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REVIEW

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Neural origins of basal diencephalon in teleost fishes: Radial versus tangential migration

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Abstract

Teleost fish possess large lateral diencephalic regions such as the torus lateralis, the preglomerular area, and the diffuse nucleus of the hypothalamic inferior lobe. While their developmental origins traditionally were suggested to lie in diencephalic midline ventricular proliferative zones, more remote midbrain origins were reported recently. This review focuses on the preglomerular region and summarizes the data supporting three existing hypotheses on its developmental origins. The conclusion is that lateral torus, diffuse nucleus of hypothalamic inferior lobe, and preglomerular region are part of the diencephalon, but have a multiregional origin provided by both radially and tangentially migrating cells forming these regions in question.

KEYWORDS

her5, mesodiencephalic dopamine cells, neuromeric model, posterior tuberculum, preglomerular complex, prosomeric model, radial glia, shh, sonic hedgehog

1 | THE POSTERIOR TUBERCULUM AND PREGLOMERULAR COMPLEX: AN ENLARGED PART OF BASAL DIENCEPHALON IN TELEOSTS OR NOT?

In this review, the embryonic origins of the posterior tubercle and preglomerular complex are discussed in the context of likely multiple origins of cells in this region due to combined radial and tangential migration of precursor cells.

The preglomerular complex of teleost fishes is a large assemblage of nuclei in the basal diencephalon. It receives ascending inputs from diverse sensory systems and relays this information to the pallial telencephalon (see below for citations). Such connectivity appears similar to that of the sensory dorsal thalamus of amniotic vertebrates, yet, both adult location and suspected embryological origins of the preglomerular complex do not correspond easily to that of the dorsal thalamus, and homology between these two areas is therefore questionable (reviewed by Mueller, 2012). In amniotes, the dorsal thalamus largely arises from the alar region of the diencephalon (see chain lines in Figure 1 for alar-basal plate boundary in various embryonic vertebrates). The embryological origins of the preglomerular complex are less clear. A sizable periventricular area called the posterior tubercle (e.g., TPp, see Figures 2 and 3a) lies between the teleostean dorsal thalamus and the hypothalamic formation, and the preglomerular nuclear complex lies ventrolaterally to TPp (see Figure 2 for three examples of high variability of this area). The teleostean posterior tubercle has remained enigmatic historically because of its relatively small amniote counterpart. However, recent basic Helix–Loop–Helix (bHLH) gene expression studies in amniotes (Osório, Mueller, Rétaux, Vernier, & Wullimann, 2010) and zebrafish (Mueller & Wullimann, 2016), as well as comparative developmental studies on dopamine cells in the basal midbrain (where dopamine cells are absent in teleosts; Meek, 1994) and diencephalon (where dopamine cells are present in all vertebrates; see Vernier & Wullimann, 2009 and Wullimann & Umeasalugo, 2019, for reviews) identified these basal diencephalic regions in all vertebrates (generally called bP1 through bP3 as shown for amniotes in Figure 1a, or N, PTd, and PTv in anamniotes; see below for more details).

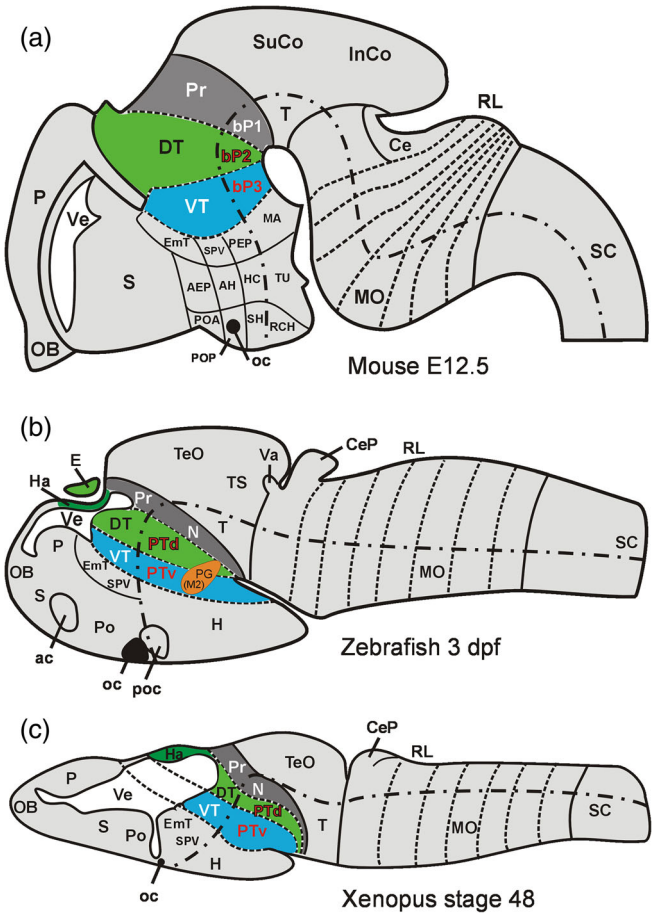

FIGURE 1 Brain schematics in lateral view for amniotes (a), teleosts (b) and amphibians (c) pointing out neuromeric divisions. Pretectal/P1 prosomere: dark gray, (dorsal) thalamic/P2 prosomere: green, ventral thalamic/prethalamic/P3: blue. Prosomeric (and rhombomeric) boundaries are indicated by dashed lines, and alar plate (dorsal) and basal plate (ventral) are separated by a chain line along the anteroposterior axes. Abbreviations: ac, anterior commissure; AEP, anterior entopeduncular area; AH, anterior hypothalamus; **bP1-3, basal parts of prosomeres 1–3**; Ce, cerebellum; CeP, cerebellar plate; **DT, dorsal thalamus**; E, epiphysis; EmT, eminentia thalami; **H, hypothalamus**; Ha, habenula; HC, hypothalamic cell cord; InCo, inferior colliculus; MA, mammillary hypothalamus; MO, medulla oblongata; N, area of the nucleus of the medial longitudinal fascicle; OB, olfactory bulb; oc, optic chiasm; P, pallium; poc, postoptic commissure; PEP, posterior entopeduncular area; **PG (=M2), preglomerular complex**; POA, anterior preoptic area; poc, postoptic commissure; **Pr, pretectum**; PTd, dorsal posterior tuberculum; PTv, ventral posterior tuberculum; Po, preoptic area; POA, anterior preoptic area; poc, postoptic commissure; POP, posterior preoptic area; Pr, pretectum; RCH, retrochiasmatic hypothalamus; RL, rhombic lip; S, subpallium; SC, spinal cord; SH, suprachiasmatic area; SPV, supraopto-paraventricular area; SuCo, superior colliculus; T, tegmentum mesencephali; TeO, tectum opticum; TS, torus semicircularis; TU, tuberal hypothalamus; Va, valvula cerebelli; Ve, brain ventricle; **VT, ventral thalamus (prethalamus)**

As outlined above, the use of the neuromeric (prosomeric) model (Puelles & Rubenstein, 1993) was highly advantageous for topological analysis of the posterior tuberculum. This model integrates the interdigitating topology of classical longitudinal domains (such as the floor, alar, basal, and floor plates) with transverse elements (segments) along the neural tube axis. These transverse elements are present in the hindbrain (rhombomeres) and forebrain (prosomeres) and are based both on developmental gene expression boundaries as well as on transitory clonal cell restriction (reviewed in Wullimann, 2017). The initial prosomeric or neuromeric model established for amniotes had been strongly based on early developmental gene expression patterns (Puelles & Rubenstein, 1993) and included six forebrain prosomeres. A three-prosomere model (Figure 1) was first suggested for the zebrafish brain based on early proliferation patterns (Wullimann & Puelles, 1999). The initial three most anterior prosomeres were newly considered to represent a large and complex so-called secondary prosencephalon with many subdivisions that are not obviously prosomeric in nature. The three-prosomere model has subsequently been strongly supported by various zebrafish brain developmental gene expression patterns (Lauter, Söll, & Hautpmann, 2013) and also has been adopted for the 2003 amniote model of Puelles and Rubenstein (2003). These three remaining prosomeres in question form the posterior forebrain, including P1 (pretectum), P2 (dorsal thalamus), and P3 (prethalamus, formerly ventral thalamus) from caudal to rostral. Equally important for the model is that the posterior forebrain has alar and basal plate components (as does the anteriorly lying hypothalamus/telencephalon or secondary prosencephalon).

Neurobiologists are generally well aware of diencephalic alar components, and, thus, prosomeres accordingly derive their names after the well-studied (alar) pretectal, thalamic, and ventral (pre-) thalamic nuclei. However, these three prosomeres also have basal plate divisions (indicated as bP1, bP2 and bP3 in the embryonic amniote model in Figure 1a) which is a general requirement following the prosomeric model (reviewed in Vernier & Wullimann, 2009). The nucleus of the medial longitudinal fascicle of anamiotes (corresponds to the interstitial nucleus of Cajal of amniotes) is considered to lie in the bP1 (reviewed in Wullimann, 2017).

Here, I will focus on the bP2 and bP3 divisions that have traditionally been called posterior tuberculum (PTd and PTv in Figure 1b,c) in anamniotes (Vernier & Wullimann, 2009). All basal divisions of midbrain (T, midbrain tegmentum, Figure 1), as well as of diencephalic bP1 through bP3, show different gene expression compared to their alar complements (Osório et al., 2010). These mesodiencephalic basal regions contain dopamine cells in amniotes and amphibians, or cartilaginous fish for that matter (reviewed in González & Smeets, 1994; Smeets & González, 2000; Smeets & Reiner, 1994a, 1994b; Vernier & Wullimann, 2009; Wullimann, 2014; Wullimann & Umeasalugo, 2019). However, in teleosts the dopamine cells of this multiprosomeric basal mesodiencephalic region are restricted to the posterior tuberculum. Thus, dopamine cells are characteristic for this medioventral part of the vertebrate mesodiencephalic basal plate area. Developmentally, this results from the fact that ventral midline cells along the entire vertebrate neuraxis which express the morphogen *sonic hedgehog* directly give rise to the dopamine cells there (reviewed in Wullimann & Umeasalugo, 2019).

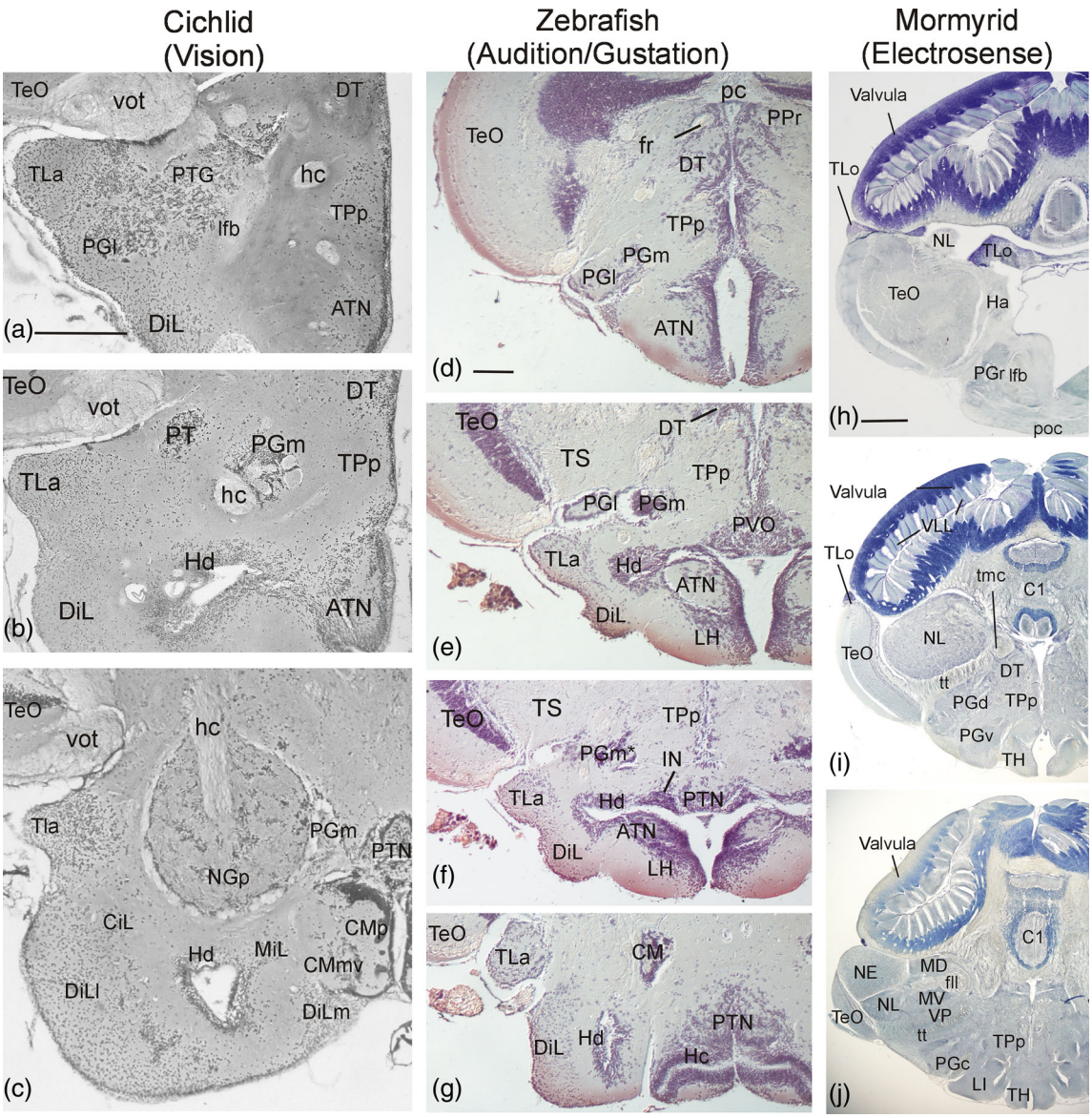

FIGURE 2 Comparison of teleostean medial (TPp, PVO) and lateral (PG) posterior tubercular regions. Transverse Bodian Silver-Cresyl stained brain sections of *Hemichromis lifalili* (a–c; vision dominant), *Danio rerio* (d–g; audition/gustation dominant) and *Gnathonemus petersii* (h–j; electroreception dominant). Panels (a–c) modified from Ahrens, K., & Wullimann, M. F. (2002). *The Journal of Comparative Neurology*, *449*; panels (d–g) modified from Yamamoto, K., Ruskaanen, J. O., Wullimann, M. F., & Vernier, P. (2010). *The Journal of Comparative Neurology*, *519*. Panels (i–j) modified from Zeymer, M., von der Emde, G., & Wullimann, M. F. (2018). *Frontiers in Neuroanatomy*, *12*. Scale bar in (a): 500 μm (applies to a–c), in (d): 100 μm (applies to d–g), in (h): 1 mm (applies to h–j). Abbreviations: ATN, anterior tuberal nucleus; Ha, habenula; C1, lobe 1 of corpus cerebelli; CiL, central nucleus of inferior lobe; CM, corpus mamillare; CMmv/CMp, magnocellular ventral/parvocellular part of CM; *DiL*, *diffuse nucleus of hypothalamic inferior lobe*; DiLl/DiLm, lateral/medial diffuse nucleus of hypothalamic inferior lobe; DT, dorsal thalamus; Ha, habenula; hc, horizontal commissure; fll, lateral longitudinal fascicle; fr, fasciculus retroflexus; Hd/Hc, dorsal/caudal zone of periventricular hypothalamus; IN, intermediate hypothalamic nucleus; lfb, lateral forebrain bundle; LH, lateral hypothalamic nucleus; LI, lobus inferior; MD/MV, mediodorsal/medioventral nucleus of torus semicircularis; MiL, medial nucleus of inferior lobe; NE/NL, exterolateral/lateral nucleus of torus semicircularis; NGp, posterior part of nucleus glomerulosus; pc, posterior commissure; *PGa/PGc/PGd/PGl/PGm/PGr/PGv*, *anterior/caudal/dorsal/lateral/ medial/rostral/ventral preglomerular nucleus*; poc, postoptic commissure; PPr, periventricular pretectal nucleus; PT, posterior thalamic nucleus; *PTG*, *preglomerular tertiarty gustatory nucleus*; PTN, posterior tuberal nucleus; PVO, paraventricular organ; TeO, tectum opticum; tmc, mesencephalo-cerebellar tract; DT, (dorsal) thalamus; TH, tuberal hypothalamus; TLa, torus lateralis; TLo, torus longitudinalis; *TPp, periventricular nucleus of posterior tuberculum*; TS, torus semicircularis; tt, toro-pre-eminential tract; VLL, valvular leaflets; vot, ventrolateral optic tract; VP, ventroposterior nucleus of torus semicircularis

In contrast, the extensive lateral posterior tubercular area in teleosts lacks dopaminergic and other monoaminergic neurons, but it is dominated instead by various nuclei concerned with ascending sensory circuitry in the form of the teleostean-typical, so-called preglomerular complex. Whereas the dorsal and ventral thalami are conservative in neuroanatomical appearance within most teleost

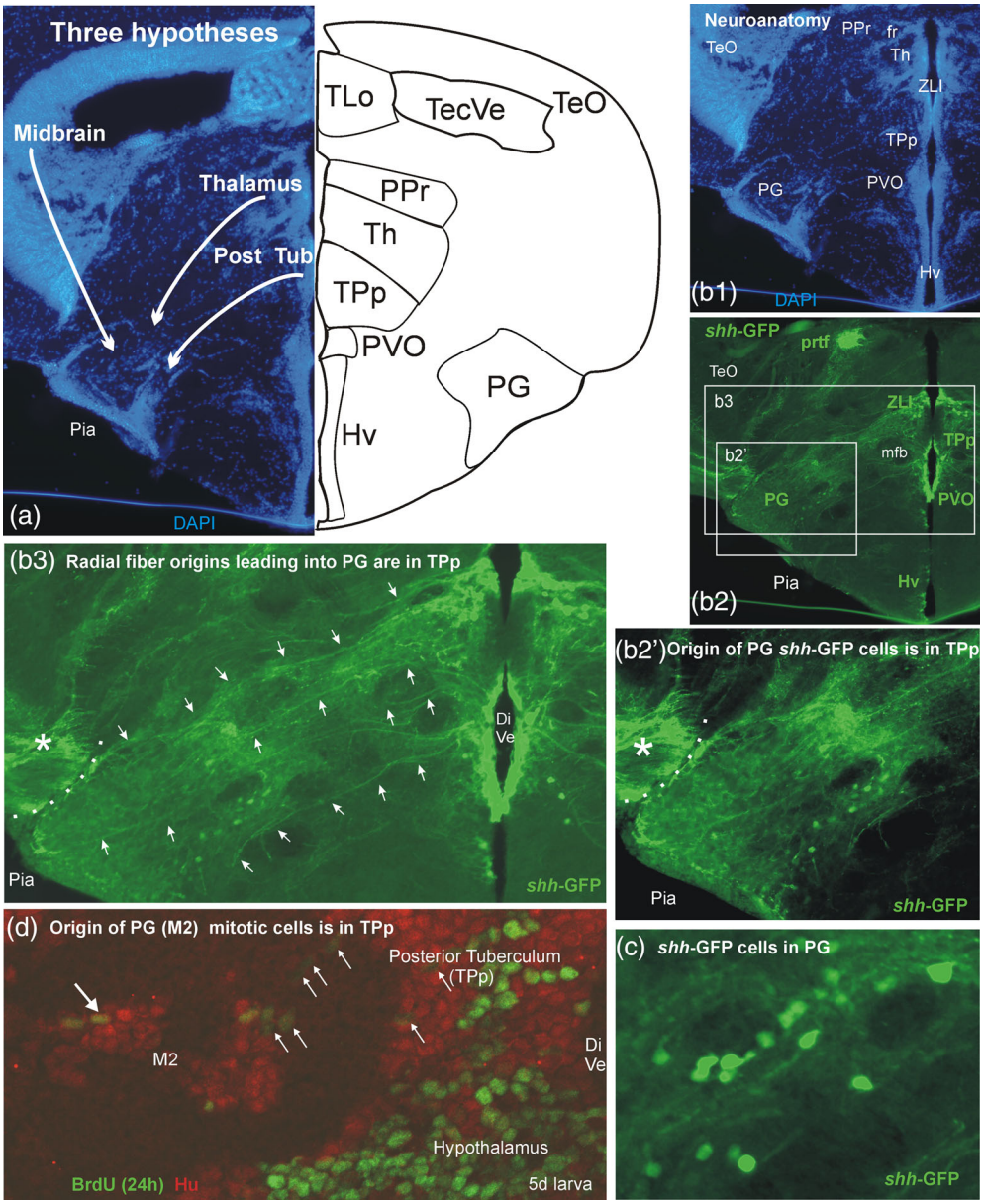

FIGURE 3 Peripherally migrated *shh*-GFP cells in the adult zebrafish brain shown in transverse views. (a) Three historically proposed hypotheses (thalamus also represents prethalamus, see text) depicted in a DAPI stained transverse diencephalic section (left side) accompanied by a sketch of relevant brain structures (right side). (b1) Enlargement of DAPI stained section with detailed neuroanatomy. (b2) Same section stained for *shh*-GFP. (b2′) Magnification of preglomerular complex containing many *shh*-GFP positive somata. Asterisk: stained retinal ganglion cell fibers within optic tectum. Dotted line: separation between optic tectum and preglomerular complex. (b3) Magnification of diencephalic posterior tubercular area from ventricle to pia emphasizing stained radial fibers (arrows). Asterisk: stained retinal ganglion cell fibers within optic tectum. Dotted line: separation between optic tectum and preglomerular complex. (c) Additional example of *shh*-GFP somata within the preglomerular complex. Panels (a–c) are modified from Wullimann, M. F., & Umeasalugo, K. E. (2020). *The Journal of Comparative Neurology*, *528*. (d) Diencephalic section of 5 day old zebrafish that received a BrdU treatment of 24 hr. Recenty postmitotic cells in peripheral larval preglomerular area M2 (thick arrow) are double-labeled for BrdU and the postmitotic neuronal marker Hu. Further, single BrdU-labeled cells, likely representing late mitotic, migrating cells that do not yet express Hu-proteins, are present between periventricular gray matter and M2 (thin arrows). This suggests that mitotic cells run from the periventricular posterior tuberculum into the larval preglomerular area (M2). Panel (d) modified from Mueller, T., & Wullimann, M. F. (2002). *Mechanisms of Development*, *117*. Abbreviations: DiVe, diencephalic ventricle; fr, fasciculus retroflexus; Hv, ventral zone of periventricular hypothalamus; *M2*, *larval preglomerular complex*; mfb, medial forebrain bundle; *PG*, *preglomerular complex*; PGa, anterior nucleus of PG; PGl, lateral nucleus of PG; PPr, periventricular pretectum; prtf, pretectal retinal terminal field; PVO, paraventricular organ; SP, superficial pretectum; TeO, tectum opticum; TecVe, tectal ventricle; *Th*, *(dorsal) thalamus*; TH, tuberal hypothalamus; TLa, lateral torus; TLo, torus longitudinalis; *TPp*, *periventricular nucleus of posterior tuberculum*; ZLI, zona limitans intrathalamica

species examined and compare even easily to cartilaginous fishes and amphibians (see, e.g., the recent paper on the frog thalamus; Morona, Bandín, López, Moreno, & González, 2020), there is great diversity in pretectal, preglomerular, or lateral hypothalamic regions (inferior lobe) (Figure 2). These areas greatly vary in teleosts depending on sensory specializations and show tremendous species or taxon-specific differences in size (note bars in Figure 2) and nuclear composition. Percomorphs, such as cichlids, have a large diencephalic nucleus glomerulosus (Figure 2a–c) which is part of a descending retino-tecto-diencephalo-tegmental pathway (Sakamoto & Ito, 1982; reviewed in Ahrens & Wullimann, 2002; Butler, Wullimann, & Northcutt, 1991; Yang et al., 2007). A main portion of the preglomerular complex lies rostral to this percomorph visual structure, which explains the formers name. In contrast, cypriniforms, such as the zebrafish (Figure 2d–g), show elaborate ascending auditory (involving anterior and lateral preglomerular nuclei; Yamamoto & Ito, 2005, 2008; Northcutt, 2006) and gustatory circuitry involving a preglomerular tertiary gustatory nucleus (PTG) in a position similar to the glomerular nucleus (included in PGm* in Figure 2f, Morita, Ito, & Masai, 1980; Kato, Yamada, & Yamamoto, 2012; see also Yáñez, Souto, Piñeiro, Folgueira, & Anadón, 2016 for zebrafish). Because of the greater prominence of the PTG (compared to zebrafish) in closely related cypriniform goldfish and carp, the latter's PTG had initially been identified as the (visual) glomerular nucleus seen in percomorphs (reviewed in Wullimann, 1998). However, comparative studies of gustatory circuitry in cypriniforms and percomorphs demonstrated which preglomerular/glomerular nuclei are either part of gustatory or visual neural networks in both taxa, respectively (reviewed in Butler et al., 1991; Wullimann, 1998; Yang et al., 2007; Yoshimoto et al., 1998). These different morphologies correlate functionally with the life styles of these two large groups of teleosts that likely evolved in brightly lit environments, probably oceanic coral reefs (percomorphs), or have specialized for chemosensory foraging in turbid fresh water (cypriniforms). Percomorphs and cypriniforms both belong to derived large assemblages of teleosts (i.e., acanthopterygians and ostariophysines, respectively) raising the question which of those forebrain states is ancestral. Studies in basal teleost groups, for example, non-electroreceptive osteoglossomorphs such as the Arowana and others (reviewed in Butler et al.,1991) showed that basal teleosts exhibit an intermediate situation with a moderately large “glomerular” nucleus (clearly located in the pretectum, hence called posterior pretectal nucleus) and associated similar retino-tecto-pretecto-diencephalic circuitry as present in percomorphs. Thus, basal teleosts may exhibit the ancestral situation for the visual and gustatory systems from which at some point both cypriniforms and percomorphs evolved.

Basal osteoglossomorph teleosts also include the electroreceptive mormyrids (e.g., the elephant-nose fish *Gnathonemus petersii*). Its preglomerular area is extensive (Figure 2h–j), and some of its nuclei project to the cerebellum. Since such projections are a hallmark of pretectal/accessory optic nuclei in other vertebrates, these mormyrid preglomerular nuclei were initially interpreted as part of the pretectum. However, connectivity studies of mormyrid preglomerular nuclei revealed that they are part of the diencephalic sensory preglomerular complex, which is dominated by mechano- and electrosensory ascending input (Bell & Szabo, 1986; Finger, Bell, & Russell, 1981; reviewed in Wullimann & Grothe, 2013) and that their cerebellar connections are a unique specialization within teleosts shared exclusively with non-electroreceptive osteoglossomorphs (reviewed in Wullimann & Northcutt, 1990). Therefore, these preglomerulo-cerebellar connections arose within osteoglossomorphs alone, but unrelated to mormyrid electroreception.

In all teleosts examined beyond these three examples discussed above, the preglomerular region has been identified as the major diencephalic relay complex for most sensory modalities ascending to the pallium, including lateral line, gustatory, somatosensory, auditory, and visual systems (Demski, 2013; Finger, 1980, 2000; Folgueira, Anadón, & Yáñez, 2005; Ito & Yamamoto, 2008; Murakami, Fukuoka, & Ito, 1986; Murakami, Ito, & Morita, 1986; Northcutt, 2006; Yamamoto & Ito, 2008). Thus, the teleostean preglomerular region clearly is a key region for plastic changes during evolution of sensory system specializations and the conventional view is that it is part of the diencephalon (see Section 2).

Additional conspicuous and large laterally located diencephalic areas in teleosts are the lateral torus (TLa) and the diffuse nucleus of the hypothalamic inferior lobes (DiL; Figure 2). Both regions are involved in gustatory circuitry (cypriniforms: Rink & Wullimann, 1998; percomorphs: Ahrens & Wullimann, 2002) with the latter also receiving visual (Butler et al., 1991) and octavolateralis system inputs (Yang et al., 2007) and their developmental origin will also be considered jointly with that of the preglomerular complex below.

2 | THE PREGLOMERULAR COMPLEX AND LATERAL HYPOTHALAMUS ARE MIDBRAIN- OR ARE THEY?

In a recent study, Bloch and colleagues (Bloch et al., 2019) used zebrafish specimens resulting from crossing transgenic lines *Tg(her5:ERT2-CreERT2)* and *Tg(βact:lox-stop-lox-hmgb1:mCherry)* in order to trace tamoxifen-inducible neural progeny of early *her5* expressing cells of the midbrain-hindbrain boundary (MHB). The bHLH transcription factor coding gene *her5* is embryonically expressed in the zebrafish MHB and increasingly expands its expression domain anteriorly into the emerging midbrain (Tallafuss & Bally-Cuif, 2003). A main conclusion of Bloch et al. (2019) is that considerable cellular contributions to the teleostean hypothalamic inferior lobe, the lateral toral nucleus, and the preglomerular complex derive from *her5* expressing progenitors coming from the alar midbrain (optic tectum). While this may well be the case, the interpretation that the inferior lobe and preglomerular area, both traditionally considered part of diencephalon (see above), are therefore part of the midbrain is highly debatable and needs to be viewed in a wider evo-devo context. As described in the previous section, the preglomerular area, on which I will focus in the following, represents a large migrated nuclear mass acting as a relay for all teleostean sensory systems to the pallial telencephalon (see

Section 1) and is apparently similar in function to the amniote sensory dorsal thalamus. Two issues are paramount here. (a) Are there alternative hypotheses on these suggested midbrain origins of part of the teleostean diencephalon? (b) In the face of multiple origins of an adult neural structure, what decides on the identification of that structure?

3 | NEURAL ORIGINS AND RADIAL VERSUS TANGENTIAL MIGRATION: HOW TO IDENTIFY BRAIN PARTS

The amniote telencephalon consists of a large dorsal (pallial/cortical) domain devoted to highest-order sensorimotor and cognitive processing and ventrally underlying motor-related basal ganglia (subpallium). During telencephalic development, two interdigitating processes occur. First, pallial glutamatergic and subpallial GABAergic cells are formed by radial migration or addition of cells along radial glia fibers. These fibers run perpendicular (radial) to the ventricular surface where their cell bodies are located and where new neurons originate. This is how the bulk of pallial neurons for the isocortex and other cortical divisions and the subpallial basal ganglia are formed, respectively (e.g., Englund et al., 2005; Marín & Rubenstein, 2001). Second, tangential migration perpendicular to the radial glia fibers is also pervasive. Such migrations were early suggested to play a major role in cortex evolution (Karten, 1997; Nauta & Karten, 1969) albeit in a different context than the following. For example, GABAergic cells destined to form pallial (cortical) interneurons originate in the ventral division of the early subpallium, that is, the medial ganglionic eminence (the future pallidum), although later contributions to inhibitory pallial interneurons also arise from the lateral (future striatum) and caudal ganglionic eminences (future subpallial amygdala; e.g., Alifragis, Liapi, & Parnavelas, 2004; Marín & Rubenstein, 2001; Wonders & Anderson, 2006). Thus, large numbers of subpallial cells migrate perpendicular to radial glia fibers out of the ganglionic eminences into the pallium (cortex) where they contribute considerably to its development in amniotes, and likely in all vertebrates. Yet, there is unequivocal agreement that the pallium does not change its identity because of this massive subpallial contribution.

An equally dramatic case of tangential migration occurs in the vertebrate hindbrain. The rhombic lip lies in the most dorsal (alar plate) embryonic hindbrain rimming the rhombic groove and produces from adjacent—but different—domains both GABAergic and glutamatergic cells which migrate considerable distances to arrive at their points of adult location. Some of these rhombic lip-derived structures, such as the inferior olive, the lateral cuneate and external cuneate nuclei, as well as cholinergic isthmic nuclei lie in the rostroventral mesencephalic and rhombencephalic tegmentum. In addition, in this case, despite their (alar plate) caudodorsal medullary origin, these precerebellar and cholinergic structures are interpreted to lie mostly in the (basal plate) rostroventral tegmentum (e.g., Nieuwenhuys & Puelles, 2016; Wullimann et al., 2011).

A third and immediately relevant example in the present context is that of the mammalian visual lateral geniculate nucleus (LGN). Ironically, even the LGN, an unquestioned sensory dorsal thalamic entity, has recently been shown to receive GABAergic interneurons originating in the midbrain optic tectum (Jager et al., 2016). However, nobody will be tempted to conclude that the LGN is midbrain, but it rather remains dorsal thalamus. This is a clear analogous case to what Bloch et al. (2019) report in zebrafish for the preglomerular region.

Critical for these three generally accepted identifications is that priority is given to the intrinsic central nervous bauplan of the radial glia system forming a "natural coordinate system of the neuraxis" (Nieuwenhuys, 1998), which defines throughout the CNS the ventricular origin of peripheral structures arising by radial migration. Tangential migration is a secondary process superimposed on this more basic phenomenon of radial migration.

Questions as to whether the pallium becomes subpallium, or the ventral tegmentum becomes dorsal tegmentum, or the LGN turns into midbrain because of these extraneous cellular contributions, would all have to be answered with yes if one follows Bloch et al. (2019) in saying that the diencephalic lateral hypothalamus and preglomerular region in teleosts is midbrain rather than diencephalon or forebrain. Clearly, such interpretations must be refuted for all of these examples of tangential invasions, but it should rather be stated that the radial glial course is the primary argument for the assignment of brain regions. Thus, the diffuse nucleus of the teleostean hypothalamus as well as the preglomerular region remains part of the forebrain (diencephalon).

4 | THREE HYPOTHESES ON THE ORIGIN OF THE TELEOSTEAN PREGLOMERULAR COMPLEX

Historically, three different hypotheses on the developmental origin of the teleostean preglomerular complex have been suggested (Figure 3a). The discussion in Bloch et al. (2019) is biased toward their preferred midbrain origin hypothesis, ignoring alternative hypotheses. Thus, I will shortly discuss these alternatives and synthesize an overall, more inclusive hypothesis.

4.1 | Alar diencephalon

Pax6 expression patterns during embryonic into larval stages in the zebrafish brain suggest that the preglomerular area in zebrafish receives cellular contributions from the prethalamus (i.e., alar diencephalon; Wullimann & Rink, 2001). This was confirmed later in medaka fish using in situ hybridization data for two *Pax6* paralogues and *dlx2* (Ishikawa et al., 2007). While these expression patterns in medaka (Ishikawa et al., 2007) are highly consistent with the earlier immunohistological findings in zebrafish in that the prethalamus contributes to the preglomerular area, this does not apply to the (dorsal) thalamus. Nevertheless, note that for simplicity only the dorsal thalamus (Th) is shown in Figure 3a, while the ventral thalamus/prethalamus is at a more anteroventral level.

4.2 | Posterior tuberculum

A study in zebrafish used the mitotic marker BrdU together with markers for early neurons to show that there is ongoing proliferation and neuron production within the early, already peripherally migrated preglomerular complex (Figure 3d; M2; Mueller & Wullimann, 2002). This study also implied strongly that these ongoing proliferative cells originate at the ventricle of the (alar plate) prethalamus and the (basal plate) posterior tuberculum. Finally, clear support for a posterior tubercular origin of preglomerular cells comes from a recent study using a *sonic hedgehog* (*shh*)—GFP transgenic zebrafish line (Wullimann & Umeasalugo, 2019). In this study, radial fibers originating from *shh*-GFP positive cell somata at the posterior tubercular ventricular lining can be followed out into the peripherally located preglomerular complex where also *shh*-GF positive cell bodies are present (Figure 3; after Wullimann & Umeasalugo, 2019).

4.3 | Midbrain-hindbrain boundary (midbrain)

As explained above, studies using *her5*-related transgenics in zebrafish, an origin of lateral hypothalamic, and preglomerular cells are suggested in the midbrain (Bloch et al., 2019) and these diencephalic areas are therefore interpreted as mesencephalic. However, the astroglial (radial glia) fiber course revealed by glial acidic fibrillary protein immunohistochemistry in the inferior lobe of the carp demonstrate that the lateral hypothalamus is pervaded by radial glia fibers into its pial periphery (Kálmán, 1998). This clearly supports that the natural radial glia fiber coordinate system mentioned earlier (Nieuwenhuys, 1998) is also present in the teleostean hypothalamic inferior lobe, and that the midbrain cells invade the lateral hypothalamus tangentially, as similarly suggested for the preglomerular region above (Wullimann & Umeasalugo, 2019). An interesting detail in the study on the carp brain (Kálmán, 1998) is that the radial glia fibers originate as usual from radial glia cell bodies at the hypothalamic ventricular lining and reach most peripherally the hypothalamic pial side, with an intermediate area where GFP is not expressed in the fibers. This suggests that the intermediate portion of hypothalamic radial glia fibers changed its cytoskeletal nature, maybe to allow for passage of tangentially invading cells as described by Bloch et al. (2019).

Thus, there may be truth to all three hypotheses and a more inclusive hypothesis might be formulated at this point: A multiregional origin for the lateral hypothalamus and preglomerular region is likely. While the course of the radial glia fibers decides about the lateral hypothalamus and preglomerular region being diencephalic, mesencephalic cells contribute to both of them by tangential invasion.

As discussed above, such multiple origins are not unusual for integrative centers. In the case of the mammalian cortex, its inhibitory interneurons arise from subpallium because of the early compartmentalization of GABA-ergic subpallial versus pallial glutamatergic cell generation (reviewed in Mueller & Wullimann, 2016). Similarly, the mostly glutamatergic cells of the PG (Maruska, Butler, Field, & Porter, 2017) likely arise from the posterior tuberculum by way of radial migration (Mueller & Wullimann, 2002), whereas its fewer inhibitory cells (mostly in adult anterior preglomerular nucleus; Mueller & Guo, 2009) likely are derivative of the prethalamus (*dlx2* positive cells; Ishikawa et al., 2007). The phenotypic identity of cells arising in the alar mibrain (Bloch et al., 2019) remains to be determined. This should be the focus of future investigations.

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AUTHOR CONTRIBUTIONS

Mario Wullimann: Conceptualization; writing-original draft; writing-review and editing.

DATA AVAILABILITY STATEMENT

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

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