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Neurochemical Organization of the Ventral Striatum's Olfactory Tubercle

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Abstract

The ventral striatum is a collection of brain structures, including the nucleus accumbens, ventral pallidum, and the olfactory tubercle (OT). While much attention has been devoted to the nucleus accumbens, a comprehensive understanding of the ventral striatum and its contributions to neurological diseases requires an appreciation for the complex neurochemical makeup of the ventral striatum's other components. This review summarizes the rich neurochemical composition of the OT, including the neurotransmitters, neuromodulators, and hormones present. We also address the receptors and transporters involved in each system, as well as their putative functional roles. Finally, we end with briefly reviewing select literature regarding neurochemical changes in the OT in the context of neurological disorders, specifically neurodegenerative disorders. By overviewing the vast literature on the neurochemical composition of the OT, this review will serve to aid future research into the neurobiology of the ventral striatum.

Graphical Abstract

The olfactory tubercle is a structure within the ventral striatum that has received relatively little attention. In this review, we provide a detailed summary of the olfactory tubercle's rich neurochemistry, including the neurotransmitters present, as well as their associated receptors, transporters, and putative functions. In addition, we briefly review the literature pertaining to neurochemical changes in the olfactory tubercle in neurodegenerative disorders. This review will serve to aid future research into the olfactory tubercle and the ventral striatum as a whole.

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Keywords

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Introduction

The ventral striatum is a collection of brain structures, including the nucleus accumbens, ventral pallidum, and the olfactory tubercle (OT) (De Olmos and Heimer 1999). While much attention has been devoted to the nucleus accumbens, a comprehensive understanding of the ventral striatum and its contributions to neurological diseases requires an appreciation for the complex neurochemical makeup of the ventral striatum's other components, including the OT.

Before addressing the neurochemical composition of the OT, first some general orientation to this structure is warranted. The OT is located in the basal forebrain of all mammals, situated within the ventral striatum immediately beneath the ventral pallidum and nucleus accumbens (Fig. 1). Interestingly, it also serves as an olfactory cortex. Indeed, while the OT shares cellular features with other regions of the ventral striatum (Martin-Lopez et al. 2019; Ikemoto 2007; De Olmos and Heimer 1999), it also receives primary sensory input directly from the olfactory bulb, and has a distinctively non-uniform trilaminar structure (Pigache 1970; Millhouse and Heimer 1984). The OT's layer 1 is the most superficial layer, also referred to as the molecular or plexiform layer, and is the site of olfactory bulb input (Scott et al. 1980). Layer 2, also referred to as the dense cell layer, is (unsurprisingly) densely populated with cell bodies. Layer 3 is the deepest and thickest layer, often called the multiform or polymorph layer, and is the site of association fiber input from the piriform cortex (Luskin and Price 1983; Schwob and Price 1984a). Throughout this review, we will simply refer to these as layers 1-3. The OT also possesses dense, distinctive clusters of granule cells, most often found in layer 3, referred to as the Islands of Calleja (ICj) (Millhouse and Heimer 1984; Millhouse 1987; Hsieh and Puche 2013; Adjei et al. 2013; Adjei and Wesson 2015).

Most of our current understanding of OT neurochemistry comes from classic autoradiography, immunohistochemistry, and *in situ* hybridization studies characterizing expression of neurotransmitters and receptors throughout the whole rodent brain. While these studies provided important data on the neurochemical organization of the brain, they often did not focus on the OT, and therefore do not always provide information regarding

layer-, cell-type-, and cell-compartment-specific expression in the OT specifically. We thus avoid being overly declarative in stating a receptor does or does not exist in specific OT cells (for instance) but refer to whether or not a method uncovered it. Similarly, minimal information is available regarding the physiological role of each of these systems for OT function. That stated, this review will provide a primary resource for our current knowledge of OT neurochemistry by summarizing its neurochemical composition. This includes its neurotransmitters, neuromodulators, and hormones present, as well as the receptors and transporters involved in each system. We also provide brief discussion on the functional roles of these systems. Finally, we discuss the ways in which the neurochemical composition of the OT may change in cases of neurological disease. Throughout this review, we identify several knowledge gaps, which will be important to fill in order to advance our understanding of this brain system. Notably, this review is not meant to cover all known aspects of the OT, and readers are encouraged to seek other content from these sources which provide additional information on the OT's anatomy and physiology (Wesson and Wilson 2011; Ikemoto 2007; Xiong and Wesson 2016; Millhouse and Heimer 1984; Scott et al. 1980; Murata et al. 2015; Wieland et al. 2015; Schwob and Price 1984b; Payton et al. 2012; Carlson et al. 2014; Carlson et al. 2018; Gadziola et al. 2015; Gadziola and Wesson 2016; Agustín-Pavón et al. 2014).

GABA

Sources of GABA in the OT

Like other striatal regions, the OT is composed primarily of GABAergic neurons, including local interneurons and medium spiny neurons (MSNs, also called 'spiny projection neurons') which may provide long-range projections outside of the OT itself, including into other striatal regions and into midbrain structures (Millhouse and Heimer 1984; Zhang et al. 2017b). While MSNs are located in all layers of the OT, many are packed densely into layer 2. Granule cells within the ICj are also GABAergic, exhibiting strong immunoreactivity for GAD65 and GAD67 (Riedel et al. 2002; Hsieh and Puche 2013; Krieger et al. 1983a). These cells possess small, thin axons and dendrites, which appear to primarily project locally within the ICj (Millhouse 1987; Millhouse and Heimer 1984), suggesting they mostly provide intra-ICj GABAergic signaling.

GABAergic interneurons in the OT are immunoreactive for multiple interneuron markers including parvalbumin (Zahm et al. 2003; Koos and JM 1999), calretinin (Riedel et al. 2002; Seifert et al. 1998; Helboe et al. 2015), calbindin (Riedel et al. 2002; Seifert et al. 1998; Helboe et al. 2015), vasoactive intestinal peptide (VIP) (Brunjes et al. 2011), neuropeptide Y (NPY) (Woodhams et al. 1985; Ubeda-Bañón et al. 2008), somatostatin (Finley et al. 1978), reelin (Ramos-Moreno et al. 2006; Martin-Lopez et al. 2019), and cholecystokinin (CCK) (Brunjes et al. 2011). Calbindin-expressing interneurons are scarce within the OT, and are found primarily in layer 3, with some cells also in layer 2 (Martin-Lopez et al. 2019). Notably, calbindin-immunoreactive fibers in the OT tend to be spatially segregated from areas which are void of tyrosine hydroxylase (TH) (Riedel et al. 2002). Parvalbumin-expressing interneurons are also found throughout the OT (Zahm et al. 2003), with the majority of these neurons in layer 3, and some in layer 2 (Martin-Lopez et al. 2019). The

majority of reelin-immunoreactive neurons are found in layer 1 in the most medial portion of the OT (Martin-Lopez et al. 2019). While some CCK-positive neurons are found within the OT (Brunjes et al. 2011), the majority of CCK immunoreactivity in the OT appears in terminal fibers arising from other regions, including the ventral tegmental area (VTA) (Záborszky et al. 1985).

GABA receptor expression in the OT

There are two major classes of GABA receptors in the brain (GABA_A and GABA_B), both of which are abundantly expressed within the OT (Table 1). GABA_A receptors are ligand-gated Cl⁻ channels composed of 5 homologous or heterologous subunits, of which there are 19 varieties (Olsen and Sieghart 2008). The rat OT shows strong diffuse immunoreactivity for the α 2, α 4, and β 3 subunits, moderate immunoreactivity for the δ subunit, and weak immunoreactivity for other GABA_A subunits (Pirker et al. 2000; Schwarzer et al. 2001). Strong immunoreactivity for the α 1 and β 2 subunits is restricted to the ventral pallidum and possibly the ICj, but is weak to moderate throughout the rest of the OT (Schwarzer et al. 2001). At the level of individual soma, interneurons show immunoreactivity for α 1, β 2, α 5, and δ , while MSNs are immunoreactive for γ 3 (Schwarzer et al. 2001). Neuronal processes exhibit immunoreactivity for the α 1 and β 2 subunits (Schwarzer et al. 2001).

GABA_B receptors are G-protein-coupled receptors (GPCRs) that regulate Ca²⁺ and K⁺ channels. There are 3 GABA_B receptor genes (GABA_{B1a}, GABA_{B1b}, and GABA_{B2}), which heterodimerize to form a functional GABA_B receptor (Kaupmann et al. 1998; Marshall et al. 1999). GABA_{B2} receptor mRNA is present at weak levels throughout the OT, but is completely absent from the ICj (Durkin et al. 1999). The OT also shows strong immunoreactivity for all subunits throughout all layers, which appears to be strongest in layer 2 for the GABA_{B1b} and GABA_{B2} subunits (Charles et al. 2001).

GABA transporters in the OT

Of the 4 GABA transporters, GAT1 and GAT3 are the two expressed in the central nervous system (for review, see (Zhou and Danbolt 2013)). GAT1 is primarily found presynaptically in GABAergic neurons, as well as some astrocytes (Minelli et al. 1995). In the OT, GAT1 mRNA is found at high levels in layer 1, and weakly in the ICj (Durkin et al. 1995). GAT3 expression is mostly restricted to astrocytic processes throughout the brain, although the OT has not been specifically investigated (Minelli et al. 1996).

Functional role of GABA signaling in the OT

In addition to its role as the major inhibitory neurotransmitter in the brain, GABA also plays an important role as a neural migration guidance cue during early postnatal development of the ICj (Hsieh and Puche 2015). ICj neurons are derived from subventricular zone neurons which migrate along a ventral pathway to the ventral striatum during the first postnatal week (De Marchis et al. 2004). Migrating neurons exclusively express the α 3 subunit of the GABA_A receptor during migration, and switch to expressing the α 1 and α 5 subunits once they form the ICj (Hsieh and Puche 2015). Further, disruption of GABA signaling with muscimol results in slower migration, indicating the functional importance of GABA signaling through GABA_A receptors during the development of the ICj (Hsieh and Puche

2015). Similarly, mRNA for the $\beta 1$ and $\beta 2$ subunits of the GABA_A receptor are transiently expressed in the OT during development, suggesting they may also play a role in the development of the OT (Zhang et al. 1991).

Glutamate

Sources of glutamate in the OT

One major source of glutamatergic input to the OT comes from olfactory bulb projections to OT layer 1 (White 1965; Fuller and Price 1988), primarily the anterolateral portion (Scott et al. 1980). These terminals are easily visualized by their calretinin immunoreactivity (Martin-Lopez et al. 2019). While mitral and tufted cells may both target the OT (Igarashi et al. 2012), the majority of inputs come from tufted cells (Scott et al. 1980; Nagayama et al. 2010; Scott 1981). Another major glutamatergic projection to the OT comes from the piriform cortex, which targets primarily the anterolateral OT (Luskin and Price 1983; Carriero et al. 2009; Schwob and Price 1984b; White et al. 2019). The bulk of this projection originates in the ventral-caudal aspect of the anterior piriform cortex (White et al. 2019) and targets all layers of the OT, with the densest fibers in layer 2 (Schwob and Price 1984b; Schwob and Price 1984a; White et al. 2019). Aside from these major sources of glutamatergic input, midbrain dopamine (DA) neurons co-release glutamate in the OT (Wieland et al. 2014; Mingote et al. 2015). Glutamate co-release also likely occurs from cholinergic interneurons (CINs) and brainstem serotonergic neurons (Gras et al. 2002; Trudeau and El Mestikawy 2018), but the functional role for this in the OT is not known.

Glutamate receptor expression in the OT.

There are two major classes of glutamate receptors in the brain: ionotropic and metabotropic. The OT abundantly expresses glutamate receptors from both classes (Table 2). Ionotropic glutamate receptors include AMPA receptors (AMPA receptors) and Kainate receptors, which are ligand-gated ion channels, and NMDA receptors (NMDARs), which in addition to being ligand-gated are voltage-gated by a Mg^{2+} plug. Autoradiographic analysis of each family of glutamate receptors revealed high expression of each of these types of glutamate receptor in the OT (Albin et al. 1992). AMPARs are homo- or hetero-tetramers assembled from a combination of four subunits, which are abbreviated as GluA1-4 (for review see (Greger et al. 2017)). AMPARs are present at high levels in the OT, as evidenced by autoradiographic (Albin et al. 1992) and immunohistochemical studies (Petrulia and Wenthold 1992). Specifically, GluA1-3 protein is present at high levels, and GluA4 at moderate levels, in the OT (Petrulia and Wenthold 1992), but cell-type- and layer-specific expression of AMPAR subunits has not been specifically investigated.

Kainate receptors are also homo- or hetero-tetramers assembled from a combination of five subunits, which are abbreviated as GluK1-5 (previously known as GluR5-7 and KA1-2; for review, see (Lerma and Marques 2013)). GluK1 mRNA is high in the granule cells of the ICj and is almost absent from the rest of the OT, while GluK2 is high in the cells just surrounding the ICj (Bischoff et al. 1997). Layer 2 contains high levels of GluK2 and GluK5 mRNA, and moderate levels of GluK3 mRNA (Bischoff et al. 1997). Similarly, layer 3 contains high levels of GluK2 and moderate levels of GluK3 (Bischoff et al. 1997).

NMDA receptors are tetramers composed of four subunits, which are abbreviated as GluN1-3. One NMDA receptor is composed of two GluN1 along with two GluN2 (GluN2A-D) or GluN3 (GluN3A-B) subunits (for review, see (Paoletti et al. 2013)). An *in situ* hybridization study of the GluN1 and GluN2 subunits revealed high levels of expression of GluN1, GluN2A, and GluN2B, low expression of GluN2D, and no expression of GluN2C in the OT (Standaert et al. 1999). At the level of protein, the OT contains GluN2A at intermediate levels and GluN2B at high levels (Wang et al. 1995).

There are 8 known variants of metabotropic glutamate receptors (mGluRs), which are GPCRs. mGluRs are divided into groups based on the specificity of agonists/antagonists and their downstream effectors: Group 1 mGluRs include mGluR1 and mGluR5, both of which are found in the OT according to autoradiographic (Lavreysen et al. 2003; Mutel et al. 2000) and immunohistochemical evidence (Cowen et al. 2005). Group 2 mGluRs include mGluR2 and mGluR3, which are also both found in the OT. Specifically, mGluR2 is expressed weakly in layer 1 and moderately in layers 2 and 3, while mGluR3 is expressed strongly in all layers of the OT (Tamaru et al. 2001; Wada et al. 1998). Group 3 mGluRs include mGluRs 4, 6, 7, and 8. mGluR7a and 8 are located in the axon terminals of projecting olfactory bulb neurons in layer 1 of the OT (Wada et al. 1998). mGluR4 and mGluR7 mRNA is expressed in the OT (Ohishi et al. 1995), and mGluR7a and 7b protein is expressed within the ICj (Kinoshita et al. 1998).

Glutamate transporters in the OT

There are five known mammalian excitatory amino acid transporters (EAAT1-5; for review see (Zhou and Danbolt 2013)), with EAAT1-4 expressed highly in the brain. EAAT 1 and 2 are strongly expressed selectively in glia (Danbolt et al. 1992; Levy et al. 1993) and EAAT2 mRNA (also known as GLT-1 in humans) is detected in the OT (Berger et al. 2005). EAAT3 is expressed in neurons throughout the whole brain (though this has not been specifically examined in the OT), and is localized to the soma and dendrites, but not axon terminals (Shashidharan et al. 1997). EAAT4 is most highly expressed in the cerebellum, but is also found throughout the rodent forebrain, including the ventral striatum (though the OT was not specifically investigated) (Massie et al. 2008).

Vesicular glutamate transporters 1-3 (VGLUT1-3) are present in the OT (Herzog et al. 2004; Freneau et al. 2001; Gras et al. 2002). VGLUT1 and 2 are expressed in axon terminals throughout the brain, and exhibit differential expression patterns in the OT, with VGLUT1 highly expressed in layers 1 and 2, while VGLUT2 is expressed at lower levels primarily in layer 3 (Freneau et al. 2001). VGLUT3 is not expressed as widely throughout the brain, but is nevertheless seen at high levels in the OT, with the highest levels of expression in layers 1 and 3 (Herzog et al. 2004). Interestingly, VGLUT3 is co-expressed with acetylcholine (ACh) and serotonin (5-HT) transporters in the striatum, suggesting that some CINs in the striatum and serotonergic brainstem neurons may co-release glutamate (Gras et al. 2002; Trudeau and El Mestikawy 2018).

Functional role of glutamate in the OT and interactions with other systems

Few studies have investigated the precise mechanisms by which glutamate neurotransmission modulates activity in the OT. White et al. (2019) explored the influence of glutamatergic input from the piriform cortex to the OT, and found that optogenetic stimulation of association fiber terminals in the mouse OT modulates odor-evoked single-unit responses of OT neurons (White et al. 2019). Specifically, odor-excited units are less excited with association fiber stimulation, while odor-suppressed units are less suppressed with stimulation, indicating that these glutamatergic projections may influence the encoding of odors in the OT (White et al. 2019). To better understand the role of glutamate corelease from midbrain dopamine neurons, Wieland et al. (2014) recorded from CINs in acute slices while optogenetically stimulating VTA projections to the OT. This revealed a glutamatergic aspect of the light-evoked response, mediated by both NMDAR and AMPAR components. This glutamate co-release along with DA from the midbrain exerts control over the firing patterns of OT CINs, which may play an important role in olfactory stimulus selection, and allows midbrain dopamine neurons to modulate activity in the OT on fast timescales as well as slow neuromodulatory timescales (Wieland et al. 2014). Mingote et al. (2015) recorded from putative MSNs in the OT while stimulating VTA projections and found that the glutamatergic component was completely blocked by AMPAR/Kainate antagonists (Mingote et al. 2015), in contrast to CINs which included an NMDAR component (Wieland et al. 2014).

Dopamine

Sources of Dopamine in the OT

DAergic neurons from the ventral tegmental area (VTA), which form the mesolimbic projection pathway, project to the OT as well as the nucleus accumbens (Watabe-Uchida et al. 2012; Mingote et al. 2015; Zhang et al. 2017a; Del-Fava et al. 2007). These fibers begin to innervate the OT as early as mouse embryonic day 13, and progressively arborize from layer 3 to layer 1 in an 'inside-out' gradient (Martin-Lopez et al. 2019). Specifically, DAergic VTA projection fibers innervate the medial OT from the posteromedial VTA, the interfascicular nucleus, and central linear nucleus (Ikemoto 2007). Synaptic connectivity between DAergic projections and OT neurons is increasingly evident (Watabe-Uchida et al. 2012; Ikemoto 2010; Mingote et al. 2015). While DA is certainly a major transmitter in the OT, VTA DAergic neurons also co-release glutamate, thereby yielding more complex effects (Mingote et al. 2015; Wieland et al. 2014).

Dopamine receptor and transporter expression in the OT

DA receptors mediate the diverse functional effects of DA neurotransmission in the brain. There are five types of DA receptors (*i.e.*, D1-D5) which are categorized into two families. The D1-like receptor family (D1 and D5) are GPCRs acting on G_s that ultimately increase intracellular cAMP while the D2 like receptor family (D2, D3, and D4) act on G_i and ultimately reduce cAMP (for review, please see (Missale et al. 1998; Surmeier et al. 2007)). The OT contains D1, D2, and D3 receptors and is comprised primarily of D1- or D2-type DA receptor expressing MSNs (Murata et al. 2015) which make up 90-95% of all OT neurons (Le Moine and Bloch 1995; Soares-Cunha et al. 2016). In the OT, D1 and D3 are

co-expressed among interneuron populations in the ICj (Le Moine and Bloch 1996; Huang et al. 1992; Diaz et al. 1997) whereas D2 and D3 seem to co-express to a much lesser extent (Bouthenet et al. 1991; Diaz et al. 1995; Murray et al. 1994).

The DA transporter (DAT) is an integral membrane protein allowing for homeostasis of synaptic DA (Torres et al. 2003; Sonders et al. 1997). The OT has robust DAT immunoreactivity, which is consistent with its midbrain DA fiber innervation (Freed et al. 1995; Ciliax et al. 1995; Vaughan et al. 1996; Revay et al. 1996; Vastenhouw et al. 2007).

Functional role of Dopamine signaling in the OT

DA is an important neurotransmitter for motivation (Wise 2004), learning (Redgrave et al. 1999; Pan 2005), reinforcement (Ikemoto 2007), and driving many behavioral responses (Ikemoto 2007). In both rodents and humans, the OT is implicated in odor hedonics and valence, as well as motivated behaviors (DiBenedictis et al. 2015; FitzGerald et al. 2014; Gadziola and Wesson 2016; Gadziola et al. 2015; Murata et al. 2015; Wesson and Wilson 2010; Wesson and Wilson 2011; Zelano et al. 2005).

Rodents readily self-administer intracranial micro-injections of psychostimulants into the OT (Ikemoto 2003; Ikemoto 2005). Specifically to cocaine, intra-OT infusions (through indwelling cannulae) are more robustly self-administered than into either the nucleus accumbens or ventral pallidum (Ikemoto 2003). These findings suggest a role for the OT in mediating the primary reinforcing effects of psychostimulants, which are driven by decreased DA uptake. Furthermore, rodents more greatly self-administer cocaine into the medial portion of the OT versus the lateral, implying unique roles for these OT subregions (Ikemoto 2003). *In vivo* voltammetry within the OT (*e.g.*, (Park et al. 2017)), or a related method to measure DA levels, may help uncover the basis for this interregional effect. DA release into the OT holds important influences on local OT neurons. For example, in acute slices of the OT, phasic DA release evokes a transient pause in CIN firing via D2 receptor activation (Wieland et al. 2014), which may be important for decision-making and behavior selection.

Consistent with DA's role in learning and reinforcement in other brain regions, OT DA is associated with the formation of learned odor preferences (Zhang et al. 2017a). Additionally, DAergic neuronal ablation in the medial OT via 6-OHDA microinjections reduce preference of sexually naïve female mice to investigate male urinary odors, while having no effect on the ability to discriminate between the odors (DiBenedictis et al. 2014). Together, these findings suggest that DA in the OT is critical for both learned and innate odor preferences, as well as the primary reinforcing effects of psychostimulants.

Acetylcholine

Sources of acetylcholine in the OT

CINs are large tonically active neurons (Aosaki et al. 1994; Morris et al. 2004) that make up a small fraction of striatal cells, each with a vast synaptic arbor that sends cholinergic projections throughout the striatum (Hebb and Silver 1961; Lim et al. 2014). CINs have been implicated in regulating the activation and modulation of striatal pathways in mice

(Centonze et al. 2003; Kaneko et al. 2000; Maurice et al. 2004; Tozzi et al. 2011; Cachope et al. 2012; Mamaligas and Ford 2016) and rats (Pisani et al. 2000). The matrix surrounding ventrostriatal MSNs is rich in cholinergic markers (Graybiel and Ragsdale 1978; Gerfen 1985; Alheid and Heimer 1988) and within the OT, the ICj are exceptionally rich in choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) (Talbot et al. 1988). Cholinergic input to the OT arrives from the horizontal limb of the nucleus of the diagonal band of Broca, nucleus basalis of Meynert (nbM), as well as the laterodorsal tegmentum and the pedunclopontine nuclei in the brainstem (Mesulam et al. 1983; Lauterborn et al. 1993; Koulousakis et al. 2019; Dautan et al. 2014). Specifically, neurons from the horizontal limb of the nucleus of diagonal band of Broca project throughout the ventral striatum, but vertical limb neurons appear to selectively target the OT (Dautan et al. 2016).

Acetylcholine receptor expression in the OT

CINs influence a wide range of postsynaptic targets through the activation of muscarinic and nicotinic acetylcholine receptors (mAChRs and nAChRs, respectively). mAChR activation can either decrease or increase cell excitability, and by virtue of its almost exclusive terminal expression, provides a long-term modulatory role in neurotransmitter release probability (Lim et al. 2014). There are 5 mAChR subtypes, which are broadly grouped as either excitatory (M1, M3, and M5) or inhibitory (M2 and M4) based upon their GPCR effectors (Wess 1996; Lin et al. 2004). Autoradiographic analyses indicate that while the OT has the greatest muscarinic receptor representation within the striatum (Corte 1986), and all subtypes are expressed in the striatum (Yan et al. 2001), only M1, M2, and M4 are reported in the OT, with the largest representation of M4 (Vilaró et al. 1991; Weiner et al. 1990; Vilaró et al. 1992). Specifically, while M4 immunoreactivity is present throughout the OT, its expression is remarkably high within the ICj (Wirtshafter and Osborn 2004). Regional differences in mAChR subunit expression throughout the striatum would convey different functional properties, which should be a subject of future research. Compared to mAChRs, nAChR activation is rapid and always has an excitatory effect. nAChRs are ligand-gated ion channels that can be expressed both pre or post synaptically, and induce depolarization and excitability (Lim et al. 2014). The pentameric structure of nAChRs includes α and β subunits ($\alpha 2$ - $\alpha 10$ and $\beta 2$ - $\beta 4$) (Patrick et al. 1993; McGehee and Role 1995; Dani 2001). The most highly expressed nAChR subunits in the striatum, as indicated by *in situ* hybridization, are $\alpha 4$, $\alpha 6$, $\alpha 7$, $\beta 2$, and $\beta 3$, however all other subunits are present at lower levels (Quik et al. 2007). Specifically, the nAChR subunits $\alpha 2$, $\alpha 4$, $\alpha 5$, $\alpha 6$ and $\beta 2$ have all been identified in the OT (Brown et al. 2007; Marubio et al. 2003; Drenan et al. 2008; Whiteaker et al. 2006; Metaxas et al. 2013; Ishii et al. 2005; Grady et al. 2002).

Acetylcholine transporter in the OT

ACh is synthesized by ChAT in the cytoplasm of cholinergic neurons and transported into synaptic vesicles by vesicular acetylcholine transporter (VACHT) (Whittaker 1988; Parsons et al. 1993; Usdin et al. 1995). While much of the striatum is rich in VACHT, the OT receives an especially dense innervation of VACHT positive fibers, with few VACHT positive neurons (Schäfer et al. 1994; Arvidsson et al. 1997; Gilmor et al. 1996; Ichikawa et al. 1997; Roghani et al. 1997; Donat et al. 2008; Sorger et al. 2009; Henny and Jones 2006). AChE hydrolyzes ACh in the synaptic cleft yielding choline and acetate, and choline uptake is

carried out by the high-affinity choline transporter, which is highly expressed in the OT (Misawa et al. 2001).

Functional roles of acetylcholine in the OT and interactions with other systems

ACh differentially modulates synaptic inputs to the OT: In acute slices, stimulation of either LOT fibers in layer 1 or association fibers in layer 3 evokes extracellular field potentials in layer 2, but layer 3-evoked responses exhibit much more significant depression in the presence of cholinergic agonists carbachol and muscarine (Owen and Halliwell 2001). Further, the authors speculate that this could be due to M4 receptors, which are present at high levels in the OT, but additional work is needed to support this hypothesis (Owen and Halliwell 2001). There are also notable interactions with DA and ACh in the OT, as mentioned above. The α_2 and β_2 subunits co-localize with DA receptors in the OT, influencing nicotine-induced DA release (Metaxas et al. 2013; Grady et al. 2002). The α_4 and α_6 subunits are also involved in nicotine-induced DA release in the OT (Drenan et al. 2008; Drenan et al. 2010; Cohen et al. 2012). Additionally, decreased ACh turnover in the OT was found following cocaine self-administration (Smith et al. 2003), which may be an effect of early drug withdrawal. Given DA's rapid control of OT cholinergic tone discussed above (Wieland et al. 2014), the behavioral significance of the interplay of DA along with ACh in the OT warrants further investigation.

Norepinephrine

Sources of norepinephrine in the OT

Norepinephrine (NE), also known as noradrenaline, is a catecholamine synthesized by noradrenergic neurons. The primary source of NE throughout the brain, and in the OT, comes from the locus coeruleus (LC) (Jones and Moore 1977; Guevara-Aguilar et al. 1982; Solano-Flores et al. 1980).

Norepinephrine receptor expression in the OT

NE receptors are broadly classified as either α_1 , α_2 , or β receptors, each of which has three subtypes (α_{1A-C} , α_{2A-C} , and β_{1-3}) (for review, see (Strosberg 1993; Bylund 1992). α_1 receptors are excitatory $G_{i/q}$ -coupled GPCRs, while α_2 receptors are inhibitory $G_{i/o}$ -coupled GPCRs. There are somewhat conflicting reports on the representation of α NE receptors in the OT. Some report weak mRNA and protein expression for α_1 receptors in rats and mice (Day et al. 1997; Strazielle et al. 1999), with even weaker α_2 protein expression (Strazielle et al. 1999). In contrast, others report quite strong α_{2C} mRNA expression (Scheinin et al. 1994) and weak α_{2C} protein expression in rats (Rosin et al. 1996) in layers 2 and 3. β receptors are G_s -coupled GPCRs that bind NE and signal through adenylate cyclase stimulation, increasing cAMP and downstream Ca^{2+} (Strosberg 1993). There is evidence for moderate mRNA (Nicholas et al. 1993) and high protein expression of β_1 and β_2 receptors in the OT (Palacios and Kuhar 1982; Strazielle et al. 1999; Rainbow et al. 1984). The ICj exhibit particularly high β_1 expression, with modest β_2 expression as well (Rainbow et al. 1984).

Norepinephrine transporter in the OT

NE release is controlled by a balance of monoamine oxidase mediated transmitter degradation and vesicular monoamine transporter (Eiden et al. 2004; Torres et al. 2003). The NE transporter (NET) is confined to adrenergic neurons and it has little-to-no expression in the OT, similar to the dorsal striatum (Hipólide et al. 2005; Strazielle et al. 1999; Sanders et al. 2005). While this is somewhat surprising, it is possible that NE homeostasis in the OT is controlled by a both DAT and monoamine oxidase activity (Demarest and Moore 1979).

Functional roles of norepinephrine signaling in the OT

NE in many brain systems has known roles in learning and memory, as well as arousal and stress (Carter et al. 2010; Uematsu et al. 2017; Morilak et al. 2005). The type and frequency of stressors produces markedly different effects on brain NE levels (Hellriegel and D'Mello 1997). For instance, chronic social isolation results in increased NE levels in the OT of mice that display increased intraspecies aggression (Garris 2003), whereas acute restraint stress decreases NE levels in the OT of pigs (Piekarzewska et al. 2000). While species differences may contribute to these effects, it is apparent that NE in the OT is subject to modulation via different types of stressors. Beyond these studies, however, the functional roles of NE in the OT have not yet been identified.

Serotonin

Source of serotonin in the OT

The raphe nuclei are the site of production of 5-HT, and both dorsal and ventral subregions of the raphe project widely throughout the brain. The OT and ICj receive dense serotonergic innervation from the ascending serotonergic pathway, originating in the raphe nuclei (Hillegaart et al. 1990; Fallon 1983).

Serotonin receptors in the OT

The 5-HT neurotransmitter system contains 14 membrane-bound receptors, which are divided into 7 families. These receptors are differentially expressed throughout the brain, peripheral nervous system, and non-neuronal tissue. All 5-HT receptors are GPCRs except for the 5-HT₃ receptor, which is a ligand-gated ion channel. Diverse receptor mechanisms and patterns of expression of 5-HT receptors contribute to the wide range of functions in the nervous system, but a lack of pharmacological specificity has posed a significant challenge to attributing specific functions to each receptor. A comprehensive discussion on the structural and functional profiles of these receptors, which is outside of the scope of this review, can be found here (Barnes and Sharp 1999; Hoyer et al. 2002).

Table 3 summarizes the profiles of mRNA (by *in situ* hybridization) and protein expression (by immunohistochemistry or autoradiography) of 5-HT receptors in the OT. Notably, 5-HT_{1B} receptor mRNA (which is homologous to human 5-HT_{1A}) is highly expressed in the OT, while protein levels are low (Bonaventure et al. 1998; Boschert et al. 1994; Voigt et al. 1991). This pattern of expression is also observed in the basal ganglia, while its major output regions express the converse (high protein and low mRNA) (Boschert et al. 1994; Voigt et al. 1991). This mismatch is in accordance with the established role of 5-HT_{1B} as an

autoreceptor, where its regulation of serotonergic reuptake is mediated by its interaction with the serotonin transporter (SERT) at presynaptic terminals (Hagan et al. 2012).

Layer 2 of the OT contains concordantly high protein and mRNA for both 5-HT_{1D} (Bach et al. 1993; Hadley and Halliwell 2010) and 5-HT_{2A} receptors (López-Giménez et al. 1997; Mijster et al. 1997). Additionally, the OT has extremely dense 5-HT₆ receptor mRNA expression (Helboe et al. 2015; Ruat et al. 1993; Kinsey et al. 2001), with protein that appears to be localized to layer 1 (Gérard et al. 1997), where the OT receives olfactory bulb input (Imamura et al. 2011).

The 5-HT system plays a critical role in neurodevelopment (Bonnin and Levitt 2011; Gaspar et al. 2003). In the OT and ICj, Waeber and colleagues (1996) reported that 5-HT₄ receptor expression is low in the prenatal brain, increases significantly during postnatal development to surpass other brain regions studied (including the hippocampus, caudate putamen, and septum), and plateaus in adulthood (Waeber et al. 1996; Grossman et al. 1993; Vilaró et al. 1996). Developmental and functional profiles of other 5-HT receptors in the OT are unknown.

Serotonin transporters in the OT

SERT is highly expressed in the OT relative to other brain regions, second only to the dorsal raphe (Chen et al. 1992; Choi et al. 2000; Ase et al. 2000). Given the high levels of 5-HT receptors in the OT, high expression of SERT is unsurprising and suggests a robust mechanism for the regulation of 5-HT neurotransmission in the OT. Additionally, the OT exhibits immunoreactivity for VMAT2 (Cliburn et al. 2017) and the low-affinity plasma membrane monoamine transporter (PMAT) (Dahlin et al. 2007).

Functional role of serotonin in the OT

Several different functions of 5-HT in the OT have been identified. One area of research focuses on the role of 5-HT in the regulation of mood and emotional reactivity, given the use of selective-serotonin reuptake inhibitors (SSRIs) for the treatment of depression and anxiety. Olfactory bulbectomy, which is used to model depressive-like behavior in rodents, produces overt intraspecies aggression and increased 5-HT levels in the OT compared to socially-isolated mice (Garris 2003), suggesting a role for OT 5-HT in aggressive behavior.

Widespread serotonergic innervation of the olfactory system suggests an important role for olfaction and odor-guided behavior (McLean and Shipley 1987; Petzold et al. 2009). However, conditional depletion of 5-HT in the adult forebrain (including the OT) has no effect on odor discrimination or conditioned odor learning (Carlson et al. 2016). While a role for 5-HT in olfactory system development cannot be ruled out by this work, more research is needed to define the contributions of 5-HT release into the OT on olfaction.

There is also evidence that 5-HT in the OT plays a role in the reinforcing effects of drugs of abuse (as also discussed in DA and opioids sections), neurotoxicity, and obesity. A rodent model of novelty-seeking behavior, which predicts sensation-seeking and substance abuse based on a heightened locomotor response (Kabbaj 2006), indicates that 5-HT₆ receptor mRNA expression in the OT is inversely correlated to locomotor response to novelty (Ballaz

et al. 2007), suggesting a possible role of OT 5-HT₆ in this behavioral phenotype. 3,4-Methylenedioxymethamphetamine (MDMA, which reduces 5-HT reuptake through its interaction with SERT) induces activation of the immediate early gene Fos in the OT, an effect that is dependent on both D1 receptor and NMDAR signaling (Hashimoto et al. 1997). Further, intracranial self-administration of MDMA into the medial portion of the OT is behaviorally reinforcing (Shin et al. 2008). Additionally, neurotoxic doses of methamphetamine results in decreased 5-HT concentrations in combined OT + nucleus accumbens tissue (Sabol et al. 2001). The OT also exhibits decreased levels of 5-HT when treated with a combination of the anorectic drugs phentermine and fenfluramine (Phen/Fen, which enhances weight loss through reductions in SERT and depletion of axonal 5-HT), indicative of neurotoxicity (Lew et al. 1997). Finally, mice that are resistant to high-fat diet-induced obesity display decreased SERT binding in the OT compared to susceptible mice and mice on a low-fat diet (Huang et al. 2004). Together, these studies indicate that the 5-HT system is altered in the OT by exposure to drugs of abuse, diet-related alterations, and neurotoxicity.

Interactions between systems

The 5-HT system is highly interconnected with other neurotransmitter systems. In the OT, DA and 5-HT activity are closely coupled in a behaviorally-relevant manner, such that 5-HT₂ receptor antagonists interact with DA-targeted typical antipsychotics in the OT to reduce negative symptoms of schizophrenia (Cools et al. 1992). There is high co-expression of 5-HT_{1B} with the cannabinoid receptor CB1 mRNA (Hermann et al. 2002). There is also co-expression of the 5-HT_{2A} receptor with both dynorphin (68%) and enkephalin (45%) in the OT, which differs from levels of co-expression reported in other areas of the ventral striatum (Mijnster et al. 1997).

5-HT also interacts with glutamatergic systems in the OT: local excitatory post-synaptic potentials are inhibited through agonism of the 5-HT_{1B/1D} receptors (Hadley and Halliwell 2010; Owen and Halliwell 2001). Finally, GABA systems are modulated by SSRIs in the OT, where chronic sertraline treatment decreased GAD mRNA expression in the OT as well as other brain areas that contribute to emotional processing (*e.g.*, nucleus accumbens, prefrontal cortex, and reticular formation) (Giardino et al. 1996). Taken together, 5-HT in the OT is poised to exert profound effects on physiology and behavior, but there are many gaps in our knowledge of the specific role of 5-HT in the OT.

Opioids

Source of endogenous opioids in the OT

Endogenous opioids (endorphins, enkephalins, and dynorphins) are locally synthesized from the transcription of protein-coding genes for their precursors, called prepropeptides. These prepropeptides undergo N-terminus cleaving upon translation, resulting in propeptides, followed by posttranslational modifications that produce the active neuropeptides. The rat OT contains dense expression of preprodynorphin and preproenkephalin in layer 2, weak expression in layer 3, and no expression in the ICj (Furuta et al. 2002; Harlan et al. 1987). There is very little (2-3%) co-expression of preprodynorphin and preproenkephalin in the

OT (Furuta et al. 2002), in accordance with the expression patterns of their respective end products characterized in D1 and D2 receptor-expressing MSNs (see above section). Additionally, the most ventral part of layer 2 contains preprodynorphin, but not preproenkephalin (Furuta et al. 2002). Endogenous morphine-like immunoreactivity has also been detected in the cell bodies of the OT with moderate intensity (Laux et al. 2011).

Opioid receptors in the OT

There are three major $G_{i/o}$ -coupled opioid receptors: endorphins share the strongest affinity for the mu opioid receptor (MOR), dynorphins for the kappa opioid receptor (KOR), and enkephalins for the delta opioid receptor (DOR), respectively (Waldhoer et al. 2004). Similar to other areas of the dorsal and ventral striatum, DOR and KOR mRNA and protein are densely distributed throughout the OT, whereas MOR mRNA and protein are sparsely distributed (Mansour et al. 1987; Mansour et al. 1994; Furuta et al. 2002).

Interactions with other systems

Throughout the dorsal and ventral striatum, D1-expressing MSNs primarily express dynorphin and D2-expressing MSNs primarily express enkephalin (Lobo et al. 2006; Surmeier et al. 1996; Le Moine and Bloch 1995). OT neurons projecting to the ventrolateral portion of the ventral pallidum (also shown by (Heimer et al. 1987)) contain preprodynorphin (60%) and preproenkephalin (40%), which is the reverse for other areas of the ventral striatum like the nucleus accumbens (Zhou et al. 2003). These are primarily non-overlapping cell populations expressing one or the other, with shared high co-expression of dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32; 74-85%) and no co-expression with markers for interneurons such as parvalbumin, calretinin, ChAT, and somatostatin (Furuta et al. 2002), consistent with D1-expressing MSNs and D2-expressing MSNs.

Functional role of opioids in the OT

The opioid system in the OT may influence the reinforcing effects of drugs of abuse. Opioid receptor subtypes have opposing behavioral effects such that MOR agonists are rewarding and KOR agonists are not only aversive, but they also block the rewarding effects of MOR agonism (Mucha and Herz 1985; Funada et al. 1993). In tissue including the OT and nucleus accumbens, systemic MOR agonists increases levels of DA metabolites and KOR agonists blocks this effect (Funada et al. 1993). Additionally, voluntary ethanol consumption in rats decreases preproenkephalin and proenkephalin mRNA expression in the OT; this effect is prevented by treatment with naltrexone, which reduces ethanol consumption through both MOR and KOR antagonism (Oliva and Manzanares 2007; Cowen and Lawrence 2001).

Hormones and neurosteroids

Source and receptors of hormones and neurosteroids in the OT

Sex steroid hormones, particularly brain-derived estrogen, plays a prominent role supporting synaptic plasticity, transcriptional activity, and learning and memory (Tuscher et al. 2016; Saldanha et al. 2011). The mouse OT is equipped to synthesize estrogen locally due to high expression of aromatase (Stani et al. 2014), the rate-limiting enzyme that catalyzes

androgens into estrogens. There is also moderately high expression of estrogen receptor α (ER α), the G protein-coupled estrogen receptor, and androgen receptors in the OT and ICj (Stani et al. 2014; Rainbow et al. 1982; Roselli and Stormshak 2012; Brailoiu et al. 2007). Other neurosteroids in the OT have been less thoroughly studied. There are relatively low levels of 5 α -reductase activity, which converts testosterone into dihydrotestosterone, in the OT (Krieger et al. 1983b). Additionally, while progesterone in the OT has not yet been characterized, its metabolite allopregnanolone, which is a modulator of the GABA_A receptor (Schumacher et al. 2014), is densely expressed in OT layer 2 (Saalman et al. 2007).

Functional role of hormones and neurosteroids in the OT

Although sex steroid hormones have potent and far-reaching effects on behavior, development, and neural function, little is known about their specific effects in the OT. 17 β -estradiol augments evoked firing of neurons in the OT upon stimulation of the posterior hypothalamus in cats (Cartas-Heredia et al. 1978). This is in line with findings from other brain regions displaying an excitatory response to estrogens, including striatal MSNs (Huang and Woolley 2012; Cao et al. 2018; Proaño et al. 2018).

Interactions between systems

Sex steroid hormones interact with virtually all other neurotransmitter systems. In the OT specifically, interactions with 5-HT, DA, and oxytocin (which is discussed in more detail below) have been noted. Briefly, 5-HT and estrogen interact in the OT via the 5-HT_{2A} receptor, which is upregulated following the surge of estradiol that follows proestrus in rats (Sumner and Fink 1997). Additionally, raloxifene (which is a selective-estrogen receptor modulator) blocks the estradiol-induced increase in 5-HT_{2A} receptor expression in the OT and D3 receptor binding in the ICj, perhaps contributing to estrogen's effects on mood and mental state (Sumner et al. 2007; Landry et al. 2002).

Oxytocin

Source of oxytocin in the OT

The supraoptic nucleus, accessory magnocellular nuclei, and paraventricular nucleus of the hypothalamus (PVN) are the main sources of oxytocin in the mammalian brain (Sofroniew 1983; Swanson and Sawchenko 1983). Oxytocin-releasing neurons in the PVN send dense projections to the posterior pituitary and the ICj, as well as less-dense projections to limbic regions, the basal ganglia, cortex, and other olfactory regions (Knobloch et al. 2012; Choe et al. 2015; Prasada Rao and Kanwal 2004).

Oxytocin receptor expression in the OT

The oxytocin receptor is a GPCR that binds oxytocin in the presence of Mg²⁺ and cholesterol, and it exerts its action through its G_q effector protein (Gimpl and Fahrenholz 2001; Devost et al. 2008). Oxytocin signaling dynamically changes throughout the lifespan and across species (for review, see (Vaidyanathan and Hammock 2017)). There are two primary patterns of oxytocin receptor expression in the brain—the “adult” pattern which emerges post-weaning and remains stable throughout adulthood, and the more transient “infant” pattern (Tribollet et al. 1989). The ICj displays a uniquely late pattern of oxytocin

receptor expression that does not emerge until postnatal day 40 in the rat (Tribollet et al. 1989); however, see (Hammock and Levitt 2013). The OT contains both oxytocin receptor mRNA and protein (Vaccari et al. 1998; Choe et al. 2015), with the strongest expression in the ICj (Tribollet et al. 1988).

Functional role of oxytocin in the OT and interactions with other systems

Given the high density of estrogen receptors in these areas (see section on hormones & neurosteroids) and the appearance of oxytocin receptors in the ICj around puberty, oxytocin in the OT may contribute to sociosexual behavior through its interaction with sex steroid hormones. In fact, the ICj as well as the ventromedial hypothalamus (VMH) are unique “hot spots” in the brain where systemic estrogen increases oxytocin receptor binding (de Kloet et al. 1986; Krémarik et al. 1995). While estrogen-oxytocin interactions in the VMH have been established for their regulation of female sexual behavior (McCarthy et al. 1994), the functional significance of this interaction in the ICj is poorly understood. It is likely that odor-guided social behaviors are impacted, since the basolateral amygdala (which projects to the OT) exhibits ER α -dependent increases in oxytocin receptor binding following estrogen treatment and plays a role in a variety of social behaviors (Young et al. 1998). There are also testosterone-oxytocin interactions, since reduced oxytocin receptor binding in the OT of male rats is linked to both aging- and castration-induced decreases in testosterone levels (Arsenijevic et al. 1995; Arsenijevic and Tribollet 1998; Johnson et al. 1991; Tribollet et al. 1990).

There may also be interactions with oxytocin and DA in the OT, since an acute infusion of oxytocin into the OT (through indwelling cannulae) blocks cocaine-induced stereotyped sniffing behavior (Sarnyai et al. 1991).

Other neurochemicals

An array of neuropeptides and neurochemicals are expressed in the OT, especially interneurons as discussed in the GABA section. Neurotensin is highly expressed in the OT, specifically among DA D2-type receptor expressing MSNs and the ICj (Schroeder et al. 2019). Projections to the OT and ICj arising from the posteromedial cortical amygdala (which receives input from the accessory olfactory bulb) are immunoreactive for neuropeptide Y and Substance-P (as well as 5-HT and TH) (Ubeda-Bañon et al. 2008), suggesting a role for these peptides in rodent sociosexual behaviors. Autoradiography of corticotropin releasing factor receptors indicates that they are localized in the OT (Weathington et al. 2014). Further, orexin receptor mRNA is highly expressed in the OT as well as faint immunoreactivity found in fibers, suggesting local synthesis of orexin in the OT (Caillol et al. 2003).

Nitric oxide (NO) is a free radical signaling molecule that can act as a neurotransmitter in the central nervous system, where it plays a role in neural plasticity, neurogenesis, and excitotoxicity (for review, see (Zhou and Zhu 2009)). NO is synthesized from L-arginine by neuronal nitric oxide synthase (nNOS), which is abundant within the OT of rodents (Rodrigo et al. 1994) and many other species (Menéndez et al. 2006; Brüning et al. 1994a; Brüning et al. 1994b). Specifically, nNOS immunoreactivity is present within fibers in layer 1 (which

likely arise from olfactory bulb mitral and tufted cells (Kosaka and Kosaka 2007)), neurons in layer 3, and fibers and granule cells within the ICj (Rodrigo et al. 1994; Bredt et al. 1990; Vincent and Kimura 1992). NO largely exerts its effects by activating soluble guanylyl cyclase, which is expressed at very high levels in the OT, especially in layer 2 cell bodies (Ding et al. 2004). Guanylyl cyclase activation by NO results in upregulation of cyclic GMP synthesis (Murad et al. 1978). This is observed in acute rat brain slices within the ICj but not the surrounding regions (De Vente et al. 1998), suggesting that NO exerts its effects locally, despite its ability to freely diffuse across cell membranes. The functional role of NO signaling in the OT is unknown, but *in vitro* studies of OT tissue suggest that NO may inhibit dopamine uptake (Pogun et al. 1994). *In vivo* studies are needed to improve our understanding of NO's function in the OT.

Neurochemical alterations in the OT in the context of neurological disorders

Striatal dysfunction is a hallmark of several neurological disorders (Murray et al. 1995; Kreitzer and Malenka 2008; Foltz et al. 2004; McGregor and Nelson 2019; Gerfen et al. 1990; Ouchi 2001). Likewise, olfactory dysfunction is observed in both aging and in numerous neurological disorders (Doty 2017; Murphy 2019; Devanand et al. 2000; Doty et al. 1984; Wesson et al. 2010b). It follows that the OT, as a component of both neural systems, would also be vulnerable to neurological disorders in ways that would influence its neurochemical composition. Here we review a few selected reports uncovering an influence of neurological disease on the OT, which may arise due to insults upon the OT itself, or due to insults upon neural systems that innervate the OT (*e.g.*, the mesolimbic DAergic system, forebrain cholinergic innervation) and thereby affect OT neurochemistry.

Parkinson's disease and some other movement disorders are characterized by dysfunction in basal ganglia systems, which include the ventral striatum. Lewy bodies, a key pathological hallmark of Parkinson's disease, are made of the aggregated protein α -synuclein and are found *post-mortem* within the OT of humans with Parkinson's disease (Ubeda-Bañon et al. 2010). The number of Lewy bodies reported in the OT however is considerably less than that found in the olfactory bulb itself, but is comparable to Lewy body presence in other olfactory cortices (Ubeda-Bañon et al. 2010). This accumulation of Lewy bodies and the accumulation of phosphorylated α -synuclein can be generated pre-clinically in rodent models by a single injection of α -synuclein preformed fibrils into the olfactory bulb (Rey et al. 2016). In this seeding model, phosphorylated α -synuclein is detected in the OT just weeks after a single injection into the olfactory bulb, suggesting transsynaptic propagation of Parkinson's pathology in the brain (Rey et al. 2016; Rey et al. 2018). The direct influence of α -synuclein aggregation in the OT on olfactory perception is unclear.

The nucleus basalis of Meynert (nbM) contains a large collection of cholinergic neurons which project into several structures, including the OT (Koulousakis et al. 2019). Lewy bodies are observed in the nbM in humans diagnosed as having dementia with Lewy bodies, and this corresponds to low levels of ChAT (Lippa et al. 1999). It is possible that in the

context of Lewy body disease, the OT is subject to aberrant influx of ACh from the nbM, which may alter OT function and subsequently influence disease states.

Alzheimer's disease is characterized by several pathological features, including the accumulation of amyloid- β aggregates known as plaques and the presence of neurofibrillary tangles. Early in disease progression, these pathological hallmarks are observed in the olfactory system (Braak and Braak 1991). Amyloid- β plaques are observed in the OT in mouse models of Alzheimer's disease, including in models overexpressing human mutations in the amyloid precursor protein (Wesson et al. 2010a) and in mice co-expressing human mutations in both the amyloid precursor protein and presenilin-1 (Saiz-Sanchez et al. 2013). In the latter mouse model, somatostatin and calretinin expression decline alongside increases in amyloid- β burden (Saiz-Sanchez et al. 2013), suggesting that somatostatin and calretinin interneurons may be particularly vulnerable to amyloidosis and/or other aspects of Alzheimer's pathogenesis. Whether these changes within the OT may contribute to olfactory dysfunction is yet to be determined.

As a final example, loss of neuromodulatory inputs to the OT are observed following head trauma. Reduced DAergic fiber innervation is detected in the OT in a rat model of mild traumatic brain injury (Haar et al. 2019). This is accompanied by OT neuroinflammation (*i.e.*, gliosis) and heightened levels of phosphorylated tau, the microtubule associated protein (Haar et al. 2019). Interestingly, the reduction in DAT fibers following mild traumatic head injury were not observed in the nigrostriatal pathway, suggesting unique roles of mesolimbic fiber degeneration, including in the OT, in the cognitive and psychiatric effects of brain injury (Haar et al. 2019).

The above results indicate how the several neurological disorders, and/or their pathogens in experimental models, impact the OT. It is possible that these changes in the OT may influence features and possibly the progression of these disorders. Determining, in a causal manner, whether the OT itself is a direct contributor to clinical manifestations of any of these disorders is an important major goal for future investigations.

Summary

Here we summarized the rich neurochemical composition of the OT, including the neurotransmitters, neuromodulators, and hormones present. We also addressed what receptors and transporters are involved in each system as well as their putative functional roles. Finally, we briefly reviewed select literature regarding neurochemical changes in the OT in the context of neurological disorders, specifically neurodegenerative disorders. We predict this will serve to aid future research into the neurobiology of the ventral striatum.

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List of abbreviations

5-HT	5-hydroxytryptamine, serotonin
Ach	acetylcholine
AChE	acetylcholinesterase
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AON	anterior olfactory nucleus
CCK	cholecystokinin
ChAT	choline acetyl transferase
CIN	cholinergic interneuron
DA	dopamine
DARPP-32	dopamine- and cAMP-regulated neuronal phosphoprotein
DOR	delta opioid receptor
EAAT	excitatory amino acid transporter
ERα	estrogen receptor α
GABA	γ -aminobutyric acid
GAD	glutamic acid decarboxylase
GAT	GABA transporter
GluA	subunits of the glutamate AMPA receptor
GluK	subunits of the glutamate Kainate receptor
GluN	subunits of the glutamate NMDA receptor
GPCR	G-protein-coupled receptor
ICj	Islands of Calleja
KOR	kappa opioid receptor
LC	locus coeruleus
mAChR	muscarinic acetylcholine receptor
MDMA	3,4-Methylenedioxymethamphetamine
mGluR	metabotropic glutamate receptor
MOR	mu opioid receptor
MSN	medium spiny neuron

mAChR	muscarinic acetylcholine receptor
nAChR	nicotinic acetylcholine receptor
nbM	nucleus basalis of Meynert
NE	norepinephrine
NET	norepinephrine transporter
NMDAR	N-methyl-D-aspartate receptor
NO	nitric oxide
nNOS	neuronal nitric oxide synthase
NPY	neuropeptide Y
OT	olfactory tubercle
PMAT	plasma membrane monoamine transporter
PVN	paraventricular nucleus of the hypothalamus
SERT	serotonin transporter
SSRI	selective serotonin reuptake inhibitor
TH	tyrosine hydroxylase
VAcHT	vesicular acetylcholine transporter
VGLUT	vesicular glutamate transporter
VIP	vasoactive intestinal peptide
VMAT2	vesicular monoamine transporter 2
VMH	ventromedial hypothalamus
VTa	ventral tegmental area.

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Figure 1. The localization of the olfactory tubercle in a rodent brain.

(Top) Diagram of a rat brain, including a coronal section indicating the nucleus accumbens, ventral pallidum, and olfactory tubercle (beige shaded region). (Bottom) Enlarged view of the olfactory tubercle, with layer 1 depicted in pink, layer 2 depicted in orange, and layer 3 depicted in yellow. An island of Calleja is depicted in red. Some examples of different cell types found in the olfactory tubercle are illustrated. Based in part upon (Xiong and Wesson 2016). M, medial; D, dorsal; MSN, medium spiny neuron; GC, granule cell; CIN, cholinergic interneuron.

Table 1.

Relative expression of GABA receptors in the OT

Class	Receptor type	Subunit	mRNA	Protein
GABA _A	Ligand-gated Cl ⁻ channel	alpha1	+++ (Duncan et al. 1995)	+++ IC _j [*] , + L1-3 (Schwarzer et al. 2001; Pirker et al. 2000)
		alpha2		+++ L1-3 (Schwarzer et al. 2001; Pirker et al. 2000)
		alpha3		+ (Schwarzer et al. 2001)
		alpha4		+++ L1-3 (Schwarzer et al. 2001; Pirker et al. 2000)
		alpha5		+ (Schwarzer et al. 2001)
		alpha6		
		beta1	- (Zhang et al. 1990)	+ (Schwarzer et al. 2001)
		beta2	+++ (Duncan et al. 1995), + (Zhang et al. 1990)	++ IC _j [*] , + L1-3 (Schwarzer et al. 2001; Pirker et al. 2000)
		beta3	+++ L2-3 (Zhang et al. 1990)	+++ L1-3 (Schwarzer et al. 2001; Pirker et al. 2000)
		gamma1		- (Schwarzer et al. 2001)
		gamma2	++ (Duncan et al. 1995)	+ (Schwarzer et al. 2001)
		gamma3		- (Schwarzer et al. 2001)
		delta		++ L1-3 (Schwarzer et al. 2001)
GABA _B	GPCR	1a		+++ (Charles et al. 2001)
		1b		+++ (Charles et al. 2001)
		2	+ (Durkin et al. 1999)	+++ (Charles et al. 2001)

- none, + modest, ++ moderate, +++ high

Cells absent of data reflect no literature available/found, or region not specified. All data cited is from non-human animal models.

* limited data to confirm the original source, but likely

L1-3, Layers 1-3.

Table 2.

Relative expression of glutamate receptors in the OT

Class	Receptor type	Subunit/receptor	mRNA	Protein
NMDAR	Ligand/voltage-gated ion channel	GluN1	+++ (Standaert et al. 1999)	
		GluN2A	+++ (Standaert et al. 1999)	++ (Wang et al. 1995)
		GluN2B	+++ (Standaert et al. 1999)	+++ (Wang et al. 1995)
		GluN2C	- (Standaert et al. 1999)	
		GluN2D	+ (Standaert et al. 1999)	
		GluN3A		
		GluN3B		
AMPA	Ligand-gated ion channel	GluA1 (prev. GluR1)	+ (Pellegrini-Giampietro et al. 2006)	+++ (Petrulia and Wenthold 1992)
		GluA2 (prev. GluR2)	++ (Pellegrini-Giampietro et al. 2006)	+++ (Petrulia and Wenthold 1992)
		GluA3 (prev. GluR3)	++ (Pellegrini-Giampietro et al. 2006)	+++ (Petrulia and Wenthold 1992)
		GluA4 (prev. GluR4)		++ (Petrulia and Wenthold 1992)
Kainate	Ligand-gated ion channel	GluK1 (prev. GluR5)	+++ ICj; - OT (Bischoff et al. 1997)	
		GluK2 (prev. GluR6)	+++ L2-3 (Bischoff et al. 1997)	
		GluK3 (prev. GluR7)	++ L2-3 (Bischoff et al. 1997)	
		GluK4 (prev. KA1)	+ L2-3 (Bischoff et al. 1997)	
		GluK5 (prev. KA2)	+++ L2 (Bischoff et al. 1997)	
mGluR	GPCR	mGluR1 (group 1)		++ (Lavreysen et al. 2003; Mutel et al. 2000) +++ ICj (Wada et al. 1998)
		mGluR2 (group 2)		++ L1-3 (Mutel et al. 2000; Wada et al. 1998)
		mGluR3 (group 2)		+++ L1-3 (Tamaru et al. 2001)
		mGluR4 (group 3)	++ (Ohishi et al. 1995)	
		mGluR5 (group 1)		++ L1-3 (Mutel et al. 2000; Wada et al. 1998)
		mGluR6 (group 3)		
		mGluR7 (group 3)	++ (Ohishi et al. 1995)	mGluR71 +++ L1, ICj (Kinoshita et al. 1998; Wada et al. 1998)
				mGluR7b +++ ICj (Kinoshita et al. 1998)
		mGluR8 (group 3)		++ L1 (Wada et al. 1998)

- none, + modest, ++ moderate, +++ high

Cells absent of data reflect no literature available/found, or region not specified. All data cited is from non-human animal models.

L1-3, Layers 1-3.

Table 3.

Relative expression of 5-HT receptors in the OT

Family	GPCR effector	Receptor	mRNA	Protein
1	G _{i/o}	5-HT _{1A}	+, ICj (Wright et al. 1995)	
		5-HT _{1B}	++++ (Bonaventure et al. 1998; Boschert et al. 1994; Voigt et al. 1991)	+ (Boschert et al. 1994)
		5-HT _{1D}	+++ L2 (Boschert et al. 1994; Bach et al. 1993)	+++ L2 (Hadley and Halliwell 2010)
		5-HT _{1E} *		
		5-HT _{1F}	++ (Bruinvels et al. 1994)	
2	G _q	5-HT _{2A}	+++ (Mijnster et al. 1997)	+++ L2 (López-Giménez et al. 1997)
		5-HT _{2B}		
		5-HT _{2C}	+++ (Wright et al. 1995)	
3	n/a (ligand-gated ion channel)	5-HT ₃		+, ICj (Kilpatrick et al. 1988; Koyama et al. 2017)
4	G _s	5-HT ₄	++++ (Vilaró et al. 1996)	+++ OT & ICj (Grossman et al. 1993; Waeber et al. 1996)
5	G _{i/o}	5-HT _{5A}	+ (Kinsey et al. 2001)	
		5-HT _{5B}	- (Kinsey et al. 2001)	
6	G _s	5-HT ₆	++++, OT & ICj (Ruat et al. 1993; Kinsey et al. 2001; Helboe et al. 2015)	++++, L1 (Gérard et al. 1997)
7	G _s	5-HT ₇	- (Kinsey et al. 2001)	

- none, + modest, ++ moderate, +++ high, ++++ extremely high

* 5-HT_{1E} receptor is not present in rats or mice.

Cells absent of data reflect no literature available/found, or region not specified. All data cited is from non-human animal models.

L1-3, Layers 1-3.