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Review

The benefits of magnetic resonance imaging methods to extend the knowledge of the anatomical organisation of the periaqueductal gray in mammals

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ABSTRACT

The periaqueductal gray (PAG) is a mesencephalic brain structure involved in the expression of numerous behaviours such as maternal, sexual and emotional. Histological approaches showed the PAG is composed by subdivisions with specific cell organisation, neurochemical composition and connections with the rest of the brain. The comparison of studies performed in rodents and cats as the most often examined species, suggests that PAG organisation differs between mammals. However, we should also consider the plurality of the methods used in these studies that makes difficult the comparison of the PAG organisation between species. Therefore, to study the PAG in all mammals including human, the most relevant *in vivo* imaging method seems to be the magnetic resonance imaging (MRI). The purpose of this review was to summarize the knowledge of the anatomical organisation of the PAG in mammals and highlights the benefits of MRI methods to extend this knowledge. Results obtained by MRI so far support the conclusions of *ex vivo* studies, especially to describe the subdivisions and the connections of the PAG. In these latter, diffusion-weighted MRI and functional connectivity seem the most appropriate methods. In conclusion firstly, the MRI seems to be the best judicious method to compare species and improve the comprehension of the role of the PAG. Secondly, MRI is an *in vivo* method aimed to manage repeated measures in the same cohort of subjects allowing to study the impact of aging and the development on the anatomical organisation of the PAG.

Abbreviations: ACC, anterior cingulate cortex; AChE, acetylcholine esterase; Amb, ambiguous nucleus; Aq, aqueduct of Sylvius; BLA, basolateral nucleus of the amygdala; CCK, cholecystokinin; CeA, central nucleus of the amygdala; CL, central lateral nucleus of the thalamus; CM, central medial nucleus of the thalamus; CT, computer tomography; Cu, cuneiform nucleus; d, dorsal PAG; dl, dorsolateral PAG; DMN, dorsomedial nucleus of hypothalamus; DMX, dorsal motor nucleus of the vagus nerve; DREADD, designer receptors exclusively activated by designer drugs; DRN, dorsal raphe nucleus; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EW, Edinger-Westphal nucleus; FC, frontal cortex; fMRI, functional magnetic resonance imaging; Hb, habenula; IC, inferior colliculi; id, inner dorsal PAG; IMD, intermediodorsal nucleus of the thalamus; -ir, immunoreactive; ivl, inner ventrolateral PAG; l, lateral PAG; lHb, lateral habenula; LV, lateral ventricle; m, medial PAG; MD, mediodorsal nucleus of the thalamus; Met-ENK, Met-enkephalin; mHA, medial hypothalamic area; MLF, medial longitudinal fasciculus; mPOA, medial preoptic area; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NADPHd, nicotinamide adenine dinucleotide phosphate-diaphorase; NST, nucleus of the solitary tract; OB, olfactory bulb; OC, occipital cortex; OcmA, oculomotor area; od, outer dorsal PAG; ovl, outer ventrolateral PAG; PAG, periaqueductal gray; PC, parietal cortex; PCR, polymerase chain reaction; PET, positron emission tomography; PeV, periventricular nucleus of the hypothalamus; Pf, parafascicular nucleus of the thalamus; PFC, prefrontal cortex; PT, pretectum; PVN, paraventricular nucleus of the hypothalamus; PVT, paraventricular nucleus of the thalamus; Re, reunien nucleus of the thalamus; RT, reticular nucleus of the thalamus; SC, superior colliculi; SN, substancia nigra; TgA, tegmental area; TgN, tegmental nucleus; TH, tyrosine hydroxylase; VB, ventrobasal complex nucleus of the hypothalamus; vl, ventrolateral PAG; VMN, ventromedian nucleus of hypothalamus; VTA, ventral tegmental area; ZI, zona incerta; 5-HT, serotonin; III, third ventricle; IV, fourth ventricle.

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Contents

1. Introduction

To demonstrate the involvement of brain structures in a specific functional or behavioural role, neurobiological methods could be organized according to three concepts: neural marker, sufficient cause and necessary cause, as proposed by Berridge to describe the neurobiology of pleasure (Berridge, 2003). Among these concepts, a large variety of methods is used as functional neuroanatomy, pharmacology, and modified genetic or injured brain models, these approaches being combined in most studies (Table 1). However, the description and comprehension of a specific function of a specific brain structure require the knowledge of the anatomical organisation of this structure. To this aim, immunohistochemistry or *in situ* hybridisation are commonly used to characterise neurochemical composition of brain structures, while neural tracer methods are used to describe their neural connections. Moreover, the development of *in vivo* imaging approaches enables new experimental strategies to study the anatomy of the brain structure of interest. Among the *in vivo* imaging methods, the most relevant is the magnetic resonance imaging (MRI) since this method could be used to describe brain anatomy (T1 weighted MRI), maturation (T2 weighted MRI, diffusion weighted imaging, DWI) and connections (diffusion tensor imaging, DTI) (Chaillou et al., 2012). From this, MRI appears to be a very complete and efficient method to study the organisation of the whole brain and its changes during lifetime.

The periaqueductal gray (PAG) is a mesencephalic structure localized between the third and fourth ventricles, ventrally borded by the Edinger-Westphal nucleus, the oculomotor area and the dorsal raphe and tegmental nuclei respectively to the rostrocaudal axis, which surrounds the aqueduct of Sylvius (Figs. 1, 2). The PAG is involved in the expression of different behaviours such as social (O'Connell and Hofmann, 2011), maternal (Noriuchi et al., 2008), aggressive (Gregg and Seigel, 2001), sexual (Holstege and Huynh, 2011), and emotional (Bandler and Shipley, 1994). Moreover, the PAG is described as a complex and non-uniform structure composed by different subdivisions in the dorsoventral axis, which are organised in columns along the rostrocaudal axis (Bandler et al., 2000; Bandler and Shipley, 1994) (Figs. 1, 2). Independently of the axis, the subdivisions of the PAG were identified by invasive functional studies (Coutinho et al., 2008; Morgan et al., 1998; Subramanian et al., 2008) and distinctly described by their cytoarchitecture, neurochemistry and anatomical connections with the rest of the brain. Despite the frequent use of MRI in neuroscience, few reported data have been concerned the PAG, the most focusing on the cortices (prefrontal cortex, PFC) or the limbic system (amygdala, hypothalamus) (Table 2). We guess that the localisation and the size of the PAG could explain that MRI reported data are rare. Indeed, the PAG is a small brain structure of grey matter surrounded by other grey matter structures that make its delineation and identification difficult because of low spatial resolution of MRI (Linnman et al., 2012). However, the development of a high-field scanner, multi-channel coil, algorithms and experimental paradigms provide a promising way to further improve our knowledge of the anatomy of the PAG.

The aim of this review is to present the state of art of the organisation of the PAG, through its cytoarchitecture, neurochemistry and anatomical connections with the rest of the brain, according to the benefits of the MRI methods to further enhance our knowledge of the anatomical organisation of the PAG in different mammalian species.

2. Cytoarchitecture of the PAG

Studies of the cytoarchitecture allow to delineate subdivisions based on the size, shape and density of the cells observed on Nissl

Table 1
Estimated prevalence of neurobiological methods upon the number of publications (PubMed, 2016.06.).

"Method"	Approximate number of publication	Number of publications in 2015	Year of first publication
Pharmacology	657 950	21 995	1910
MRI	194 035	13 915	1980
Immunochemistry	78 740	1 480	1964
Lesion	68 860	3 370	1845
Electrophysiology	45730	1025	1946
PCR	44 010	1 870	1988
Western blot	41915	2 846	1983
CT	40 810	2 435	1970
PET	22 460	1 543	1969
Northern blot	11 560	17	1982
Tracer	11 550	415	1949
In situ hybridisation	5 630	120	1973
Southern blot	3 265	52	1980
Optogenetic	2 015	600	2006
DREADD	91	32	2011

Keywords: ("Method") AND (brain OR spinal OR neuron OR glia OR pituitary) Abbreviations: CT: computer tomography, DREADD: designer receptors exclusively activated by designer drugs, MRI: magnetic resonance tomography, PCR: polymerase chain reaction, PET: positron emission tomography.