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The MCH neuron population as a model for the development and evolution of the lateral and dorsal hypothalamus

Sandrine Chometton [a], Sophie Croizier [b], Dominique Fellmann [a], Pierre-Yves Risold [a,*]

[a] EA 3922, SFR FED 4234, UFR Sciences Médicales et Pharmaceutiques, Université de Franche-Comté, 19 rue Ambroise Paré, 25000 Besançon, France
[b] The Saban Research Institute, Neuroscience Program, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA 90027, USA

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ABSTRACT

The LHA contains neurons producing melanin-concentrating hormone (MCH) or hypocretin (Hcrt) that have emerged as being more conspicuous and representative of the posterior LHA. In this review, we focus on MCH neurons and show that they have unique qualities. Their distribution is conserved in the posterior hypothalamus of all vertebrates and their ontogenetic differentiation is very precocious in the rodent embryo. In mammals, interspecific differences in their medio-lateral distribution suggest that the LHA differentiation may follow species specific strategies. These characteristics make a very valuable tool of MCH neurons to study the development as well as the phylogenetical origin and differentiation of the LHA.

1. Introduction

The lateral hypothalamic area (LHA) is a poorly understood brain structure. The medial forebrain bundle (mfb) is one of its major components (Nieuwenhuys et al., 1982), prompting the sentiment of an apparent homogeneity within the lateral hypothalamic zone (i.e. lateral preoptic + lateral hypothalamic areas, Swanson, 2004). But the LHA is heterogeneous. It contains collections of cells that are diffusely distributed among the fascicles of the mfb, with dendrites often organized perpendicular to this tract (Millhouse, 1979). The chemical phenotype of these cells varies along the axis provided by the mfb. Among those cells, neurons producing melanin-concentrating hormone (MCH) or hypocretin (Hcrt) emerged as being more conspicuous and representative of the posterior LHA (Bittencourt et al., 1992; Nambu et al., 1999). MCH neurons have two unique qualities which were utmost to produce a strong corpus of data showing that these neurons may constitute a noteworthy model to study the phylogenetical differentiation of the LHA and its development in mammals:

- These neurons have a conserved distribution in the posterior hypothalamus of all vertebrates (Croizier et al., 2013),
- They have a very precocious phenotypical differentiation in the rodent embryo (Croizier et al., 2011).

In the present work, we will show in what these qualities are essential to understand the phylogenetical and developmental origins of the LHA, with a preponderance on the developmental aspect.

2. Conserved distribution of MCH neurons in the posterior hypothalamus

A thorough review of the comparative distribution of MCH neurons was provided in a former paper (Croizier et al., 2013) and we shall only briefly evoke this aspect in the present work. The main features resorting from this previous study was that MCH neurons are present in the posterior and dorsal periventricular hypothalamus in all vertebrate classes, from cyclostomes to mammals. Furthermore, in all species they send abundant ascending and descending projections that initially course through the mfb. However, aside this dorsal periventricular location, more lateral cell groups differentiate in some species. An abundant neuroendocrine group of cells is found in a lateral and ventral nucleus (the ventral tuberal nucleus) of the teleostean and holostean lateral hypothalamus (Baker and Bird, 2002). In amniotes, cells are also observed in a lateral position (Cardot et al., 1994, 1999). These cells are far more abundant in mammals than in reptiles and birds, but in all they project in a more or less

* Corresponding author. Tel.: +33 363 082 223; fax: +33 363 082280.
E-mail address: pierre-yves.risold@univ-fcomte.fr (P.-Y. Risold).

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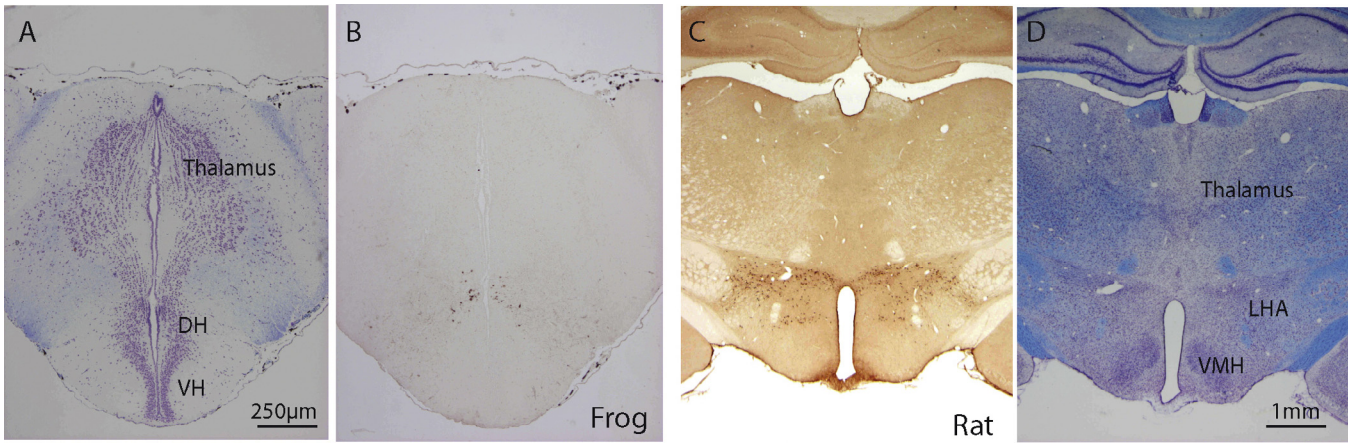

Fig. 1. *MCH distribution in the dorsal hypothalamus.* (A and B) Distribution of MCH cell bodies in the dorsal hypothalamus of a frog (B). The adjacent section (A) is stained by the Kluver–Barrera method for cytoarchitectonic purpose. Note that MCH cells are observed in a periventricular position. (C and D) Distribution of MCH cell bodies in the rat dorsal hypothalamus (C). The adjacent section (D) is stained by the Kluver–Barrera method for cytoarchitectonic purpose. MCH perikarya distribute from the dorsal periventricular to lateral hypothalamic area. Abb: DH: dorsal hypothalamus, LHA: lateral hypothalamic area, VH: ventral hypothalamus, VMH: ventromedial hypothalamic nucleus.

diffuse pattern throughout the telencephalon and reticular core. We hypothesized in Croizier et al. (2013) that lateral differentiation in bony fishes and amniotes could be the results of convergent evolutionary processes, despite their very different projection patterns. Still, comparative data in tetrapodes suggest that lateral hypothalamic MCH neurons derivate from the dorsal hypothalamus, corroborating the idea that most of the LHA has a dorsal hypothalamic origin (Croizier et al., 2013) (Fig. 1).

Within the mammalian class, the organization of the MCH neuron population also differs depending of species. The dorsal lateral distribution of cell bodies is not total in most species: they are dorsolateral in rodents (Swanson et al., 2005; Croizier et al., 2010), while they occupy a medial area between fornix and third ventricular surface in human (Bresson et al., 1989) and they are lateral and ventral to the fornix, closer to the pial surface, in the sheep or pig (Tillet et al., 1996; Chometton et al., 2014) (Fig. 2). Unfortunately, the distribution of projections is not detailed in all these species, but data in rodent and pig suggest that different patterns of projections accompany the different patterns of perikarya distribution (Croizier et al., 2010; Chometton et al., 2014). The functional significance of the divergences in the anatomy of the MCH neuron population among mammals has not yet been investigated, but distinct projection patterns indicate that MCH roles might be dissimilar in different mammalian orders. It is worth to signal here that to date, Hcrt neurons seem to show less interspecific differences in their distribution (Croizier et al., 2013).

To conclude, we observed that MCH neurons are a specific maker of a caudal and dorsal hypothalamic region. However, these neurons show very different lateral or medial patterns of distribution within this hypothalamic sector, depending class and orders in mammals.

3. MCH neuron development in the rodent brain

Conserved location in the posterior hypothalamus of vertebrates suggests that developmental mechanisms involved in the production and differentiation of MCH expressing cells are also somewhat conserved. Most data on this subject are from rat and mouse models (Brischoux et al., 2001; Shimogori et al., 2010; Croizier et al., 2011). In both species, these neurons differentiate in a specific region of the hypothalamic anlage, characterized by the co-expression of transcription factors, including Nkx2.1, Nkx2.2, Dlx1.2, and under the control of the morphogen protein Sonic Hedgehog (Croizier et al., 2011; Alvarez-Bolado et al., 2012). Most of these results were obtained because MCH expression is precocious and therefore it was quite easy to compare the distribution pattern of the first MCH expressing cells with that of transcription factors. Ontogenesis and birth dating with BrdU showed that the first MCH neurons are generated very early, but the production of these cells persist over several days in the rat and mouse embryos, with a peak of neuronal birth at E12-13 in the rat and E11 in mice (Brischoux et al., 2001; Croizier et al., 2010). Correspondingly, Nkx2.1 and Nkx2.2 co-expression domain, which is very narrow at early stages, enlarges as more MCH neurons differentiate, so that distribution patterns of these transcription factors and MCH are coincident during the whole period (Croizier et al., 2011). This observation might be important as it suggests

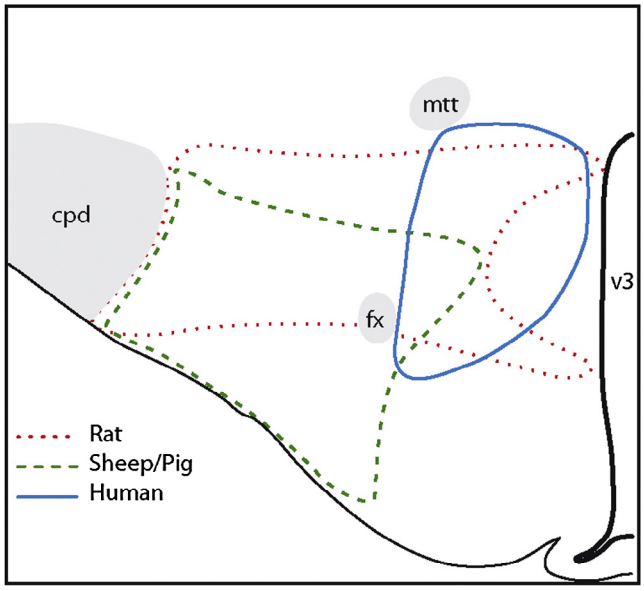

Fig. 2. *Mediolateral MCH distribution in the mammalian hypothalamus.* Line drawing of a typical mammalian coronal section through the posterior hypothalamus to illustrate the distribution of MCH neurons relative to the ventricular or pial surfaces. In the human hypothalamus, MCH cell bodies are in the dorsal hypothalamus mostly between fornix and the ependyme of the third ventricle. By contrast in the sheep or pig, MCH cell bodies are massively in the far lateral and ventral LHA. In rodents and especially rats, these neurons extend mostly dorsal to the fornix from the cerebral peduncle to the ventricular surface. Abb: cpd: cerebral peduncle, fx: fornix, mtt: mammillothalamic tract, v3: third ventricle.