Cell Reports

CellPress
OPEN ACCESS

Preview

# Good heavens! Finally a landslide analysis of basal ganglia circuitry in teleosts

Mario F. Wullimann[1,2,*]
[1]Genes – Circuits – Behavior, Max-Planck-Institute for Biological Intelligence, Am Klopferspitz 18, 82152 Martinsried, Germany
[2]Department Biology II, Division of Neurobiology, Ludwig-Maximilians-University (LMU Munich), 82152 Martinsried, Germany
*Correspondence: wullimann@bio.lmu.de
https://doi.org/10.1016/j.celrep.2024.113915

**Tanimoto et al.[1] report essential information on teleostean basal ganglia circuitry. This analysis opens gateways into studying neurophysiology, neuropharmacology, and behavior in zebrafish, guided by this complex functional neural system common to all vertebrates.**

After decades of only limited progress in the area of teleostean basal ganglia circuitry research, when compared to the wealth of information gained in tetrapods, the paper by Tanimoto and colleagues (see the related paper in this issue of *Cell Reports*)[1] present a cornucopia of information on the zebrafish brain. These data will facilitate combined neurophysiological, neuropharmacological, and behavioral, as well as modeling, studies to test functional aspects of teleostean basal ganglia.

The authors hierarchically ordered every segment of suspected teleostean basal ganglia circuitry starting from glutamatergic pallial cells via GABAergic striatal and pallidal populations to the (dorsal) thalamus, and they furthermore describe a glutamatergic pathway via the thalamus back to the pallium (Figure 1C). They use various transgenic lines that characterize inhibitory striatal cell subpopulations in the zebrafish central and dorsal nuclei of the ventral telencephalon (Vc/Vd). For example, they use a tac1-line that addresses a precursor of substance P (and neurokinin A) typical for amniote direct-pathway striatal cells, and a penkb-line that addresses proenkephalin b, a neuropeptide present in amniote indirect-pathway striatal cells (Figure 1A and 1B). Similar pathways were described in all tetrapods, including reptiles and amphibians (mammals: Mink in Squire et al.[2]; birds: Reiner[3]; amphibians: Marin et al.[4]; and for more, see Wullimann[5]).

Respective zebrafish transgenic lines are used for characterizing and distinguishing pallidal cells, such as those expressing *nkx2.1* in the lateral ventral telencephalic nucleus (Vl), specifying the external pallidum, and internal pallidal cells expressing either *npy* (neuropeptide y) or *crhb* (corticotropin releasing hormone b) in the dorsal entopeduncular nucleus (dEN). Together with using transgenic wheat germ agglutinin (WGA), the authors visualize particular projections to characterize adult zebrafish basal ganglia circuits (Figure 1C). In ambiguous cases, such as the connection between Vl and dEN, minute applications of the tracer carbocyanine dye DiI or virus-based VSV-mCherry neuronal tracing are used to corroborate connections. Additionally, single-cell RNA sequencing is used to sort out the dEN cells that project to the thalamus (*crhb*-positive cells) or pallium (both *crhb*- and *npy*-positive cells), and this approach also shows convincingly that pallial and ventral entopeduncular nucleus (vEN) cells are glutamatergic, whereas subpallial (Vc/Vd/Vl and dEN) cells are GABAergic.

The main conclusions from these circuitry data (Figure 1C) suggest that, in the teleost telencephalon, Vc and Vd together represent the striatum, whereas Vl corresponds to the external pallidum and the dEN is the internal pallidum. The data are interpreted as direct and indirect basal ganglia pathway segments in Figure 1D (comparison with amniotes is shown in Figure 1A and 1B).

Furthermore, the paper not only claims an evolutionarily conserved pathway between teleosts and tetrapods/amniotes, but also features circuitry specific to teleosts. This is often neglected in the search for evolutionary neural conservation. This search must remain futile considering the phylogenetic diversity particularly present between ray-finned fishes (including derived teleosts) and lobe-finned fishes (containing tetrapods), which split already in the Devonian. Derived features are, for example, the expression of *npy* and *crhb* in dEN (the internal pallidum homolog) and the direct projection of *crhb*-positive dEN cells to the pallium. Also critical is the apparent absence of a subthalamic nucleus. These aspects need attention and explanation in functional terms.

Interestingly, this paper contrasts conserved zebrafish circuitry and features (such as glutamatergic, GABAergic, and neuropeptidergic transmission) with evidence showing derived zebrafish basal ganglia system characters. Most critical is the absence of an excitatory (indirect pathway) link from Vl (GPe) to dEN (GPi) that, in amniotes, is provided by the intermittent (glutamatergic) subthalamic nucleus (or ALa in birds; Figure 1B). The striatal output cells of the direct and indirect pathways carry different dopamine receptors, D1 and D2, respectively. Due to the opposite response upon dopamine input to the striatum of these two dopamine receptors, a change of the sign of the re-entrant (indirect pathway) thalamic input to pallium occurs, resulting in strong pallial (i.e., cortical) activation. In tetrapods, this depends on the presence of a subthalamic nucleus. Theoretically, zebrafish excitatory thalamic neurons could provide this (indirect pathway) link by a projection to pallidum (dEN), but this connection is not revealed in the present study. Other derived teleostean features, such as pallidal *npy* and *crhb* expression and the direct inhibitory output of these pallidal cells to the pallium, could also be

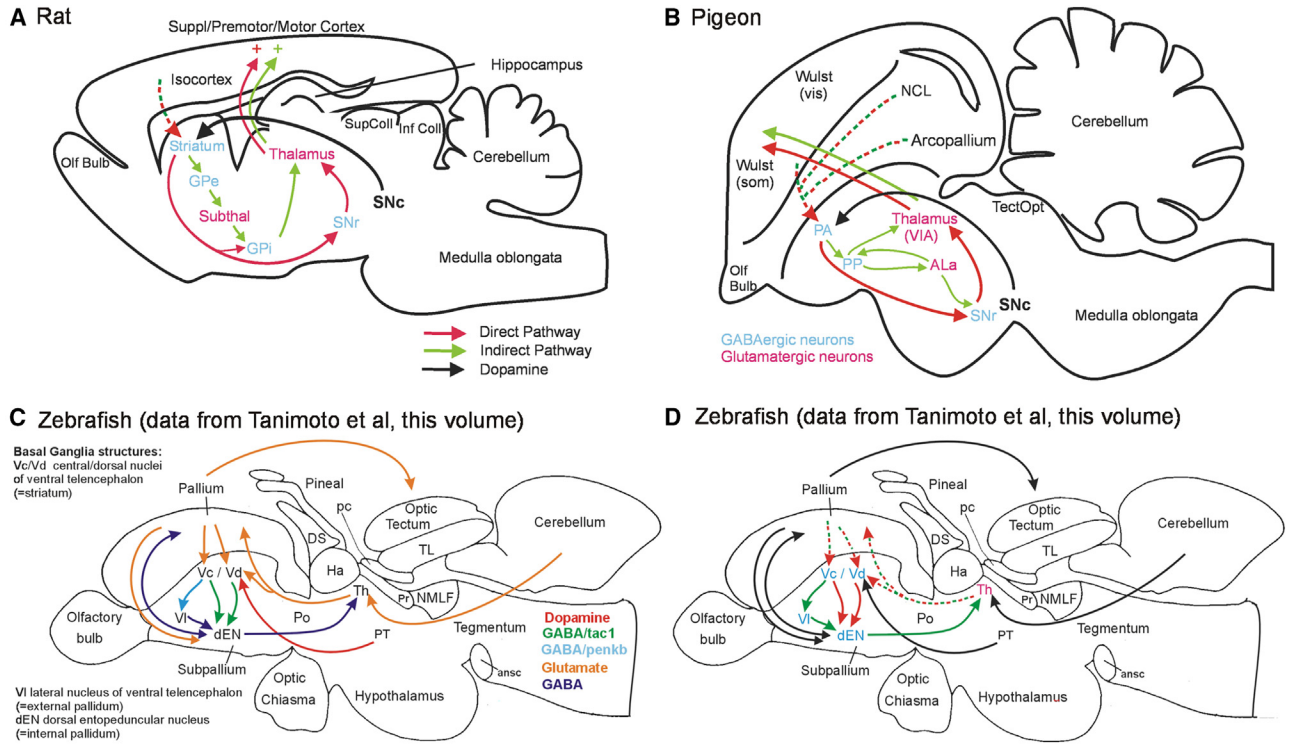


**Figure 1. Lateral views of simplified basal ganglia circuitry in vertebrates**

The focus is on direct and indirect basal ganglia pathways. Figure modified from Wullimann (see there for further discussion and original literature[5]).
(A) Data for mammals. The ++ indicate activation of cortex by both direct and indirect pathways upon dopamine release on striatum.
(B) Data for birds.
(C) Data on basal ganglia circuitry in teleosts reported by Tanimoto and colleagues (zebrafish).
(D) Same data shown in (C) interpreted in terms of direct and indirect basal ganglia pathways as in (A) and (B).
Mammals (rat): GPe (external globus pallidus), GPi (internal globus pallidus), SNc (substantia nigra compacta), SNr (substantia nigra reticulata). Birds (pigeon): ALa (anterior nucleus of ansa lenticularis [represents the subthalamic nucleus]), NCL (caudolateral nidopallium), PA (paleostriatum augmentatum [represents the lateral striatum]), PP (paleostriatum primitivum [represents the pallidum]), SNc (substantia nigra compacta), SNr (substantia nigra reticulata), VIA (ventrointermediate thalamic area).Teleosts (zebrafish): ansc (ansulate commissure), dEN (dorsal entopeduncular nucleus), DS (dorsal sac), Ha (habenula), NMLF (nucleus of the medial longitudinal fascicle), pc (posterior commissure), po (preoptic region), pr (pretectum), PT (posterior tuberculum), Th ([dorsal] thalamus), TL (torus longitudinalis), Vc/Vd/Vl (central/dorsal/lateral nucleus of the ventral telencephalon).

involved in the different functioning. In any case, the paper offers now the possibility to address functional questions on teleostean basal ganglia circuitry more aptly than ever before.

The previously established dopamine input to the striatum in teleosts is complementary to the data provided in this paper. The origin of this critical dopaminergic reward signal input to the teleostean striatum (Vd/Vc), within adult zebrafish basal ganglia circuitry, is exclusively located in the posterior tuberculum (zebrafish: Rink and Wullimann[6]), as opposed to land vertebrates, in which both posterior tuberculum and basal midbrain give rise to dopaminergic striatal innervation.[5] Importantly, this input is both dopaminergic and glutamatergic, unlike the common dopaminergic/GABAergic nature of other dopamine systems.[7] This dopamine input to the striatum is upstream of events spreading through basal ganglia circuits, which Tanimoto and colleagues now describe in teleosts, and starts a motor initiation or decision process in all vertebrates.

Developmental information already pointed to the recognition of a medial ganglionic eminence homolog and, thus, of a pallidum in teleosts. Thus, a subdivision of the larval Vd into striatum and pallidum exists in the developing zebrafish brain. Within the periventricular larval Vd (i.e., Sd), a genoarchitectonically different ventral division (Sdv) was recognized as pallidum based on *lhx 6/7* expression, which is absent from the more dorsal striatal subdivision (Sdd; Muller et al.[8]). In addition, as expected, both striatal and pallidal divisions of Vd share *dlx* and GABA expression.[7] Furthermore, the larval dEN is GABAergic and, thus, likely part of the laterally migrated pallidum (i.e., corresponding to globus pallidus internus was stated), as opposed to the excitatory, non-GABAergic vEN, which is part of the thalamic eminence and projects to the habenula.[9] Finally, expression studies on various *dlx* genes recently identified the teleostean Vc and Vl as migrated parts of the basal ganglionic Vd (and not of the septal Vv) formation.[10] These data on the development of subpallial basal ganglia structures are highly consistent with and supportive of the present report on adult zebrafish basal ganglia circuitry by Tanimoto et al.[1] Therefore, these two (i.e., developmental and adult circuitry) lines of evidence in zebrafish research converge to form a coherent picture of basal ganglia functional neuroanatomy in teleosts.

## DECLARATION OF INTERESTS

The author declares no competing interests.

## REFERENCES

1. Tanimoto, Y., Kakinuma, H., Aoki, R., Shiraki, T., and Higashijima, S. (2024). Transgenic tools targeting the basal ganglia reveal both evolutionary conservation and specialization of neural circuits in zebrafish. Cell Rep. *43*, 113916.
2. Squire, L.R., Bloom, F.E., Spitzer, N.C., du Lac, S., Ghosh, A., and Berg, D. (2008). Fundamental Neuroscience, 3rd ed. (New York, NY: Academic Press).
3. Reiner, A. (2002). Functional circuitry of the avian basal ganglia: implications for basal ganglia organization in stem amniotes. Brain Res. Bull. *57*, 513–528.
4. Marín, O., Smeets, W.J., and González, A. (1998). Basal ganglia organization in amphibians: evidence for a common pattern in tetrapods. Prog. Neurobiol. *55*, 363–397.
5. Wullimann, M.F. (2017). Nervous system architecture in vertebrates. In *The Wiley Handbook of Evolutionary Neuroscience*, S.V. Shepherd, ed. (Chichester: John Wiley & Sons, Ltd), pp. 236–278.
6. Rink, E., and Wullimann, M.F. (2001). The teleostean (zebrafish) dopaminergic system ascending to the subpallium (striatum) is located in the basal diencephalon (posterior tuberculum). Brain Res. *889*, 316–330.
7. Filippi, A., Mueller, T., and Driever, W. (2014). *vglut2* and *gad* expression reveal distinct patterns of dual GABAergic versus glutamatergic cotransmitter phenotypes of dopaminergic and noradrenergic neurons in the zebrafish brain. J. Comp. Neurol. *522*, 2019–2037.
8. Mueller, T., Wullimann, M.F., and Guo, S. (2008). Early teleostean basal ganglia development visualized by zebrafish Dlx2a, Lhx6, Lhx7, Tbr2 (eomesa), and GAD67 gene expression. J. Comp. Neurol. *507*, 1245–1257.
9. Turner, K.J., Hawkins, T.A., Yáñez, J., Anadón, R., Wilson, S.W., and Folgueira, M. (2016). Afferent connectivity of the zebrafish habenulae. Front. Neural Circ. *10*, 10–30.
10. Solek, C.M., Feng, S., Perin, S., Weinschutz Mendes, H., and Ekker, M. (2017). Lineage tracing of dlx1a/2a and dlx5a/6a expressing cells in the developing zebrafish brain. Dev. Biol. *427*, 131–147.