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Dopamine systems in the forebrain

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Abstract

The brain contains a number of distinct regions that share expression of dopamine (DA) and its requisite biosynthetic machinery, but otherwise encompass a diverse array of features and functions. Across the vertebrate family, the olfactory bulb (OB) contains the major DA system in the forebrain. OB DA cells are primarily periglomerular interneurons that define the glomerular structures in which they receive innervation from olfactory receptor neurons as well as mitral and tufted cells, the primary OB output neurons. The OB DA cells are necessary for both discrimination and the dynamic range over which odorant sensory information can be detected. In the embryo, OB DA neurons are derived from the ventricular area of the evaginating telencephalon, the dorsal lateral ganglionic eminence, and the septum. However, most OB DA interneurons are generated post-natally and continue to be produced throughout adult life from neural stem cells in the subventricular zone of the lateral ventricle and rostral migratory stream. Adult born OB DA neurons are capable of integrating into existing circuits and do not appear to degenerate in Parkinson's disease. Several genes have been identified that regulate the differentiation of OB DA interneurons from neural stem cells. These include transcription factors that modify the expression of tyrosine hydroxylase, the first enzyme in the DA biosynthetic pathway and a reliable marker of the DA phenotype. Elucidation of the molecular genetic pathways of OB DA differentiation may advance the development of strategies to treat neurological disease.

Index

AP-1; Aromatic amino acid decarboxylase (AADC); Beta-galactosidase (LacZ); Cortex; CREB; D2 receptor; Dlx; Dopamine (DA); Dopamine receptor; Dorsal lateral ganglionic eminence (dLGE); Er81; FosB; Gamma amino butyric acid (GABA); Glomerulus; Glutamic acid decarboxylase (GAD); Glutamatergic; Granule cell; Green fluorescent protein (GFP); Gsh2; Immediate early gene (IEG); Meis2; Migration; Mitral cells; Neuroblast; Neurogenesis; Nurr1; NGFI-B; Odor deprivation; Olfactory bulb (OB); Olfactory receptor neuron; Pax6; Periglomerular neuron Post-natal neurogenesis; Rostral migratory stream (RMS); Septum; Stem cell; Striatum; Subventricular zone (SVZ); Telencephalon; Transit amplifying cell; Tufted cell; Tyrosine hydroxylase (TH); Zic 1,3

Introduction

The dopaminergic (DA) neuronal systems of the brain exhibit substantial diversity. All DA neurons express the requisite enzymes for dopamine biosynthesis, but there are regional differences in the morphology and co-expression of other neuroactive substances, as well as the capacity for regeneration and the susceptibility to neurodegenerative diseases. For example, substantia nigra DA neurons co-express glutamate and CCK, and have long projections into the striatum that are essential for control of movement. These midbrain DA neurons also

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selectively degenerate in Parkinson's Disease (PD).[1] By contrast, olfactory bulb (OB) DA neurons co-express GABA, and have short axonal projections that remain within the main OB that are necessary for processing of odorant sensory information from olfactory receptor neurons.[2–4] Furthermore, the OB DA neurons are continuously generated through out the lifespan of the adult[5–7] and do not degenerate in PD.[8] The molecular and genetic mechanisms responsible for the common DA phenotype (that is, the production of dopamine) as well as the wide variety of associated features remain an area of intensive study.

This chapter will focus primarily on the anatomical, molecular genetic and physiological characteristics of the OB DA neurons. These neurons are the major endogenous DA-producing system in the forebrain.[9, 10] The OB DA neurons are a subgroup of a diverse population of interneurons in the OB that have been intensively studied in an effort to understand the mechanisms regulating neurogenesis and the generation of neuronal diversity.[11–13] The OB DA neurons are an integral component of circuitry that serves as a powerful model for neural network learning, memory consolidation and behavioral plasticity.[14–16] Much of the information presented in this chapter is derived from studies with the rodent OB (specifically, the mouse and rat), but a growing number of studies have revealed that the data derived from rodent studies extend into primates, including humans.[17]

Anatomy and function of OB DA neurons

In some vertebrate species, including monkeys and humans, DA-producing cells are found in forebrain regions such as the striatum.[18, 19] However, the main OB contains the major forebrain DA system common to all vertebrates.[20] Thus, this chapter will focus primarily on the OB DA neurons.

Approximately 5% of neurons in the main OB are DA interneurons. They show a distinct laminar distribution that is limited primarily to the glomerular layer.[21] Most OB DA cells are small, periglomerular (PG) interneurons (about 5–10 μm in diameter), although some are larger external tufted cells (about 10–15 μm in diameter; Fig. 1).[2, 20, 22] Several studies indicate that 10%–16% of all PG neurons are DA cells.[23–25] Glomeruli are distinctive spheroid neuropil structures (50–150 μm in diameter in rodents) that are defined by a layer of PG and glial cells.[20] These structures serve as the initial processing center of sensory information from the olfactory receptor neurons. The neuropil within the glomeruli is composed of the axon terminals from the olfactory receptor neurons, the apical dendrites from mitral and tufted (M/T) projection neurons, dendritic processes from OB juxtaglomerular neurons (including the DA cells), and terminals from centrifugal innervation of both basal forebrain cholinergic neurons and dorsal raphe cell serotoninergic projections.[26–28]

Within the glomeruli, OB DA interneurons receive region-specific axo-dendritic innervation from the axon terminals of the olfactory receptor nerve fibers, and make dendro-dendritic contacts with the apical dendrites of OB M/T cells (Fig. 2).[29, 30] These synaptic connections are distinct from other groups of PG interneurons. For example, both calretinin- and calbindin-expressing interneurons, which do not co-express DA, only make dendro-dendritic contacts with the M/T cells within the OB glomeruli.[23, 31, 32] This heterogeneity in synaptic organization within the glomeruli suggests that OB DA interneurons have a function in the processing of olfactory sensory information distinct from the other sub-groups of OB interneurons.

Across all vertebrate species, OB DA neurons are readily identified by the expression of tyrosine hydroxylase (TH), the first enzyme in the DA biosynthetic pathway.[33, 34] The OB does not contain noradrenergic (NE)-producing neurons, but centrifugal NE afferents from the locus ceruleus to the OB also express TH.[2, 35] However, TH expression in the NE terminations is very low and does not complicate analysis of OB DA neuronal function.[2]

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In contrast to TH, expression of aromatic amino acid decarboxylase (AADC), the second and last enzyme in the DA biosynthetic pathway, exhibits cross species variation. For example, AADC is readily observable in the rat OB, but it is detectable at only low levels in the mouse OB.[36] Other markers of functional DA cells, such as dopamine transporter (DAT) and both D_1 and D_2 DA receptors, are expressed at either low or variable levels.[37–40] Thus, TH expression is considered the most reliable marker of OB DA neurons.

TH expression in OB PG interneurons is dependent on afferent synaptic activity in the olfactory receptor neurons.[2, 21, 22, 41] Both TH mRNA and protein expression are dramatically down-regulated in the OB by perturbations that compromise either odorant access to the olfactory epithelium or cyclic nucleotide-gated channel function in the olfactory receptor cells (Fig. 1).[22, 42] Studies in which animals were subjected to odor deprivation by either naris occlusion, chemical or surgical deafferentation have shown that the loss of TH is concomitant with a loss of detectable DA[2, 43] as well as a dramatic increase in D_2 receptor expression.[44] As discussed below, the activity dependence of TH expression and DA production is likely critical for both odorant identification and detection of odorant intensity.

Almost all OB DA interneurons also co-express GABA.[23, 31, 45] GABA, the major inhibitory neurotransmitter in brain, is found in about 55% of the interneurons in the glomerular layer and almost all interneurons in the granule cell layer.[23, 25, 31] OB GABAergic interneurons are typically sub-divided by the co-expression of other neuroactive substances such as DA, calbindin, calretinin and CCK.[31, 46] Activation of DA receptors are reported to modulate the response of GABA receptors within the same cell.[47] These results suggest that the co-release of DA with GABA may modify the response of both the olfactory receptor neurons and M/T cells to the inhibitory effects of GABA.

OB DA interneurons are a necessary element in the processing of afferent sensory information from the olfactory epithelium (Fig. 3). Within the glomeruli, the axons of glutamatergic olfactory receptor neurons provide excitatory input to both M/T and PG neurons, including DA cells.[48–50] Glutamate released from M/T cells is also excitatory on DA neurons and other PG cells.[51] Stimulation of PG GABAergic interneurons results in the release of GABA which inhibits both olfactory receptor and M/T neurons [52–55] as well as other PG neurons.[56, 57] OB DA interneurons also release dopamine that acts pre-synaptically on D_2 receptors to modulate the release of glutamate from olfactory receptor neurons.[51, 58, 59] Although somewhat controversial, several studies have reported that M/T neurons are also pre-synaptically inhibited by DA through D_2 receptors.[60–62] Together, GABA and DA modify the output of sensory information from the OB by directly modulating the excitation of both the olfactory receptor and M/T neurons.

The activity dependent expression of TH suggests that DA is essential for the regulation of odorant information processing in response to either high or low levels of afferent odor-induced synaptic activity. When odorant access to the OE is prevented by naris occlusion, the M/T cell responses to odor stimulation show enhanced sensitivity.[3, 4] The finding that expression of the isoforms of the GABA biosynthetic enzyme, glutamic acid decarboxylase, are not activity dependent suggests that this enhanced M/T cell sensitivity is likely the result of diminished DA-mediated inhibition.[63, 64] Furthermore, on restoration of sensory input following prolonged odorant sensory deprivation, M/T neurons show impaired discrimination of individual odorants.[4] Thus, the OB DA system is critical for both discrimination and the dynamic range over which odorant sensory information can be relayed from olfactory receptor neurons to other brain regions.

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OB DA neurogenesis

Embryonically (E)-derived OB interneurons are predominantly generated from progenitor cells located in the subventricular zone (SVZ) of the dorsal lateral ganglionic eminence (dLGE) beginning at about E14 in the mouse (Fig. 4).[65] The dLGE is a proliferative zone in the developing telencephalon that is defined by the expression of transcription factor proteins such as Pax6, Gsh2, Er81, and Dlx-1,2,5,6.[66, 67] Immature OB interneurons tangentially migrate from the dLGE to the developing OB and then radially migrate to their final glomerular or granule cell layer positions.[7, 68, 69]

Although the dLGE is considered the primary source of embryonic OB DA interneurons, additional sites of origin have been proposed. A recent study suggested that precursor cells localized to the ventricular layer of the evaginating telencephalon may also contribute neurons to the embryonic OB, including DA interneurons (Fig. 4).[70] These OB neural stem cells have molecular features distinct from OB progenitors originating from the dLGE. A second alternative embryonic origin may be the medial septum (Fig. 4).[71] Neural progenitors in the medial septum also have molecular features distinct from the dLGE, including the expression of the Zic1 and Zic3 transcription factor proteins. The consequences of these alternative embryonic origins and their distinct molecular features are not clear, but the OB DA neurons derived form these alternative origins may have functional properties that differ from those cells of the dLGE lineage.

Although the generation of OB DA interneurons is initiated during mid-embryonic development, the majority of these interneurons are born during late embryonic and neonatal time periods.[65, 72, 73] These late-embryonic and post-natal neurons are generated in the rostral migratory stream (RMS) and subventricular zone (SVZ) of the lateral ventricle, which is believed to be, in part, a remnant of the embryonic LGE. Nearly all of the transcription factors that define the embryonic dLGE are also expressed in the post-natal SVZ.[66, 67, 74–79] In the mouse, neurogenesis of OB interneurons peaks between E18 and post-natal (P) day 5.[65] These late embryonic and post-natally generated neurons migrate tangentially through the RMS before moving radially to their final positions in the granule and glomerular layers of the OB. Although their proliferation rate decreases after P5, neurogenesis of OB interneurons, including DA cells, continues throughout the lifetime of the adult, including humans.[17, 80]

The predominant hypothesis is that late-embryonic and post-natally generated OB interneurons, including DA cells, are derived from slowly dividing neural stem cells located in SVZ and RMS (for a comprehensive review, see refs. [5, 81–84]). These neural stem cells have several features attributed to astrocytes, such as the expression of GFAP, but they can also be cultured in the presence of EGF to generate both neurons and glia. In both the RMS and SVZ, these slowly dividing stem cells produce transit amplifying cells that express markers such as NG2 and Olig2. The transit amplifying cells give rise to migrating neuroblasts, which can be identified by the expression of such genes as PSA-NCAM, doublecortin and neuron-specific type III-tubulin (TuJ1). These neuroblasts (precursor cells) tangentially migrate through the SVZ and RMS in chains that are enclosed in tubes formed by transit amplifying cells, slowly dividing neural stem cells and glia. It has been estimated that approximately 30,000 per day progenitors enter the adult OB, but only a small percentage of these cells mature and differentiate into functional OB neurons.

There is a growing consensus that progenitors for specific OB interneuron subtypes, such as DA cells, are generated in distinct regions within the SVZ and RMS. Consistent with this idea is the observation that the location of stem cells in the SVZ and RMS reflect different embryonic origins.[85] For example, the majority of cells lining the lateral ventricle are derived from the Gsh2 expressing regions in the LGE, whereas the ventral and dorsal regions of the SVZ contain stem cells derived from the Nkx2.1 expressing region of the MGE and the Emx1 expressing

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regions of the embryonic cortex, respectively. There is a general agreement that the majority of post-natally derived OB DA neurons are generated from the more dorsal neurogenic regions in the SVZ.[85, 86] However, there is controversy as to whether there is a preferential rostral-caudal origin of OB DA cells. Some studies have suggested that PG interneurons, including DA neurons, are preferentially derived from stem cells in the RMS.[16] By contrast, other studies have suggested that OB DA cells are generated from stem cells within a long neurogenic region that includes the dorsal SVZ and subcallosal zone.[86] Generation of neuronal diversity may also show temporal-dependence, suggesting that distinct PG interneuron sub-types are produced during different developmental windows.[24] Current controversies surrounding the spatial and temporal origins of OB neurons may result from the use of different experimental techniques, but there is a clear consensus that stem cells within the neurogenic SVZ and RMS regions are not a homogenous population.

Identification of the specific origin for DA progenitors in both the embryonic and post-natal animal is also complicated by the fact that there are no known markers specific to DA cells prior to terminal differentiation. Both requisite biosynthetic enzyme proteins for DA production, TH and AADC, are expressed only in the differentiated neurons in the glomerular layer and not in migrating immature DA precursor cells.[36] The transcription factor Pax6, Er81, Meis2 and Dlx-1,2,5,6 proteins are co-expressed in both the immature and terminally differentiated neurons.[16, 66, 75, 77, 87–92] However, these transcription factor proteins are expressed in other OB interneuron sub-types that do not express TH and, thus, these proteins do not specifically label DA precursor cells.

Although TH protein is expressed only in the glomerular layer (Fig. 5A), several studies have shown that the upstream gene regulatory region of TH is transcriptionally active in areas outside of the glomerular layer. TH mRNA is expressed in the superficial granule cell layer, even though TH protein is not detectable in this layer (Fig. 5B).[88, 93] Transgenic mice containing either GFP or LacZ reporter genes under the control of either 9kb or 4.5kb of the TH upstream gene regulatory region also exhibited transgene expression in the superficial granule cell layer as well as in the RMS (Fig. 5C).[93–95] Together, these studies suggest that there are spatially dependent translational regulatory mechanisms that limit the expression of TH protein, and consequently DA biosynthesis, to the OB glomerular layer. It is possible that the cells in the superficial granule cell layer which contain TH promoter activity, but lack TH protein, are immature DA neurons. However, these cells do not appear to migrate and express NeuN, a marker of terminally differentiated neurons.[88]

Although the OB is the major DA system in the forebrain, there is TH gene activity in other regions. In mice, TH mRNA and reporter gene expression under the control of the TH promoter has been detected in both the cortex and striatum.[96] The human and primate striata contain a small number of projection neurons that express TH protein.[18, 19] Although the origin of these cells with TH gene activity is not presently known, it is interesting to note that some cortical interneurons and striatal projection neurons are also derived from the LGE.[97, 98] The functional role of these non-OB neurons with either TH mRNA and/or TH protein in the forebrain remains to be determined.

Molecular genetic mechanisms of OB DA neuron differentiation

The underlying molecular genetic pathway of midbrain DA neuron differentiation is well established. Briefly, midbrain DA neurons originate in the ventral mes-diencephalic neuroepithelium where Sonic hedgehog (Shh) and FGF8 signaling pathways cooperatively interact. This interaction between Shh and FGF8 initiates expression of the transcription factors Otx1, Nkx2.2 and Sox2 in neuroblasts. Midbrain neural progenitor cells develop from these neuroblasts and express transcription factors such as Lmx1a, Msx1 and Ngn2. The committed midbrain DA neuronal precursor cells express AADC and the transcription factors Lmx1b, and

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En1. Subsequently, terminal differentiation of midbrain DA neurons occurs with the expression of genes such as TH, VMAT2, DAT and the transcription factors Nurr1 and Pitx3.

By contrast, the molecular genetic pathways that regulate OB DA differentiation are not well defined. A significant challenge associated with defining the molecular genetic pathways necessary for OB DA neurons is that there is no single spatial and temporal origin specific to these neurons. As discussed above, there is evidence for multiple embryonic origins of these neurons, and the origin of post-natally derived neurons within either the RMS or SVZ is ambiguous. Furthermore, it is not clear whether these various origins have either the same, partially overlapping or unique molecular genetic pathways for differentiation of OB DA neurons.

Despite the ambiguity surrounding their spatial and temporal origins, several genes involved in the differentiation of OB DA neurons have been identified and are summarized in Tables 1–3. One such gene, Er81, is expressed in both the embryonic dLGE and post-natal SVZ, RMS and OB.[66, 77] Almost all OB TH immunoreactive cells also contain Er81, and TH expression is drastically reduced in Er81 deficient mice (Fig. 6). Like TH, Er81 expression levels are also dependent on afferent synaptic activity of olfactory receptor neurons.[77] However, Er81 is not specific for DA differentiation since it also expressed in some OB interneurons that do not contain TH, such as calretinin containing neurons.[90]

The transcription factor Pax6 is also critical for OB DA differentiation. The $Pax6^{Sey}$ mutation is embryonic lethal when homozygous, but heterozygous $Pax6^{Sey}$ mutant mice are viable and have an almost total loss of TH expression in the OB. In wild-type mice, nearly all OB DA cells co-express TH and Pax6.[87] However, a significant fraction of Pax6 immunoreactive cells lack TH expression, suggesting that Pax6 is not specific to OB DA neurons. Also, Pax6 expression in the OB is not dependent on afferent synaptic activity of the olfactory receptor neurons (Fig. 7). The molecular genetic mechanism by which Pax6 regulates differentiation of OB DA neurons is unclear, in part, because the Pax6 gene encodes at least three different DNA-binding protein isoforms that each have a unique consensus target DNA binding sequence.[99–103] The relevant Pax6 isoforms and the target genes of these isoforms necessary for OB DA differentiation have not been identified. Furthermore, Pax6 has been reported to influence neuronal progenitor migration and proliferation.[104–107] These non-specific, general neurogenic functions of Pax6 complicate analysis of specific contributions to OB DA differentiation.

The immediate early gene (IEG) family is likely to be essential for mediating the synaptic activity-dependent expression of TH in OB DA precursor cells. The homologous IEG family members Nurr1 and NGFI-B are orphan nuclear receptor transcription factors, which are expressed in the OB in a synaptic activity-dependent manner. Nurr1, but not NGFI-B, is also expressed in the midbrain.[108, 109] However, there is no evidence that either midbrain TH or Nurr1 expression is activity dependent. Nurr1 can also modulate TH gene expression through binding sites in the TH proximal promoter.[110, 111] In Nurr1 deficient mice, TH expression is absent in the midbrain, but still present in the OB as a likely consequence of NGFI-B functional redundancy.[108, 112, 113]

The TH proximal promoter also contains evolutionarily conserved binding sites for the IEG basic-leucine zipper (bZip) transcription factor proteins CREB and AP-1 (the latter is a heterodimer formed by members of the Fos and Jun protein families).[114, 115] In vivo mouse studies have shown that mutation of either the AP-1 or CREB binding site in the TH proximal promoter can disrupt reporter gene expression under the control of the 9kb TH promoter in the OB.[94, 116] However, there are several IEG bZip proteins expressed in the OB glomerular layer in a synaptic activity dependent manner that can bind these consensus sites.[117] Thus, like Nurr1

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and NGFI-B, there is likely to be redundancy in the regulation of TH expression by bZip IEGs. For example, expression of the bZip FosB protein in the OB glomerular layer is activity dependent and FosB can bind the AP-1 binding site, [117] but TH immunoreactivity and enzymatic activity are normal in mice lacking FosB (Fig. 8).

There is a dearth of knowledge regarding the membrane channels and receptors as well as their cognate intra-cellular signaling pathways in the DA progenitor cells that mediate DA differentiation in response to afferent synaptic activity. Studies with primary cultures of OB and forebrain organotypic slice cultures indicate that L-type calcium channels are critical for activity dependent expression of TH.[118, 119] It is tempting to speculate that the activation of calcium channels induces IEG expression, and consequently TH expression, through well established calcium second messenger signaling pathways.[120] Forebrain slice cultures have also suggested that OB TH expression is modulated by GABA (unpublished observation). As stated above, a majority of the PG interneurons are GABAergic and the DA interneurons also contain GABA-A receptors. GABA plays well documented roles in regulating proliferation, migration and gene expression in neural progenitors in both the SVZ and hippocampus.[24, 121–126] It is possible that the modulation of TH expression by GABA is necessary for the terminal differentiation of DA progenitor cells.

There are also genes that modulate the OB DA phenotype through either general aspects of neurogenesis (Table 2) or olfactory receptor neuron function (Table 3), rather than specifically regulating OB DA differentiation. For example, the loss of either Notch1 or Arx impairs proliferation and migration of OB interneuron progenitors.[127, 128] Alternatively, the loss of Dlx5 disrupts olfactory receptor neuron innervation of the OB,[75] and mutations in the cyclic nucleotide gated channel 2 (CNG2) gene blocks signal transduction in olfactory receptor neurons.[129] Thus, the regulation of OB DA neuron differentiation is complex and requires the convergence of diverse molecular genetic pathways.

Expression and function of forebrain DA receptors

Dopamine acts through five receptor variants, D_1 – D_5, that are expressed in distinct and partially overlapping patterns within the forebrain (for an extensive review, see refs. [130, 131]). D_1, D_2 and D5 receptors are widely expressed in the striatum, limbic system and OB as well as the pre-frontal, pre-motor, cingulate and entorhinal cortices. D_5 receptor levels are notably lower than either the D_1 or D_2 receptors in most regions. Both D_3 and D_4 receptor expression is largely limited to the limbic system, although D_4 receptors are also highly expressed in the frontal cortex.

Forebrain neurons expressing DA receptors are innervated primarily by midbrain DA cell groups. The mesostriatal DA projections from the substantia nigra, ventral tegmentum and retrorubral nucleus (area A9, A10 and A8, respectively) innervate several regions within the striatum as part of the neural circuitry that controls movement.[132] As stated above, loss of the substantia nigra DA neurons and their associated projections is the hallmark of Parkinson's Disease (PD). In addition to the mesostriatal system, the mesolimbic/mesocortical DA projections that originate largely from the ventral tegmentum (area A10) innervate limbic system regions that include the hippocampus and amygdala as well as cortical regions that include the cingulate and pre-frontal cortex.[133] These mesolimbic/mesocortical DA projections have been implicated in several neurological conditions, including drug addiction (reward and reinforcement mechanisms)[134] and schizophrenia,[135] as well as learning and memory.[136]

Prospective directions for OB DA neurobiology

The mechanisms for OB DA differentiation may be important for advancing cell-replacement therapeutic strategies to treat neurodegenerative disorders, such as PD. OB DA neurons have

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several advantageous properties that include a capacity to readily integrate into pre-existing circuitry[11] and a resistance to degeneration in PD.[8] Emerging cell-transplant therapeutic strategies use replacement DA neurons generated from stem cells (either embryonic or adult-derived), but efficient production of functional replacement DA neurons remains elusive.[137–139] Also, DA production alone is not sufficient, and other neuronal properties are also critical, to generate cells suitable for transplant.[140, 141] Thus, it is important to not only delineate the various molecular genetic pathways that afford DA production, but also the pathways that generate the diverse array of features and functions of DA neurons in the brain. Elucidation of these diverse pathways may enable the engineering of replacement neurons that incorporate the unique, advantageous properties of OB DA neurons in order to improve the clinical effectiveness of replacement cells.

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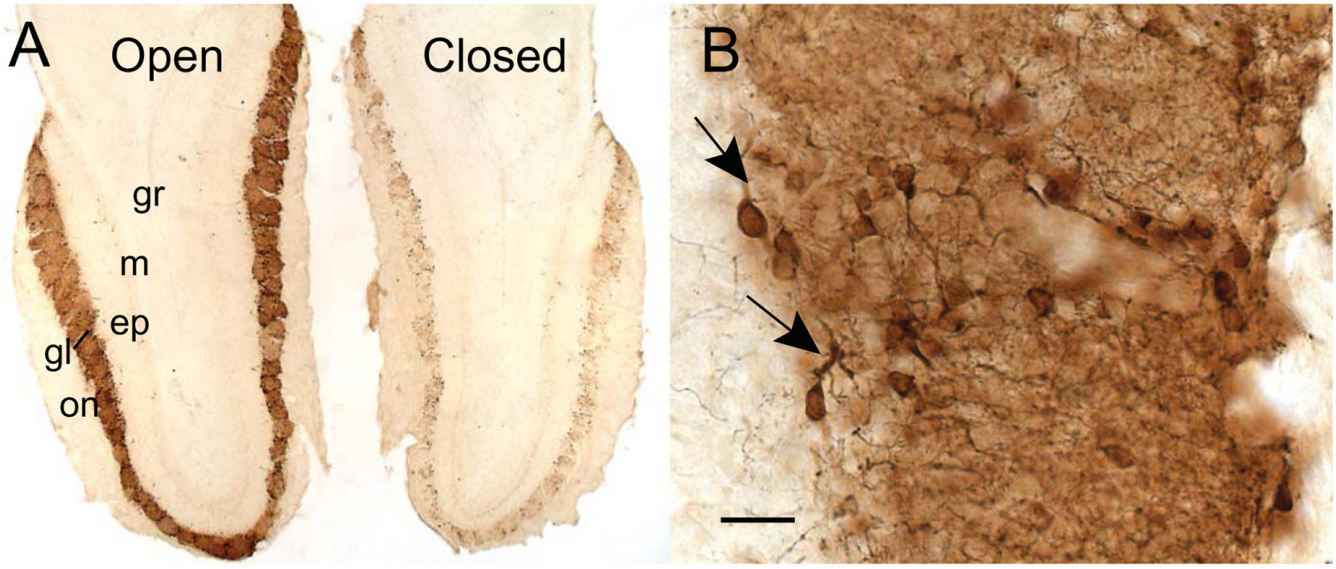

Figure 1.

Laminar distribution of TH-immunoreactive dopamine neurons in a horizontal section of olfactory bulbs taken from an adult mouse with unilateral naris closure. (**A**) A low magnification image shows the normal distribution of PG DA neurons in the glomerular layer of the OB contralateral to naris closure (open). The OB ipsilateral to the closure (closed) displays a drastic reduction in the number of TH-immunoreactive cells and processes. (**B**) A higher magnification micrograph illustrates the processes (arrows) of the PG DA neurons entering the glomeruli. Bar = 200 μm in **A**, and 20 μm in **B**. Abbreviations: epl, external plexiform layer; gl, glomerular layer; gr, granule cell layer; m, mitral cell layer; on, olfactory nerve layer.

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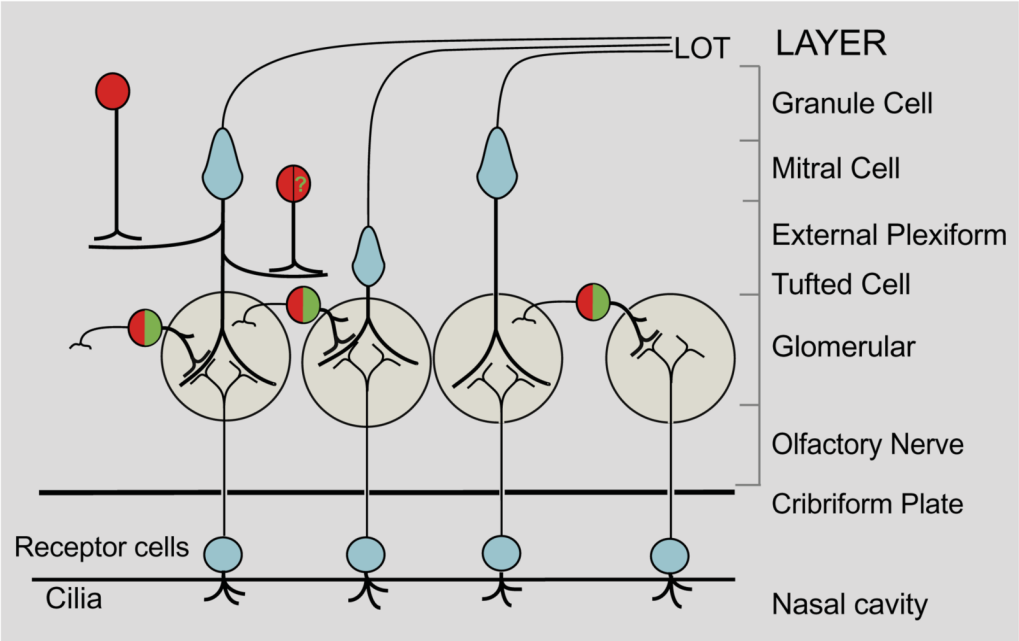

Figure 2.
Schematic representation of selected synaptic connections in the olfactory system. Axons from olfactory receptor neurons (small blue circles) make axo-dendritic synapses with apical dendrites of the mitral cells (large blue cells), tufted cells (small blue cell), and processes of PG cells, including the DA neurons (green). Axons from glutamatergic mitral/tufted cells are the primary output neurons of the OB through the lateral olfactory tract (LOT). DA interneurons are stimulated by both olfactory receptor neurons and mitral/tufted neurons. Mitral/tufted neurons also make dendro-dendritic synapses with granule cell interneurons. Both DA PG and granule cells express GABA (red). A population of granule cells in the mitral cell layer (red cell with green "?") express GABA and TH mRNA, but not TH protein.

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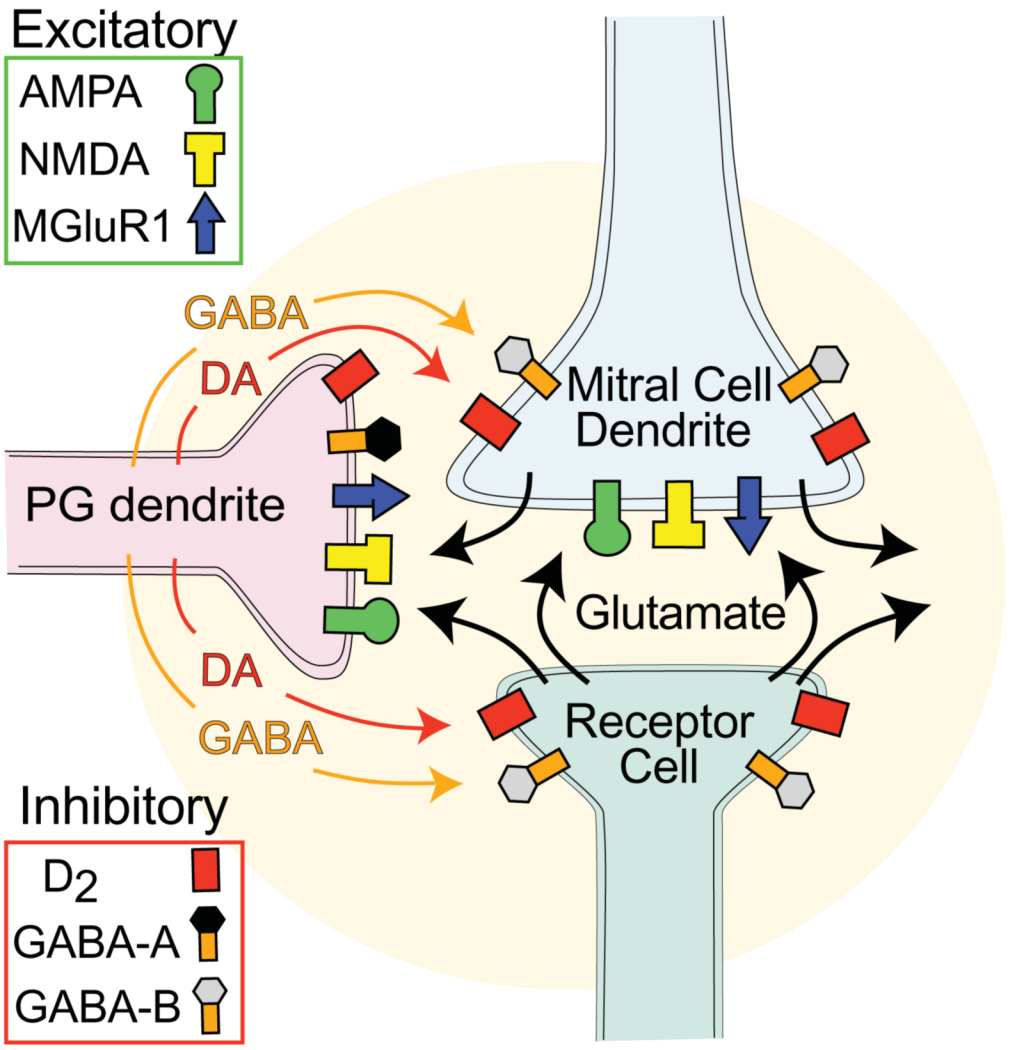

Figure 3.
Schematic representation of selected neurotransmitters and their cognate receptors in OB glomeruli. Olfactory receptor axon terminals release glutamate that excite mitral/tufted and PG cells through AMPA, NMDA and mGluR1 receptors. PG DA neurons release both DA and GABA that inhibit both olfactory receptor and mitral/tufted neurons through D_2 and GABA-B receptors. GABA can also inhibit PG neurons through GABA-A receptors.

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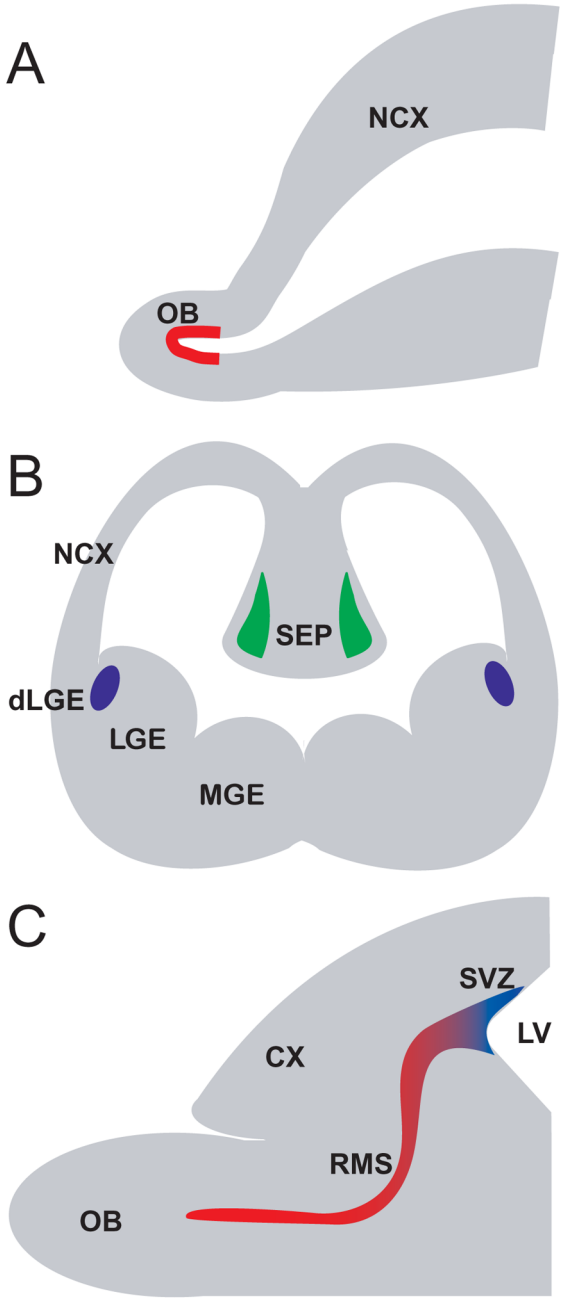

Figure 4.
Schematic representation of embryonic and post-natal origins of OB DA neurons. (**A**) The earliest reported origin of DA cells are derived from stem cells in the evaginating telencephalon (red layer), at approximately E13.5 in the mouse. (**B**) Mid-embryonically derived OB DA neurons originate from the dorsal lateral ganglionic eminence (blue regions) and the medial septum (green regions), at about E16.5 in the mouse. (**C**) Post-natally and adult derived OB DA neurons are generated from progenitors in the subventricular zone of the lateral ventricle. These progenitors migrate to the OB through the rostral migratory stream, which is also a putative source for some OB DA neurons. Abbreviations: CX, cortex; dLGE, dorsal lateral ganglionic eminence; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence;

NCX, neocortex; OB, olfactory bulb; RMS, rostral migratory stream; SVZ, subventricular zone.

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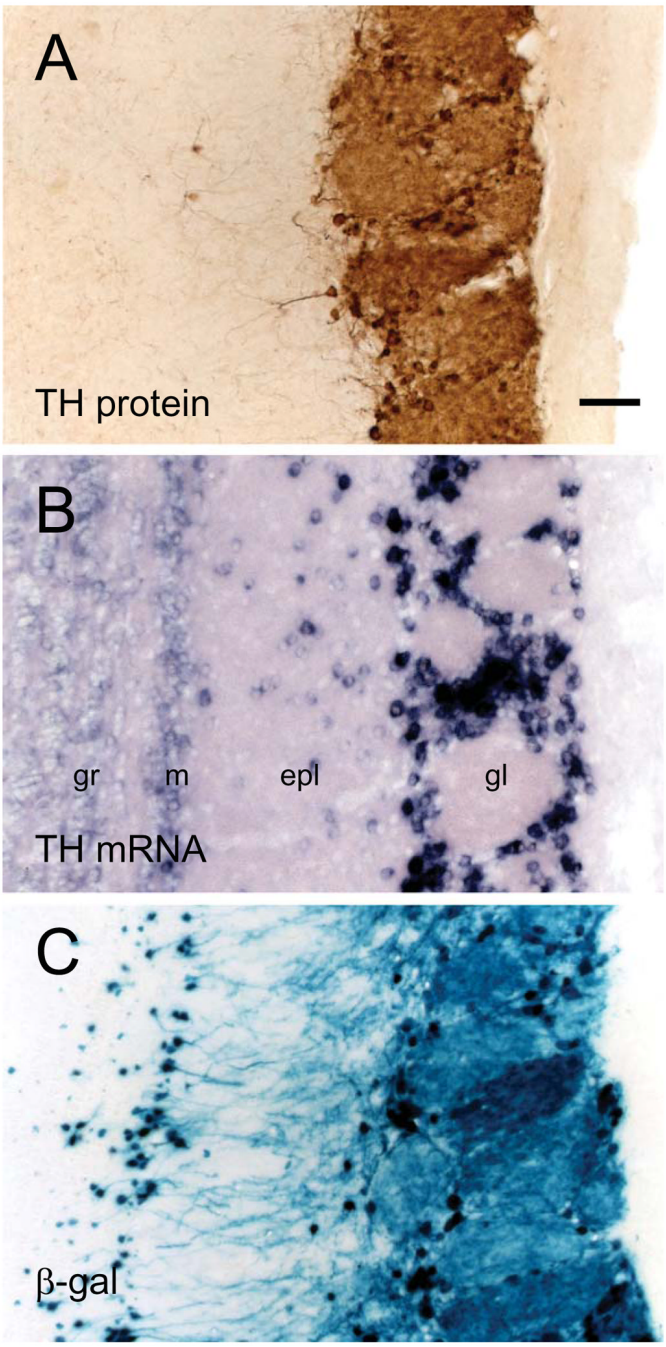

Figure 5.
Patterns of both TH protein and TH mRNA expression as well as TH/LacZ reporter gene activity in the adult OB. (**A**) TH protein immunoreactivity is restricted to the glomerular layer. (**B**) High level expression of TH mRNA is seen both in the glomerular layer and in cells scattered in the external plexiform layer. Lightly-labeled cells are found in the mitral and superficial granule cell layers. (**C**) An X-gal stained section reveals expression of the LacZ reporter gene under the control of the 9kb upstream TH gene regulatory region. X-gal activity can be detected in the same layers as the TH mRNA. Bar = 50 μm. Abbreviations: epl, external plexiform layer; gl, glomerular layer; gr, superficial granule cell layer; m, mitral cell layer.

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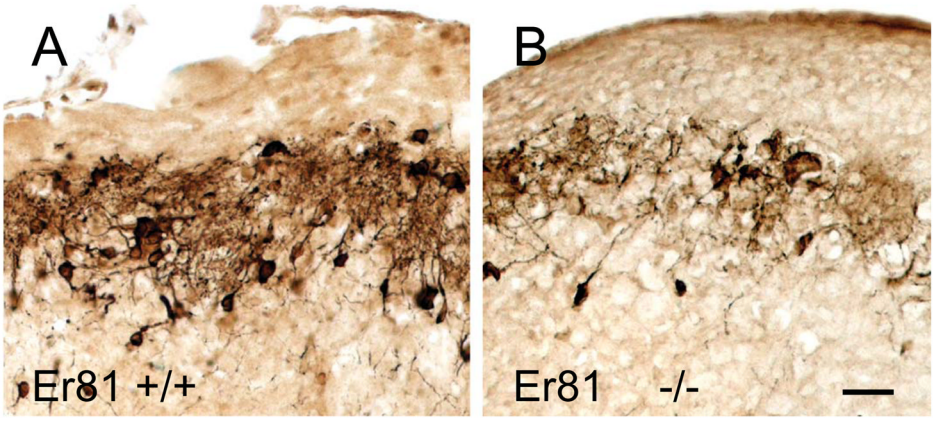

Figure 6.
TH immunoreactivity in wild-type and Er81-mutant mice. (**A**) TH immunoreactivity in the OB glomerular layer of a wild-type mouse. (**B**) Homozygous mutation of the Er81 gene drastically reduces TH immnoreactivity. Bar = 20 μm.

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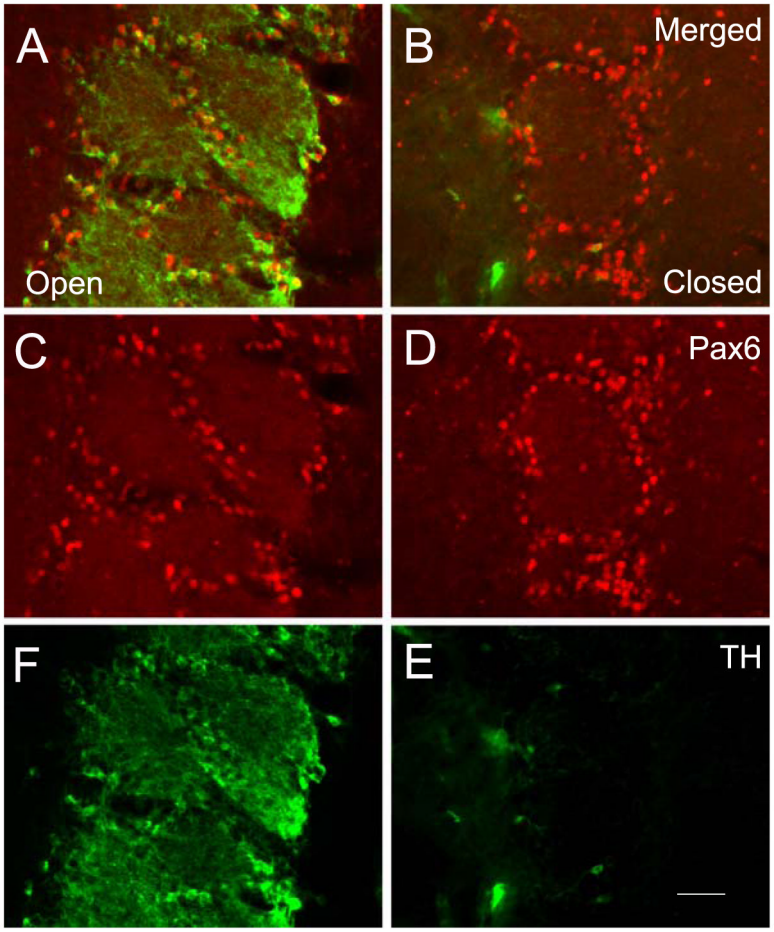

Figure 7.

Pax6 and TH expression in the glomerular layer of an adult mouse with unilateral naris closure. Expression of Pax6 and TH is red and green, respectively. As shown in (**A**, **C** and **F**), almost all neurons with perikaryal TH immunofluorescence also contain Pax6 in the OB contralateral to naris closure, although there are several cells with Pax6 that lack TH. As shown (**B**, **D** and **E**), Pax6 immunofluorescence in the OB ipsilateral to the naris closure is unchanged even though only a few cells express TH. Bar = 100 μm.

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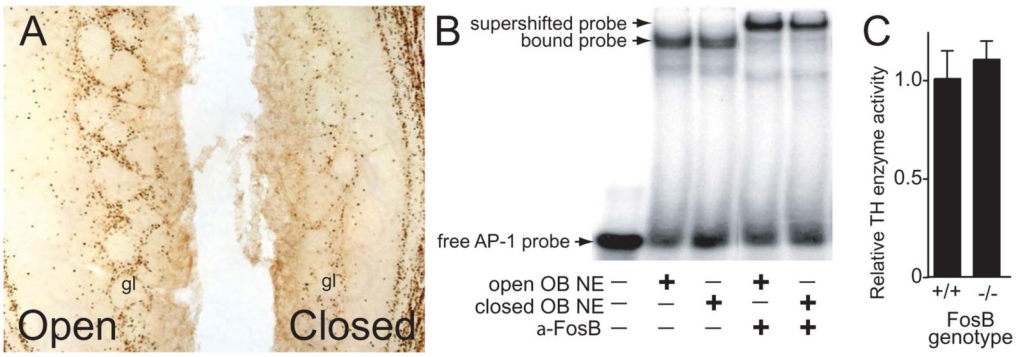

Figure 8.

Functional redundancy of FosB in the regulation of TH within the OB. (**A**) Immunohistochemistry in an adult mouse with unilateral naris closure reveals that FosB expression in the glomerular layer (gl) is dependent on olfactory neuron afferent synaptic activity (cf. open versus closed). (**B**) FosB antibody super-shift electromobility gel-shift assays reveal that FosB is present in OB nuclear extracts (OB NE) and can bind a probe containing the AP-1 binding site in the TH proximal gene promoter. The FosB supershift with OB NE ipsilateral to unilateral naris closure (closed) presumably results from residual FosB expression. (**C**) Relative TH enzyme activity in the OB is not significantly different in mice lacking FosB relative to wild-type mice.

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Table 1

Potential Key Regulators of OB DA Interneuron Differentiation	
AP-1	Heterodimer formed by members of the Fos and Jun basic-leucine zipper transcription factors; several Fos and Jun family members are expressed in the OB and the expression of some members is dependent on olfactory neuron afferent synaptic activity (Liu 1999); mutation of AP-1 binding site in TH proximal promoter eliminates reporter gene expression in the OB of transgenic mice;[94] OB expression of FosB and JunD is activity dependent and both proteins in OB cell lysates bind an AP-1 binding site in the TH promoter.[117]
CREB	Basic-leucine zipper transcription factor; CREB is expressed in the post-natal OB granule and glomerular layers;[117] mutation of an evolutionarily conserved CRE binding site in TH proximal promoter eliminates reporter gene expression in the OB of transgenic mice.[116]
Dlx-family	Homeodomain transcription factors; Dlx1,2,5,6 are expressed in the LGE and post-natal SVZ, RMS and OB;[66, 74–76, 93, 142–144] Dlx2 is expressed in transit amplifying cells and migrating neuroblasts within the SVZ and RMS;[91] mice lacking Dlx1 or Dlx2 have a modest or strong reduction of OB TH+ cells, respectively, whereas mice lacking both Dlx1 and Dlx2 have a near total loss of OB TH+ cells;[145, 146] mice lacking Dlx5 have a strong reduction in the number of OB TH+ cells;[75] TH+ cells in the OB overlap with reporter gene expression driven by a Dlx5/6 gene regulatory fragment.[90, 92]
Er81	ETS-DNA binding domain transcription factor is expressed in the dLGE, SVZ, RMS and OB;[66, 77] Er81 is co-expressed with TH in periglomerular interneurons;[77] Er81 expression in the OB is activity dependent;[77] there is a major loss of TH+ cells in homozygous Er81 mutant mice (Cave and Baker, unpublished).
Gsh2	Homeodomain transcription factor protein; expressed in the embryonic LGE and post- natal SVZ, RMS and OB[67, 79, 147]; mice lacking Gsh2 have a large loss of OB TH+ cells.
Meis2	TALE homeodomain protein; Meis2 is expressed in the embryonic LGE as well as the post-natal SVZ, RMS and OB;[90] Meis2 is co-expressed in OB TH+ cells.[90]
Nurr1/NGFI-B	Homologous orphan nuclear receptor transcription factors; both proteins are expressed in the superficial granule cell and glomerular layers of OB in a synaptic activity-dependent manner;[117] TH proximal promoter contains a functional Nurr1 binding response element.[110, 111]
Pax6	Paired box and homeodomain transcription factor; Pax6 is expressed in the embryonic dLGE and post-natal SVZ, RMS and OB;[78, 87–89] nearly all TH+ cells in OB also co- express Pax6 and there is an almost total loss of OB TH+ cell in mice heterozygous for Pax6 Sey mutation.[87]
Zic1,3	Zinc finger transcription factors; Zic1,3 are expressed in the embryonic septum as well as the glomerular and granule cell layers of the post-natal OB;[71] mice lacking both Zic1 and Zic3 have a significant loss of OB interneurons, including TH+ cells.[71]

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Table 2

Non-specific Regulators of OB Interneuron Differentiation	
Arx	Homeodomain transcription factor; Arx is expressed in the embryonic LGE as well as the post-natal SVZ, RMS and OB,[128, 148] mice lacking Arx have impaired SVZ-progenitor proliferation and migration as well as a substantial loss of TH+ cells in the OB.[128]
Dcx	Microtubule-associated phosphoprotein; migrating neuroblasts in the post-natal SVZ, RMS and OB express Dcx,[149–151] knock down of Dcx diminishes migration of SVZ- derived neuroblasts.[152]
Ephrins	Ephrins are membrane-bound ligands for Eph receptor tyrosine kinases; ephrins A2, B2 and B3 and Eph receptors A4, A7 and B1–3 are expressed in the post-natal SVZ and RMS where they regulate progenitor proliferation and migration.[153, 154]
Mash1	Basic-helix-loop-helix transcription factor; Mash1 is expressed in the embryonic LGE[76, 155–157] as well as the post-natal SVZ and RMS;[158] transit amplifying precursor cells express Mash1, and loss of Mash1 substantially reduces the number of TH+ cells in the OB [158].
Myst4	Histone acetyltransferase; Myst4 is expressed in the embryonic LGE and post-natal SVZ;[159] Myst4 is critical for progenitor proliferation, and mice lacking Myst4 have a progressive loss of TH+ cells in the OB.[159]
Notch1	Transmembrane receptor that proteolytically releases a transcription co-activator upon ligand binding; Notch1 and its ligands Jagged1 and Delta1 as well as its downstream target gene Hes5 are expressed in the post-natal SVZ and RMS[160–164]; Notch1 is critical for proliferation of SVZ progenitors, and over-expression of activated Notch1 drastically reduces the number of SVZ-derived migrating progenitors.[127]
Olig2	Basic helix-loop-helix transcription factor; Olig2 is expressed in the transit amplifying precursor cell;[16, 165] positive regulator of oligodendritic cell fates and negative regulator of neuronal lineages in precursor cells.[16]
PK2	Cysteine-rich secreted protein; PK2 and its receptors are expressed in complementary patterns within embryonic and post-natal OB where PK2 acts as a chemoattractant for migrating SVZ-derived progenitors;[166] periglomerular layer is indiscernible or malformed in mice lacking PK2.[166]
PSA-NCAM	Polysialylated neural cell adhesion molecule; PSA-NCAM is expressed in migrating neuroblasts and is critical for tangential migration in the SVZ and RMS.[167–170]
Reelin	Secreted glycoprotein that promotes shift from tangential to radial migration of SVZ- derived progenitors in the OB;[171] in the OB, Reelin is highly expressed in the olfactory nerve layer, mitral cell layer and in a descending gradient through the granule cell layer;[171] the Reelin receptor ApoER2 is strongly expressed in the RMS.[171]
Shh	Secreted signaling protein; Shh is expressed in the slowly dividing neural stem cell and the transit amplifying cell (type B and C cells, respectively) in the post-natal SVZ, and Shh is critical for maintenance and proliferation of these cells.[172–174]
Slit1, 2	Secreted ligand proteins that bind Robo receptors; Slit1,2 are expressed in both embryonic and post-natal septum whereas the Robo1,2 receptors are expressed in the post-natal SVZ and RMS;[175–178] Slit proteins are chemorepellants that guide migrating SVZ-derived progenitors.[175, 178–180]
Tenascin-R	Extracellular matrix glycoprotein that promotes radial migration of progenitor cells by initiating detachment of tangentially migrating SVZ-derived neuroblasts;[181] in the post- natal OB, Tenascin-R is expressed in the granule cell and internal plexiform layer, and is dependent on olfactory receptor neuron synaptic activity.[181]
Vax1	Homeodomain transcription factor; Vax1 is expressed in the embryonic LGE [182] as well as the post-natal SVZ and RMS;[183] loss of Vax1 results in disorganization of the RMS and impaired OB interneuron progenitor migration.[183]

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Table 3

Regulators of OB DA Differentiation Through Olfactory Neuron Innervation of the OB	
Arx	Homeodomain transcription factor; Arx is expressed in the embryonic LGE as well as the post-natal SVZ, RMS and OB;[128] mice lacking Arx have a loss of olfactory neuron innervation of the OB and a substantial decrease of TH+ cells in the OB.[128, 184]
Dlx5	Homeodomain transcription factor; Dlx5 is expressed in the LGE, SVZ, OB as well as olfactory epithelium and olfactory placode;[185] in mice lacking Dlx5, olfactory receptor neurons fail to properly innervate the OB and there is a strong reduction in the number of OB TH+ cells.[185]
CNG2	Transmembrane cyclic AMP gated channel; CNG2 (OCNC1) is expressed in the olfactory epithelium and is required for signal transduction in olfactory receptor neurons; loss of CNG2 results in abnormal pruning of olfactory receptor neuron fibers, as well as a block of afferent olfactory receptor neuron synaptic activity in the OB which dramatically reduces TH expression.[42]
Zic1,3	Zinc finger transcription factors; olfactory receptor neurons fail to properly innervate the OB in mice lacking both Zic1 and Zic3.[71]