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Review

Mechanisms and potential treatments for declining olfactory function and neurogenesis in the ageing brain

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The role of olfactory function in maintaining quality of life and as a potential surrogate marker of neurogenic activity in the elderly brain is an underappreciated topic. The olfactory system is complex and is unusual in that its function is maintained by neurogenesis at multiple sites throughout the lifetime of an organism, which in humans may be over 80 years in length. Declines in olfactory function are common with advancing age and this is associated with reductions in the quality of life, the perception of flavour and neurogenesis. These reductions in neurogenesis may simply be a consequence of advancing age or may reflect the nascent development of underlying neurological dysfunction. There are a number of potential therapeutic interventions that can result in a gain of olfactory function, these range from behavioural modification, to dietary supplementation and pharmaceutical intervention but they are all thought to work in part by increasing hippocampal and olfactory neurogenesis. This review discusses the mechanisms underlying olfactory decline in the elderly, reviews a number of potential strategies for improving olfactory function and hypotheses that increasing the rate of neurogenesis in the ageing brain would improve the quality of life not only by improving olfaction but by improving a range of cognitive processes that are dependent on neurogenesis including mood.

Key words: Olfaction, Ageing, Neurogenesis, Depression, Flavour

INTRODUCTION

A declining ability to detect, identify and correctly interpret the environmental significance of olfactory cues is a common feature of advancing age [1-9]. This often leads to a decline in the quality of life, reduced environmental awareness and a reduction in the appreciation of "taste" and "flavour", which is thought to result in a diminished appetite and nutritional neglect. In elderly human populations attempts to definitively link olfactory decline with nutritional neglect have yielded ambiguous results [10-13]. This is despite the fact that a high incidence of "taste" dysfunction is actually reflective of declines in olfactory function [14]. And that the perception of "flavour" is thought to be generated by a multimodal integration of taste, olfactory, textural and temperature information in a distributed network encompassing the tractus nucleus solitarious, insula, operculum, orbitofrontal, pyriform, and anterior cingulate cortices [15 16]. Despite a degree of ambiguity concerning the exact relationship between olfactory decline and nutritional neglect a number of studies have shown that declines in olfactory function are associated with an increased risk of mortality in the elderly [17-20]. One recent study in particular demonstrated that declines in olfactory function were strongly associated with an increased risk of mortality but declines in visual or auditory function were not [17]. It has long been presumed that a decline in olfactory function is part of the normal ageing process [1-14] that parallels a generalised decline in sensory and cognitive function that occurs in the absence of obvious neurological disease states and impaired olfactory function does predict generalised cognitive decline in the elderly [21]. However, a number of diseases common in the

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elderly, are also associated with olfactory dysfunction. These include depression [22-25], Alzheimer's disease [24-27], prion disease [26], epilepsy [28 29], Parkinson's disease [30 31], stroke [32, 33], physical trauma [34] and diabetes [35 36]. In some instances olfactory decline precedes the onset of clinical symptoms by a considerable margin [30 31], suggesting that the olfactory declines seen in "normal" ageing patients may also be contributed to by the nascent development of neurological diseases often seen in the elderly.

The obvious questions that arise from these observations are: What mechanisms contribute to a decline in olfactory function in the "normal" ageing brain? Are there practical strategies for improving olfactory function? And would improving olfactory function lead to an increase in the quality of life and improvements in health in the elderly population? In this review we focus on the importance of a number of mechanisms that contribute to olfactory decline and examine the development of a number of strategies that may lead to a gain in olfactory function and subsequent improvements in the quality of life.

CHANGES IN THE OLFACTORY SYSTEM DURING THE AGEING PROCESS

An appreciation of how the human olfactory system extracts physiologically and behaviourally salient information from the environment is complicated by the fact that most research into olfactory function is conducted in rodents who possess two functional and neuroanatomically distinct olfactory systems. The vomeronasal system in rodents is thought to be primarily responsible for the transmission of inter-species reproductive, social and physiological salient information transmitted by pheromones contained in urine. The alternative main olfactory system is considered to function as an analyser of "general" volatile odours. In primates, the vomeronasal system becomes evolutionarily redundant around the time that trichromic colour vision evolves [37] and as a consequence the human olfactory system relies on the main olfactory system only. This can make extrapolation of data derived from rodents problematic, but the main olfactory and vomeronasal epithelial systems in rodents are functionally very similar in that their receptor neurons are generated from stem cells throughout the life of the organism and differentiate into neurons that express 1-2 single olfactory receptors per cell.

THE OLFACTORY EPITHELIUM

In humans the main olfactory epithelium is localised in the nasal cavity and is positioned around the cribiform plate. Its olfactory receptor neurons are unusual in that they continue to be generated throughout life from stem/ progenitor cells, which differentiate into odorant-detecting olfactory receptor neurons which send projections into the mucous layer to sample the olfactory environment and unmyelinated axons through the cribiform plate to transfer information to the olfactory bulb [38 39]. On differentiation, each olfactory receptor neuron expresses one olfactory selected from around 1,000 subtlety different G-protein coupled odorant receptor genes [39-41]. The proximal cues that influence this selection process are poorly understood but in the functionally similar but closely studied murine vomeronasal system the differentiation and selection process the cue is urinary pheromones, which act to initiate differentiation and influence the receptor selection process [42 43].

During ageing a number of changes are thought to occur to the olfactory epithelium primarily the number of differentiating stem cells are reduced [44-47], a process that in rodents occurs in parallel with reductions in the differentiation of vomeronasal stem cells [48-50]. This decline in neural differentiation is accompanied with a decline in the expression of Asc11, a pro-neural gene required for generation of olfactory sensory neurons [51] and epidermal growth factor signalling [39]. The olfactory epithelium also demonstrates remarkable anatomical [52] and functional [53] regenerative capabilities. Following olfactory lesions anatomical recovery is evident with ~45 days and odorant expression patterns are re-established within 90 days [54]. It has been hypothesised that there may be a reduction in the regenerative capacity of the olfactory epithelium as an animal ages and this is supported by evidence in the mouse. The efficacy of the regenerative process following a methimazole-induced lesion at the age of 16 months was considerably lower than that occurring at 10 days or 3 months old, the number of olfactory receptor neurons being around a third of those in the younger groups [55].

Two potential consequences of age that these studies fail to address is that the epigenetic stimuli that induce the transformation of olfactory stem cells into functional receptor neurons are unclear, in the mouse vomeronasal system this stimulus is urinary pheromones [42 43]. The mouse vomeronasal organ also expresses 44 main olfactory receptors with the same 1 olfactory receptor per neuron expression pattern displayed in the main olfactory epithelium and the differentiation and olfactory receptor expression of these neurons is also under the control of urinary pheromones [43]. In both systems differentiation is reduced with age, in the vomeronasal system this may reflect a reduction in the sensitivity of vomeronasal stem cells to the transformative epigenetic effects of urinary pheromones, and this reduction in sensitivity to the environmental epigenetic cues that influence differentiation may also occur in the main olfactory

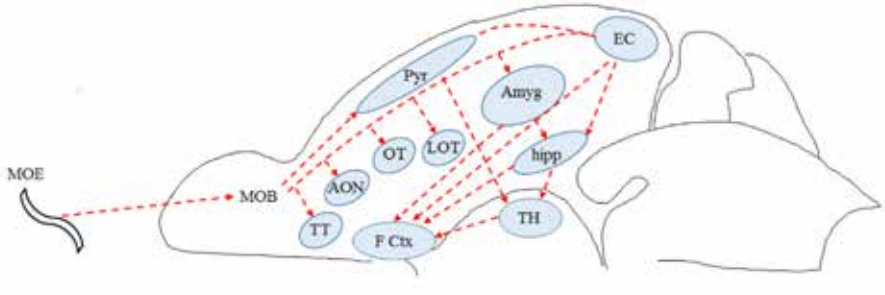
epithelium. Delivering drugs targeted to the olfactory epithelium by an aerosol is technically very feasible and investigation of the epigenetic mechanisms that control the differentiation of olfactory stem cells into functional olfactory receptor neurons may lead to treatments that support increased olfactory function in the elderly. One other problem that these studies do not address is that olfactory receptor neurons send unmyelinated projection to the glomerular layer of the olfactory bulb, this is a difficult process requiring successful axonal targeting and transport over a considerable distance. Although this is an underexplored topic in the olfactory system, these axonal processes in other models decline considerably with age [56-58] and it is likely that a similar process occurs in the olfactory system.

Primary olfactory processing. The olfactory bulb

The main olfactory system for an underappreciated sensory modality is surprisingly complex and many of the important but subjective experiences with an olfactory component including the perception of "palatability" or "flavour" rely on multisensory integration of olfactory with other inputs including taste, texture and temperature [16], which adds a further layer of complexity to attempts to appreciate olfactory function. A diagram illustrating the basic structure of the main olfactory system is outlined in Figure 1.

Axonal processes from olfactory receptor neurons synapse on the dendrites of the primary projection neurons of the olfactory bulb, the mitral and tufted cells, which together form a structure called the glomerulus. They are excitatory glutaminergic neurons, their dendrites project to a single glomerulus, and as well as receiving input from olfactory receptor neurons they have extensive input from lateral dendrites. Despite being excitatory neurons, the modification of these cells occurs by reciprocal dendrodendritic connections with γ-aminobutyric acid (GABA)ergic granule cells, the activity of which is modulated by centrifugal input from neurons outside the olfactory bulb. The incoming axons from the olfactory receptor neurons also synapse on local GABAergic interneurons (periglomerular cells) that are activated by glutamate released from mitral and tufted cells and provide an inhibitory influence within the glomerulus. Glomeruli are the first synaptic relay in the olfactory pathway and play a basic role in smell perception. A second level of olfactory processing occurs at the granular layer of the olfactory bulb by inhibitory GABAergic neurons that are activated by glutamate released from lateral dendrites of mitral cells, which act to inhibit the network in contrast to enhancement between mitral cells [59]. The olfactory bulb is also unusual in that its neurons are replenished throughout life by neuroblasts generated in the sub ventricular zone and transported via the rostral migratory stream [60].

The volume of the olfactory bulb and the number of its laminae are thought to decline with age, but this decline in volume is thought to interact with a number of environmental influences including smoking [61-63]. Olfactory bulb volume is a gross measurement but correlations have been found between volume and odour recognition thresholds in the normal ageing brain [62]. Changes in the expression of proteins normally thought to be associated with dementia may also increase in the "normal" ageing brain. The proliferation of neurodegenerative fibrillatory tangles occurs in 35.5 to 40.5% of non-demented older patients [64] and the expression of α-synuclein increases as a consequence of ageing in the marmoset brain [65]. The efficient function of the olfactory bulb is also dependent on the continuous replenishment of neurons generated in the sub-ventricular zone, a process that is reduced in number and disrupted with regard to spatiotemporal organisation as a consequence of age [66 67].



MOE: main olfactory epithelium, MOB: main olfactory bulb, TT: taenia tecta, AON: accessory olfactory nucleus, OT: olfactory tubercle, LOT: lateral olfactory tract, Pyr: pyriform cortex, FCtx: frontal cortex, Amyg: amygdala, hippo: hippocampus, TH: thalamus and EC: entorhinal cortex.

Figure 1. Simplified structure of the main olfactory system, showing basic interconnectivity and convergence on the frontal cortex.

Secondary and tertiary olfactory processing. A distributed network

Axons from the olfactory bulb project into a distributed olfactory processing network. The engagement of each part of this network contributes to the processing of olfactory cues, the formation and recall of olfactory memories, the exact contributions of each stage of this network are beyond the scope of this review and are extensively covered elsewhere [68]. The first relays in this network are the anterior olfactory nucleus, olfactory tubercle and the pyriform cortex, (a large planar cortical olfactory area) [69]. The functional interconnectivity of the network is complex but olfactory information from these three areas are then routed through a distributed network encompassing the amygdala [70-72], entorhinal cortex [73 74], hippocampus [75] and the frontal cortex [76 77]. Many of these areas send projections back to the olfactory bulb where they terminate primarily in the granule layer.

A number of changes occur within this network as a consequence of ageing, these include a reduction in the volume of the hippocampus, amygdala, pyriform cortex and accessory olfactory nucleus [78]. The volume, neuronal organisation and localisation of the Islands of Calleja is altered by advancing age and is thought to contribute to a decline in olfactory function [79]. Neurofibrilatory and α-synuclein pathology in the olfactory bulb is associated with olfactory dysfunction in elderly non-demented patients, which is likely to compromise the ability of mitral and tufted cells to project to their appropriate targets [64 65]. The olfactory system with its dependence on lifelong neural replenishment and the requirement that these new neurons be correctly integrated into existing neural structures is a classic example of extreme neuroplasticity. The mechanisms underlying neuroplasticity are extremely complex and warrant a review of their own but the mechanisms mediating neuroplasticity do decline with age. The expression of brain derived neurotrophic factor also declines with age [80] which is likely to compromise the ability of new neurons to integrate successfully into pre-existing networks.

THE AGEING OLFACTORY SYSTEM AS A THERAPEUTIC TARGET

The olfactory system is unusual in that its function is dependent on the continuous replenishment of neurons throughout the lifetime of an individual. In elderly humans, this process therefore needs to be maintained over an 80 year period, which given the relative decline in other cognitive processes is an impressive feat. This occurs in four levels of the olfactory system: the olfactory epithelium [37-43], the olfactory bulb [81], sub ventricular zone, which provides replacement GABAnergic interneurons to the olfactory bulb [60 66 67] and the dentate gyrus of the hippocampus [82 83]. Increasing neurogenesis does provide a route to improve olfactory function in the elderly, which also has the advantage that it may improve other indices of life quality, including mood. The importance of olfaction to human wellbeing is underappreciated but some interventions that may improve olfactory function are simple and may provide other benefits.

Behavioural modification; It is well recognised that increases in physical activity promote increased neurogenesis and immature neuron survival in both the hippocampus [84] and sub-ventricular system olfactory system [85] but not in the olfactory bulb itself [86]. A number of different mechanisms have been proposed to mediate the interactions between exercise and adult neurogenesis including brain derived neurotrophic factor [87 88], insulin-like growth factor 1 (IGF1) [89 90], vascular endothelial growth factor (VEGF) [91] and the Wnt signalling pathway [92 93]. Neurogenesis induced by exercise is also thought to function as one of the experience driven mechanisms that promote neural plasticity [94]. For obvious reasons conclusive attempts to link exercise, neurogenesis and increases in olfactory function in elderly patients are problematic but human epidemiological based studies have demonstrated that exercise does reduce olfactory decline in elderly patients [95]. The olfactory system expressing high levels of plasticity is responsive to its environment. Olfactory environmental enrichment is also associated with increases in neurogenesis [96 97], improvements in short-term odour memory [98] and olfactory discrimination [99 100]. This work has been undertaken in rodents and the practical extrapolation of this approach to elderly humans is unclear. Olfactory function is also decreased in the obese, a phenotype that is likely to interact and be associated with ageing and low activity levels [101 102]. Hippocampal neurogenesis is thought to be reduced in depression which may contribute to the development of deficits in olfactory function [22-25], one effect of antidepressants is that they increase neurogenesis and this is probably contributed too by reductions in stress that occur with an increase in mood. Treating depression in the elderly by alternative non-pharmaceutical means including cognitive behavioural therapies may also contribute to improvements in olfactory function [103-105].

Pharmacological treatment; a range of pharmacological interventions may induce gains in olfactory function, these range from dietary supplementation to more traditional pharmacological treatments.

The consumption of omega-3 fatty acids increases olfactory function [106 107], an effect that may be associated

with increased neurogenesis [108]. A range of other dietary supplements may also promote neurogenesis which as an advantageous side effect may improve olfactory function, these include curcumin [109], flavonoids [110 111], vitamin A [112] and caffeine [113].

Olfactory function and neurogenesis is also reduced in depression and it is noteworthy that anti-depressives are thought to work in part by increasing neurogenesis in the dentate gyrus [22-25 103-105]. However it is thought that they also induce increases in olfactory neurogenesis and olfactory function in rodents [104], this is likely to be an effect replicated in humans as recovery from depression is thought to result in gains of olfactory function [105]. Other drugs can also induce olfactory neurogenesis and differentiation, these include valproic acid and other histone deacetylase inhibitors used to treat epilepsy [114 115]. Two other non-pharmacological interventions for depression also increase neurogenesis and increase olfactory function, electroconvulsive therapy and transcranial magnetic stimulation [116-119].

CONCLUSIONS

The neural systems supporting olfactory function are complex and are unusual in that they rely on the continuous neurogenesis throughout life. This occurs at four separate sites, the olfactory epithelium [38-43], endogenously in the olfactory bulb [81], the sub-ventricular zone [60 66 67] and the dentate gyrus [82 83]. Olfactory function declines with advancing age and this is thought to reflect a reduction in this process [1-14 44-47]. A range of neurological disorders common in the elderly are also associated with reductions in neurogenesis and a decline in olfactory function may therefore be a surrogate marker or a harbinger of a developing neurological condition [22-35]. Olfaction is an underappreciated sensory modality in humans but declines in olfactory function are predictive of mortality in the elderly, whilst declines in the more appreciated senses of vision and auditory function are not [17-21]. This may reflect the reliance of olfaction on neurogenesis, a decline in which may be a robust surrogate marker of declining neurological function. Declines in olfactory function also lead to a reduction in the quality of life including the reduction of “flavour” or “palatability”, which in turn may be reflective of this decline in neurogenesis [10-16]. There are a number of potential mechanisms by which olfactory function may be improved in the elderly and given olfaction’s reliance on neurogenesis it is unsurprising that many of these are thought to work by improving this function. Olfaction is an underappreciated sensory modality and its role in the maintenance of a high quality of life and as a potential harbinger of mortality in the elderly is an underexplored topic that warrants further investigation. In particular improvement of neurogenesis in the elderly by a variety of approaches may yield improvements in a range of cognitive functions in parallel with olfaction including mood.

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