricolfi F, Bejot Y, Nonent M, Ben Salem D. Hippocampus: a "forgotten" border zone of brain ischemia. J Neuroimaging 2013; 23: 98–101.

Yoshimine T, Yanagihara T. Regional cerebral ischemia by occlusion of the posterior communicating artery and the middle cerebral artery in gerbils. J Neurosurg 1983; 58: 362–7.