NEURAL REGENERATION RESEARCH
September 2017, Volume 12, Issue 9
www.nrronline.org

INVITED REVIEW

Odorants could elicit repair processes in melanized neuronal and skin cells

Barbara Pavan[1,*], **Alessandro Dalpiaz**[2]
1 Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy
2 Department of Chemistry and Pharmaceutical Sciences, University of Ferrara, Ferrara, Italy

How to cite this article: *Pavan B, Dalpiaz A (2017) Odorants could elicit repair processes in melanized neuronal and skin cells. Neural Regen Res 12(9):1401-1404.*
Funding: *This work was supported by the University of Ferrara (F72I15000470005) in the frame of the project FAR2014.*

Abstract
The expression of ectopic olfactory receptors (ORs) in melanized cells, such as the human brain nigrostriatal dopaminergic neurons and skin melanocytes, is here pointed out. ORs are recognized to regulate skin melanogenesis, whereas OR expression in the dopaminergic neurons, characterized by accumulation of pigment neuromelanin, is downregulated in Parkinson's disease. Furthermore, the correlation between the pigmentation process and the dopamine pathway through α-synuclein expression is also highlighted. Purposely, these ORs are suggested as therapeutic target for neurodegenerative diseases related to the pigmentation disorders. Based on this evidence, a possible way of turning odorants into drugs, acting on three specific olfactory receptors, OR51E2, OR2AT4 and VN1R1, is thus introduced. Various odorous molecules are shown to interact with these ORs and their therapeutic potential against melanogenic and neurodegenerative dysfunctions, including melanoma and Parkinson's disease, is suggested. Finally, a direct functional link between olfactory and endocrine systems in human brain through VN1R1 is proposed, helping to counteract female susceptibility to Parkinson's disease in quiescent life.

Correspondence to:
Barbara Pavan, Ph.D.,
pvnbbr@unife.it.

orcid:
0000-0001-8942-9310
(Barbara Pavan)

doi: *10.4103/1673-5374.215246*

Accepted: *2017-08-18*

Key Words: *OR51E2; OR2AT4; VN1R1; melanoma; Parkinson's disease; β-ionone; sandalore; hedione*

Pigmentation Disorders and Neurodegenerative Diseases

The main source of dopamine in the brain is provided by mesencephalic dopaminergic (mDA) neurons, consisting essentially of two groups of projecting cells: the A9 neurons of the substantia nigra (SN), that form the mesostriatal system, and the A10 cells of the ventral tegmental area (VTA), that constitute the mesocorticolimbic pathway (Ikemoto, 2007). These cells share many features including the enzymatic pathways involved in dopamine synthesis, release and metabolism. They also show common intrinsic electrophysiological properties such as spontaneous pacemaker activity in the absence of synaptic inputs. SN neurons are involved in regulating voluntary movements and postural reflexes, whereas VTA cells play a fundamental part in reward and attention. Dysfunction of mDA neurons has been implicated in several neurodegenerative disorders, such as selective degeneration of A9 cells leading to Parkinson's disease (PD) (Grison et al., 2014). Besides the catecholaminergic neurotransmitter type, the dopaminergic neurons of the SN and the noradrenergic neurons of the locus coeruleus are prominently characterized by their pigmentation, due to the intraneuronal accumulation of neuromelanin (NM). NM is a dark, non-autofluorescent polymeric pigment produced almost exclusively in human catecholaminergic neurons, mainly in the SN, whereas it is less generated in some other non-human primates, and it is absent from the brain in many lower species (Fedorow et al., 2005). Function of NM is considered to be especially protective, due to its ability to chelate metals, mostly iron, the level of which increases gradually with age. NM may also bind mitochondrial toxins. Finally, it removes excess of cytosolic dopamine (DA) not stored in synaptic vesicles, hence protecting the neuron from oxidative stress related to DA autoxidation (Bobela et al., 2015). In particular, in the cytosol of dopaminergic neurons, DA can be oxidized *via* iron-mediated catalysis and then react with β-sheets-structured proteins to form a melanin-protein complex. During the polymerization process, the melanin-protein conjugate can also bind high amounts of metals, especially iron. The resulting NM is taken up into autophagic vacuoles that subsequently fuse with lysosomes; here NM interacts with lipids and proteins already present, thus forming the mature NM-containing organelles. Therefore, by analogy with peripheral melanins, NM could function *in vivo* to attenuate the effects of damaging stimuli, but, unlike melanin in skin and retina, NM is not present in SN dopaminergic neurons of humans during foetal development or at birth, but develops over the first few decades of life (Fedorow et al., 2005). Further, human foetal dopamine neurons, when implanted as a treatment into the striatum of patients with PD, exhibit a precocious production of the pigment. This supports the concept that factors involved in neuronal maturation are important for the production of NM (Pavan et al., 2017).

Concerning the recognized high correlation at a physiopathological level between brain and skin, an attendant development of skin cancer melanoma and neurodegenerative disorder of PD has been observed (Huang et al., 2015). These two diseases share genes involved in the synthesis of melanin and dopamine, such as the *SNCA* gene encoding for the protein α-synuclein (Pan et al., 2012). The SN together with hippocampus are the brain structures with the highest levels of α-synuclein small soluble protein, suggesting its important role in neuronal homeostasis (Bobela et al., 2015). Actually, the abnormal accumulation of α-synuclein

insoluble aggregates in neuronal or glial cells leads to the onset of the so-called neurodegenerative PD and Alzheimer's α-synucleinopathies. Interestingly, PD α-synucleinopathy is not only confined to the dopaminergic neurons, but affects chronologically first the colonic nerves, adrenal medulla, the cardiac sympathetic system, and the olfactory bulb (Bobela et al., 2015). Regulation of melanogenesis was usually shown to involve activation of the second messenger signal cascade adenylyl cyclase/cyclic adenosine monophosphate (cAMP) and activation of cAMP-dependent protein kinase (PKA). Activated PKA is involved in the phosphorylation of cAMP-responsive element-binding protein (CREB) (Roh et al., 2013), which then activates the gene expression of microphthalmia-associated transcription factor (MITF), a master regulator gene of melanocyte development and differentiation (Hirobe, 2011). In melanocytes, the protein expression of α-synuclein may be regulated by MITF, driving the expression of melanogenic enzymes tyrosinase and tyrosinase-related proteins (TYRP1 and TYRP2), and it is also associated with melanoma development and progression (Hirobe, 2011). Overexpression of α-synuclein inhibits phosphorylation of both the rate-limiting enzyme in dopamine synthesis, tyrosine hydroxylase (TH), and of the enzyme that catalyzes the conversion of L-DOPA to dopamine, L-aromatic amino acid decarboxylase (AADC), reducing their activity (Khan et al., 2012). The implication of α-synuclein in the biosynthesis of melanin in melanocytes and of DA linked to the NM in dopaminergic neurons enables us to advance the hypothesis that α-synuclein might be the link between the biosynthesis of NM in brain and of melanin in skin.

Midbrain and Skin Pigmented Cells Express Ectopic Olfactory Receptors (ORs)

It is noteworthy that overexpression of α-synuclein in catecholaminergic brain regions, such as SN and locus coeruleus, causes olfactory deficits in mice similar to that observed in patients with PD (Magen et al., 2015). The axons of olfactory neurons directly project from the nasal cavity to the brain, bypassing the blood-brain barrier (BBB; Xiao et al., 2014). Thus, the OR repertoire expressed in the olfactory neuroepithelium constitutes a biomolecular interface between the chemical exogenous world and the brain, and enables humans to detect, discriminate and categorize a multitude of chemically diverse volatiles (Krautwurst, 2008). Under normal circumstances, immune cells and detoxifying enzymes in the olfactory system prevent xenobiotics from entering and damaging the brain (Xiao et al., 2014). Interestingly, the expression of ORs and vomero-nasal receptors (VNRs) subtypes of G-protein coupled receptors (GPCRs) is also well demonstrated in various non-olfactory tissues, where they are indicated as 'ectopic' ORs (Grison et al., 2014). Ectopic expression of ORs in neurons of the human and murine brain together with their down-regulation in neurodegenerative diseases have been stated (Grison et al., 2014; Ferrer et al., 2016), although their role as well as the nature of their putative ligands unfortunately are still unknown (Ferrer et al., 2016). It has been suggested that small natural molecules present in the brain, such as presumed exogenous ligands transported into the brain or local autocrine or paracrine compounds (for example hormones) could bind to these receptors and mediate their effects on brain cells (Ferrer et al., 2016). Moreover, whether or not the ectopic ORs can detect the same specific molecules of ORs expressed in the olfactory neuroepithelium is still controversial (Ferrer et al., 2016). Although the basis for olfactory dysfunction in PD is currently unknown, we might hypothesize that ORs expressed in the catecholaminergic brain regions could be regulatory targets of SNCA gene and so they might be involved in the biochemical steps of NM synthesis. The hypothesis can be supported by these very recent knowledge: actually, the expression and activation of the ectopic OR51E2 has been recently demonstrated inducing pigmentation and differentiation of human skin melanocytes (Gelis et al., 2016) and inhibiting proliferation of melanoma (Gelis et al., 2017); furthermore, several ectopic ORs have been identified as expressed also in the human SN, such as OR51E1, OR2J3 and OR51E2, and some of them have been shown deregulated in PD (Grison et al., 2014). As a consequence, taking into account association of PD with melanoma, we think that it might be pioneering by a therapeutic point of view the investigation of the role of OR down-regulation in dopaminergic neurons of the SN in PD patients, through experimental models suitable to reproducing melanogenesis impairments.

Turning Odorants into Drugs

Discovery of potential ectopic ORs supporting a bridge between cell pigmentation and PD could open new therapeutic applications of voluptuary or flavoring compounds, such as β-ionone, sandalore, brahmanol, hedione and cinnamaldehyde. In this regards, among the first selected odor molecules acting on ectopic ORs in the central nervous system, carvone and menthone have been evidenced to stimulate Olfr287 and trigger Ca^{2+} signaling in isolated primary mDA neurons of mice (Grison et al., 2014). In addition, the isoprenoid β-ionone, a violet-like scent, has been demonstrated to activate the olfactory receptor OR51E2 expressed in pigment-producing melanocytes of the human skin (Gelis et al., 2016). OR51E2 is also known as prostate-specific G-protein-coupled receptor (PSGR) and acts as a cell surface steroid receptor that mediates rapid, nongenomic, steroidal signaling in prostate cancer cells (Neuhaus et al., 2009). OR51E2 appears activated by compounds characterized, as β-ionone, by the presence in their molecular structure of a carbonyl group conjugated to a butadiene system, such as α-4,6-androstadiene-17-ol-3-one, 6-dehydrotestosterone or 1,4,6-androstadiene-3-17-dione (Pavan et al., 2017) (**Figure 1**). Therefore, OR51E2 activating steroids or terpenoids might provide novel compounds for the treatment of pigmentation disorders and proliferative pigment cell disorders such as melanoma. In addition, taking into account that a carbonyl group conjugated to a butadiene system belongs also to cinnamaldehyde (**Figure 1**), this compound or its derivatives may be OR51E2 promising ligands. Relying on the putative relationship between pigment and neural disorders, a key role of OR51E2 could also be hypothesized in the progression of PD, if OR51E2 expression and responsiveness to β-ionone should be characterized in healthy and PD affected human SN.

Another olfactory receptor subtype, OR2AT4, was expressed and significantly activated by the synthetic sandalwood odorant sandalore (**Figure 1**), inducing the increase of the intracellular Ca^{2+} and cAMP levels in human keratinocytes (Busse et al., 2014). Interestingly, OR2AT4 was also detected in melanocytes and dendritic cells, and melanocytes have been proposed as key sensory cells in human skin hence providing a protective pigmented barrier (Busse et al., 2014). Therefore, it could also be interesting to explore the potential

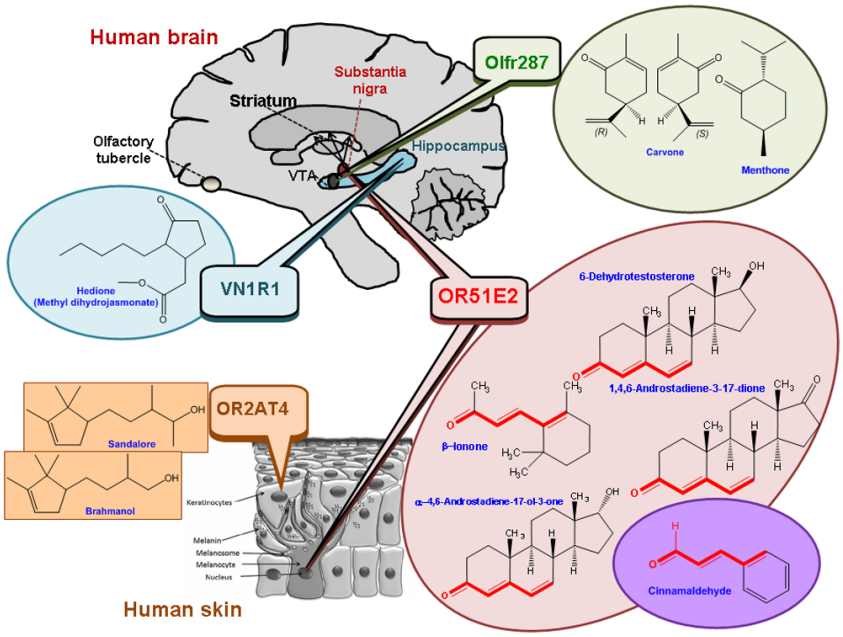

Figure 1 Ectopic olfactory receptors expressed in human brain and skin pigmented cells with related binding odorant molecules.
OR51E2 is expressed in human skin melanocytes and in substantia nigra of the brain. The compounds characterized by the presence in their molecular structure of a carbonyl group conjugated to a butadiene system (red highlighted) are known as strong OR51E2 ligands. Cinnamaldehyde is not known as ligand OR51E2, but according to its structure, itself or its derivatives may be. Olfr287 is expressed in the substantia nigra of the brain and activated by the odorants carvone and menthone. OR2AT4 is expressed in skin keratinocytes and activated by the synthetic sandalwood odorant sandalore. VN1R1 is expressed in hippocampus and amygdale of the brain and activated by the odorous molecule methyl dihydrojasmonate, known as hedione.

involvement of Sandalore-activated OR2AT4 in melanogenic processes of neurons and skin. Moreover, the synthetic sandalwood compounds were already shown to exert dual activities both on human ORs and nuclear estrogen receptors (ERs), evidenced as naturally co-expressed by certain olfactory sensory neurons, providing a direct functional link between the olfactory and hormonal systems in humans (Pick et al., 2009).

The odorous molecule methyl dihydrojasmonate, also known as hedione (**Figure 1**), is considered as a reference ligand to the receptor VN1R1, ectopically expressed in limbic areas (amygdala, hippocampus) of human brain, where it has been proposed to modulate a gender-specific secretion of sex hormones (Wallrabenstein et al., 2015). In our opinion, a noteworthy challenge would be to enquire if the enhanced activation of the VN1R1 in limbic areas by hedione might mimic a more sustained estrogen release in the female brain during aging, thus helping to counteract its susceptibility to PD in quiescent life. Besides, it is intriguing to hypothesize that hedione could also induce the release of steroids by VN1R1 activation. As above reported, the steroids characterized by the presence in their molecular structure of a carbonyl group conjugated to a butadiene system are strong ligands of OR51E2, as β-ionone (**Figure 1**). Since the human OR is also regarded as a steroid receptor, this type of steroids, when released following VN1R1 activation, might target OR51E2 expressed in the mesencephalic neurons, maybe counteracting its potential down-regulation in PD. At this regards, the recent investigation by Natale et al. (2016) revealed that sex steroids regulate pigment production by binding to the G protein-coupled receptors, which may serve as therapeutic targets for treating inflammation-based pigmentation disorders in human melanocytes, thus providing an additional cue to the link with inflammation-based neurodegenerative diseases.

Finally, it is useful to state that the advantage of turning odorants into drugs stems primarily from the evidence that brain is isolated and protected from the outside environment by several specific systems, first of all the BBB, a tight tissue junction surrounding the brain and resulting in a greater trans-endothelial electric resistance which often hinders drug transport. Over the last few years, the intra-nasal route has emerged as a promising approach for the direct delivery of drugs to the brain, bypassing the BBB (Illum, 2003; Hanson and Frey, 2008; Casettari and Illum, 2014; Pavan et al., 2014). We have recently contributed to demonstrate that appropriate nasal formulations, constituted by biocompatible microparticles and polymeric adsorption enhancers, induce the uptake in the central nervous system (CNS) of drugs or prodrugs that are normally unable to cross the BBB (Dalpiaz et al., 2014; Rassu et al., 2015), allowing to obtain therapeutic concentrations (Dalpiaz et al., 2015). The fact that odorants, acting on ORs expressed in the olfactory neuroepithelium have been shown to be active also on specific ORs into the brain and potentially useful against neurodegenerative disorders, may encourage the development of nasal formulations of these odorants, in order to achieve the patient compliance and specific therapeutic effects in the CNS.

Moreover, it is important to take into account that appropriate nasal formulations can be useful also for systemic drug delivery (Casettari and Illum, 2014), due to the abundance of blood vessels in the respiratory nasal mucosa, which contributes to drug absorption almost equally to intravenous injections in some instances (Rashed et al., 2016). Thus, in the case of potent and selective odorants for ORs, it may be possible to hypothesize that the latter goals of their nasal administration would be reached directly both into the brain against PD and systemically against melanoma, or for their prevention.

Concluding Remarks and Future Perspectives

Studies investigating the association of neurodegenerative diseases with pigmentation disorders, and activation by odorants or odorant-like compounds of ORs expressed in midbrain neurons and skin melanocytes, could provide a novel class of therapeutics for treatment of such diseases. In the light of all the foregoing considerations, the challenge would be to investigate if NM production in dopaminergic neurons should be elicited by odorants experienced during life or by odorant-like endogenous compounds, as sex steroids, during the maturation of neuronal circuits. It might be that odorant-like molecules with hormonal valence could help restoring the protective action of NM in dopaminergic neurons depleted by

PD. In addition, good compliant intra-nasal formulations of β-ionone, sandalore, hedione, cynnamaldehyde and/or their analogs may be therapeutics suitable to directly reach both PD-affected midbrain and the systemic route for the treatment of melanoma. Besides, it should be taken into account that results of Grison et al. (2014) indicated that OR genes as well as components of the olfactory signaling system are expressed in mDA neurons. At this purpose, critical features have been recently demonstrated as shared by the olfactory and mDA neurons vulnerable to PD-related degeneration (Cave et al., 2016). Therefore, if novel biomarkers to facilitate early-stage detection of PD should be discovered in the olfactory neurons, nasal delivery of odorants formulations would be also conceivable for development of preventive treatments.

Author contributions: *BP designed and discussed the patho-physiological implications of ectopic olfactory receptors activation in pigmented cells and AD conceived and discussed the types of odorant molecules binding to the related receptors together with their potential nasal formulations.*
Conflicts of interest: *None declared.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer review report:
Reviewer: *Chen Shen, Cold Spring Harbor Laboratory, USA.*
Comments to authors: *This review article summarizes the current research on the relationship between odor receptors and neurodegenerative disorders. Specifically, the authors have described the importance of dopamine pathway in the pigmentation process. Also, the authors have pointed out the existence of olfactory receptors in both midbrain and skin pigmented cells. With this findings, the authors have thus introduced a possible way of turning odorants into drugs. Two specific olfactory receptors, OR51E2 and OR2AT4, are introduced in the article. The research on these pathways was proved to serve as a direct functional link between olfactory and endocrine systems in human body. Various odorous molecules were shown to interact with the olfactory receptors and the authors have suggested a therapeutic potential for these molecules.*

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