

● REVIEW

Factors that modulate olfactory dysfunction

Kate Beecher^{1,2,3}, James A. St John^{3,4}, Fatemeh Chehrehasa^{1,2,3,*}

1 School of Biomedical Science, Queensland University of Technology, Brisbane, Queensland, Australia

2 Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia

3 Clem Jones Centre for Neurobiology and Stem Cell Research, Griffith Institute for Drug Discovery, Griffith University, Brisbane, Queensland, Australia

4 Menzies Health Institute Queensland, Griffith University, Brisbane, Queensland, Australia

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Abstract

The olfactory system is one of a few areas in the nervous system which is capable of regeneration throughout the life. Olfactory sensory neurons reside in the nasal cavity are continuously replenished with new neurons arising from stem cells. Some factors such as aging, neurodegenerative diseases, head trauma, brain tumor extraction and infection cause olfactory dysfunction which significantly influences physical wellbeing, quality of life, mental health, nutritional status, memory processes, identifying danger and is associated with increased mortality. Therefore, finding a treatment to improve olfactory dysfunction is needed. Recent research efforts in the field have shown some very promising new approaches to treat olfactory dysfunction. This review explores the current studies that have addressed therapeutic approaches to improve olfactory neuron regeneration based on cell transplantation therapy, modulation of physiological olfactory dysfunction and drug treatments.

Key Words: olfactory; neuron; regeneration; anosmia; loss of smell; degeneration; bulbectomy; ensheathing cells; growth factor; epithelium; receptor

Introduction

The olfactory system has a unique ability to regenerate throughout life. Stem cells that reside in the olfactory epithelium lining the nasal cavity, generate new neurons throughout life. The capacity for ongoing neurogenesis in the adult mammalian exists not only in the main olfactory epithelium (OE) lining rostral part of nasal cavity but in the neuroepithelium lining vomeronasal organ (VNO) localised at the basal part of nasal septum. Olfactory receptor neurons (ORNs) in OE which are responsible for detection of odour project their axons to the olfactory bulb (OB, in the brain) to make functional connection with the second order neurons, mitral cells. VNO neurons which are responsible for detection of pheromones extend their axons to the accessory olfactory bulb (AOB) which localise posteriorly to the OB (**Figure 1A**). Both olfactory axon fascicles (olfactory nerve) and VNO neurons axons are wrapped by unique glial cells, olfactory ensheathing cells (OECs) (**Figure 1C, D**) which are thought to contribute to regeneration of olfactory sensory axons throughout life (Chehrehasa et al., 2010; Pellitteri et al., 2010). After injury, both ORNs and VNO neurons degenerate, however they are rapidly replenished by new neurons arising from stem cells which localise in the basal layer of OE and VNO epithelium (**Figure 1B**).

Unfortunately, regenerative capacity of the olfactory system decreases with age, neurodegenerative diseases, inflammation, chronic sinus infection and anterior skull base surgery (Keller and Malaspina, 2013). Where regeneration of ORN fails, either through normal aging or other pathophysiological processes, this leads to clinical olfactory dysfunction or anosmia.

Olfactory dysfunction increases the mortality of adult individuals up to four times (Pinto et al., 2014). It affects quality of life of the affected individual, through difficulties in detecting hazardous events such as natural gas leaks, fires, hazardous chemical vapors and decayed food (Miwa, 2001; Santos et al., 2004; Bonfils et al., 2008; Nordin et al., 2011).

Therefore, finding potential treatments or strategies to improve sense of smell is critical. Recent research efforts in the field have shown some promising approaches to treating anosmia. The aim of this review is to outline factors regulating olfactory nerve dysfunction and possible treatments to improve olfactory function.

Physiological Modulation of Olfactory Dysfunction

Olfactory dysfunction and the amount of regeneration of olfactory receptor neurons after injury depends upon the degree and type of injury. Olfactory nerve transection is a common type of injury in which the olfactory nerve is severed as it traverses the cribriform plate. An alternative type of injury is unilateral removal of the OB which eliminates target tissue and leads to degeneration of ORNs (Chehrehasa et al., 2008) (**Figure 1B**). Kobayashi and Costanzo (2009) showed using different types of metal blades for olfactory nerve transection could affect the extent of scar formation and subsequently the level of olfactory nerve regeneration.

Peripheral damage to olfactory epithelium is another type of injury which can be induced by exposure to methyl bromide (MeBr) (Holbrook et al., 2014), Triton X-100 (Jo et al., 2015) or methimazole (Chehrehasa et al., 2010). In these

*Correspondence to:

Fatemeh Chehrehasa, Ph.D.,
fatemeh.chehrehasa@qut.edu.au.

orcid:

0000-0002-3702-9179
(Fatemeh Chehrehasa)

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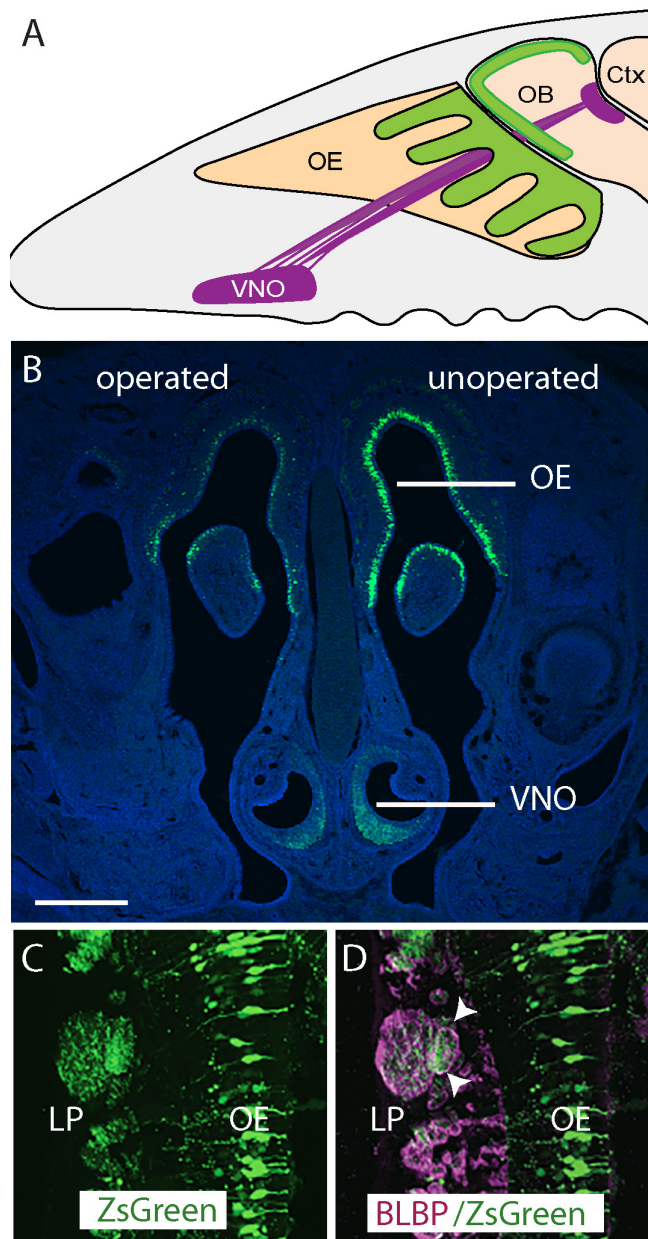


Figure 1 Degeneration of olfactory neurons in response to injury. (A) Schematic sagittal view of the mouse nasal cavity showing the location of main olfactory epithelium (OE). (B) Coronal sections of the nasal cavity of ZsGreen mice after unilateral bulbectomy showing OE and VNO contain numerous neurons (green) in the unoperated side compared to the bulbectomized side. (C, D) Anti-BLBP immunostaining of main olfactory mucosa revealed that OECs (magenta) wrapped the olfactory axons (green) projected in lamina propria where they formed fascicles (arrowheads). Scale bar is 540 μ m in B; 50 μ m in C, D. OB: Olfactory bulb; VNO: vomeronasal organ; AOB: accessory olfactory bulb; Ctx: cortex; LP: lamina propria.

cases, the overall olfactory nerve is left mainly unaffected however there is some glial reaction to the large scale of axonal degeneration (Williams et al., 2004).

Olfactory dysfunction is modulated by cytokines. Leukaemia inhibitory factor (LIF) and nitric oxide (NO) are known to play essential roles in regeneration of the olfactory epi-

thelium after injury. A study by Lopez-Arenas et al. (2012) showed LIF promotes proliferation of neuronal progenitor cells via increasing level of inducible form of nitric oxide synthase (iNOS) in the olfactory epithelial cell culture. NO is a diffusible intercellular messenger which is produced upon activation of the enzyme nitric oxide synthase (NOS) and it plays an important role in neurogenesis of the olfactory epithelium (Lopez-Arenas et al., 2012).

Cell Transplantation Therapy with Olfactory Dysfunction

Cell transplantation therapy has been studied as a therapeutic target for the functional restoration of the olfactory epithelium. Mesenchymal stromal stem cells are known to secrete and induce neurotrophic factors and angiogenic cytokines (Joyce et al., 2010). There is a correlation between restoring olfactory function and the expression of neurotrophic factors like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Jo et al., 2015). Therefore, mesenchymal stromal stem cells, theoretically, would be an effective therapeutic target for treating anosmia. Bone-marrow derived stem cells (BM-MSC), adipose tissue derived stem cells (A-MSC) and human cord blood-selected CD133⁺ stem cells (HSC) are all mesenchymal stromal stem cells that have been tested and transplanted into the injured olfactory epithelium.

BM-MSC transplantation has proven to be effective in restoring olfactory epithelium after injury. Jo et al. (2015) induced degeneration of the OE in male rats by using Triton X-100, followed by the introduction of BM-MSC intranasally. Four weeks after transplantation, OE thickness and cellular composition returned to normal. Restoration rate of the olfactory function after BM-MSC transplantation was significantly higher in treated animal than the control group (Jo et al., 2015).

This study also found expression levels of both nerve growth factor NGF and BDNF increased significantly in the transplanted group compared to the control, suggesting the transplanted cells restored neurotrophic factors to help regeneration of the olfactory neurons (Jo et al., 2015).

Another study also examined the effectiveness of BM-MSC transplantation on olfactory mucosa. Olfactory degeneration was induced by unilateral Triton X-100 irrigation on Sprague-Dawley rats. Morphological restoration of the olfactory mucosa was observed at 4 weeks after transplantation which were higher in the treated side compared to the control (Kwon et al., 2016).

In another study, BM-MSC were transplanted into lateral ventricle of the brain after radiation therapy to rescue the animals. This study showed that although the transplanted cells migrated and reached the OB, they were not able to incorporate into OB interneurons. The structural and functional damage to the OB persisted up to one year post injury (Díaz et al., 2011) indicating long term effects of cell transplantation requires more investigation.

Franceschini et al. (2014) transplanted A-MSC to immu-

nodeficient mice with permanent damaged in dorsomedial olfactory region (induced by dichlobenil inoculation). This study showed the transplanted cells integrated in the lesioned olfactory epithelium and clusters of differentiated cells were observed in the epithelium. There was a marked increase in the thickness of the epithelium and OMP immunoreactivity in the transplanted group compared to the control group (Franceschini et al., 2014).

Another study by Kim et al. (2009) also confirmed transplantation of A-MSC on olfactory epithelium following olfactory transection in rats promoted regeneration of olfactory epithelium.

HSC were transplanted into injured olfactory epithelium of *nod-scid* mice. This study showed the transplanted animals exhibited improved neuronal recovery with an increase expression of growth associated protein 43 (GAP-43) which is a marker of regenerating neurons (Franceschini et al., 2009). Overall BMSC's have shown the most promise out of the MSC transplantation currently being investigated.

Neural stem cells (NSC) have also been investigated as a potential treatment for anosmia. Lee et al. (2010) studied transplantation of NSC into injured olfactory epithelium. In this study, extracted NSC of the olfactory bulb from GFP transgenic mice, were transplanted into injured olfactory epithelium. Behavioural tests and histological studies showed the transplanted group had a better recovery of olfactory function in terms of the food-finding test and the expression of OMP compared to the control (Lee et al., 2010).

Olfactory ensheathing cells (OECs) are another potential for cell transplantation therapy. They are a unique glial cell type that ensheath olfactory axons into large bundles as they traverse from the lamina propria to the nerve fibre layer of the olfactory bulb. They express guidance cues and extracellular matrix molecules to assist in growth and provide directional and tropic support to the primary neurons to successfully reach the olfactory bulb (Cao et al., 2010). Chehrehasa et al. (2010) showed that the presence of a permissive environment by initial migration of OECs ahead of regenerating axons enhanced axonal regrowth and regeneration. Olfactory degeneration was induced by unilateral bulbectomy followed by methimazole administration which caused a delay in olfactory axonal regrowth and allowed OECs to migrate ahead of the regenerating axons into the operated cavity (Chehrehasa et al., 2010). This study showed the presence of indigenous OECs ahead provided a permissive environment which improved regeneration of olfactory nerve.

Transplantation of purified DsRed-fluorescent OECs (exogenous) into the operated cavity of wild type mice also improved olfactory axon regeneration (Chehrehasa et al., 2010). The regenerated olfactory axons projected significantly deeper into the operated cavity in the transplanted animal compared to control group (Chehrehasa et al., 2010).

Another characteristic of OECs is proliferation and migration along the olfactory pathway in response to a widespread injury, unilateral bulbectomy. The proliferation of OECs occurred not only in the operated cavity but in the lamina propria of olfactory mucosa (Chehrehasa et al., 2012). This

study confirmed proliferated OECs migrated from the lamina propria into the injury site (operated cavity) (Chehrehasa et al., 2012). Similar results were found in the accessory OECs as they proliferated in response to bulbectomy similar to the main olfactory OECs (Chehrehasa et al., 2014).

It is believed that the phagocytic capacity of OECs is a key factor in improving olfactory axonal regeneration, as they can potentially accelerate the removal of debris from the injury site and thereby improve conditions for neuronal regeneration (Lankford et al., 2008). An increase in phagocytic activities of main and accessory olfactory OECs confirmed after olfactory epithelium injury (unilateral bulbectomy or methimazole administration) and it has been confirmed they were responsible for major phagocytosis of the cell debris after widespread degeneration of primary olfactory and VNO neurons (Nazareth et al., 2015a, b). A recent study showed OECs secrete transforming growth factor (TGF)- β 1 which can increase their phagocytic activity through regulating integrin/MFG-E8 signalling pathway (Li et al., 2017).

Drug Treatment of Olfactory Dysfunction

Statins or HMG-CoA reductase inhibitors are traditionally used for lowering cholesterol. They have putative neuroprotective properties on the nervous system (Douma et al., 2011). The regenerative action of statins is demonstrated in Kim et al.'s study where the injured rat olfactory mucosa was treated with statin. This study showed the statin treatment group had an increase in expression level of olfactory marker protein and thickness of olfactory epithelium compared to control. The behavioural test also confirmed the treatment group had a higher pass rate in a food-finding test compared to control group (Kim et al., 2012).

Valproic acid (VPA), a histone deacetylase inhibitor, has shown some promising neuroregenerative properties in rodents with spinal cord injury (Lv et al., 2012). Ogawa et al. (2014) explored the effects of VPA on the regeneration of olfactory sensory neurons. Degeneration of the olfactory epithelium was induced by methimazole injection, after which the animals received daily VPA orally. The results showed the treatment increased epithelial thickness and number of olfactory marker protein (OMP) positive cells, Ki-67 (proliferative cells) and growth-associated protein-43 in the olfactory epithelium (Ogawa et al., 2014). These results suggest VPA stimulates proliferation and differentiation of olfactory precursor cells which in turn promotes regeneration of the olfactory system.

Glucocorticoid is an anti-inflammatory corticosteroid that shows promise in the regeneration of the olfactory system. Kobayashi and Costanzo (2009) studied effects of glucocorticoid (dexamethasone) after olfactory nerve transections in mice to determine whether anti-inflammatory steroid treatment can enhance recovery of the olfactory nerve after sever injury. This study showed the treatment improved regeneration of the olfactory nerve and reduced inflammatory response and scar tissue formation in the injury site (Kobayashi and Costanzo, 2009).

Another study investigated the efficacy of glucocorticoids

for improvement of olfactory function in patients suffering postviral olfactory loss. Seo et al. (2009) treated some patients with prednisolone only and the rest were treated with prednisolone plus *Ginkgo biloba* (herb used for brain health). Olfactory function tests were performed before and after treatment which showed both groups had improvement in the olfactory function test, however the combined therapies of prednisolone plus *Ginkgo biloba* were more efficient in patients with post viral olfactory dysfunction (Seo et al., 2009). This was further confirmed with a more recent study finding after application of glucocorticoid, the expression of OMP in the olfactory mucosa was upregulated in allergic rhinitis animal models (Wang et al., 2017). Schriever et al. (2012) treated anosmic patients with systemic corticosteroids (methylprednisolone) for 14 days. The treatment resulted in an improvement in olfactory performance tests in almost half of the total patients (Schriever et al., 2012). Xu et al. (2016) investigated the effects of triamcinolone (a corticosteroid) in improvement of olfactory function in patient with rhinosinusitis that underwent endoscopic surgery. This study found a significant improvement in the olfactory functions among anosmic and hyposmic patients after operation compared to pre-operation in the treatment group compared to control (Xu et al., 2016).

Vitamins and minerals are essential for healthy nervous system. Vitamin A helps to form and maintain healthy body structures and has recently been shown to play a role in the regeneration of olfactory receptor neurons. Hummel et al. (2017) investigated the effectiveness of topical vitamin A in patients with post-infectious and post-traumatic smell disorders. This study showed thirty-seven percent of all post-infectious patients treated with vitamin A exhibited functional improvements compared to twenty-three percent improvement observed in the control group (Hummel et al., 2017).

Growth factors treatment is another potential treatment to improve olfactory regeneration. They stimulate cellular growth, proliferation and regeneration and are important for regulating cellular processes (Iwata et al., 2010), therefore, introducing them into the injury site can potentially restore homeostasis and encourage normal neurogenesis.

The effect of basic fibroblast growth factor (bFGF) was studied on olfactory epithelium of young and aging mice. bFGF was intranasally administered in animals and proliferating cell nuclear antigen (PCNA), OMP, and GAP43 immunolabelling were used to detect any changes in the olfactory epithelium. These results showed a significant increase in the number of GAP-43 positive neuron, however there was no significant change in the number of OMP positive cells or mature olfactory receptor neurons (Nishikawa et al., 2009).

Nota et al. (2013) examined the effect of bFGF on the injured olfactory epithelium of mice. The anosmic mice received intranasal bFGF either in forms of hydrogel or drip infusion. Their results showed bFGF-hydrogel increased epithelium thickness and there was an increase in the number of mature ORNs expressing OMP (Nota et al., 2013).

Overall these studies showed daily injections of bFGF and TGF- α after injury can increase proliferation rate of olfac-

tory progenitors cells in the olfactory epithelium which can improve olfactory neuron regeneration.

Conclusion

The sense of smell is a necessity to the human existence. Olfactory dysfunction significantly influences executive functions including: physical wellbeing, quality of life and nutritional status. Currently, there is no proven effective treatment. Research in this field is hopefully bringing us closer to finding a potential therapeutic target. Cell transplantation therapy, anti-inflammatory drugs, organic substances, and growth factors treatment have been shown to alter the environment to improve olfactory regeneration. The potential treatment modulate olfactory dysfunction by stimulation of progenitor cells proliferation and differentiation to repopulate the olfactory epithelium, reducing scar tissue formation at injury site and modulation of immune response. All therapies need further investigation and perhaps combining therapies might be the future for an effective therapy.

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