

## “ECTOPIC” GUSTATIVE AND OLFACTORY RECEPTORS IN THE BRAIN – NEW TARGETS FOR NEURODEGENERATION THERAPY?

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### Abstract

Taste receptors (TR), as well as olfactory receptors (OR), have been recently detected in human brain, but their roles in nervous physiology are still unclear. The expression of these “ectopic” receptors is dysregulated in human subjects with neurodegenerative diseases, in a gradient compatible with disease staging. Various plant-derived tastants proved neuroprotective activity. Interestingly, in traditional Chinese medicine (TCM), medicinal plants activities are dependent on their flavour, which is the result of their blended gustative and olfactory properties. According with this ancient theory, various flavours have specific systemic therapeutic effects, mediated by the flavour itself. Bitter, sweet and pungent medicinal plants are used to treat neurodegenerative diseases in TCM. The purpose of this paper is to integrate the traditional and modern knowledge on neurodegenerative diseases and to elaborate a new (ethno)pharmacological hypothesis according to which one of the multiple mechanisms of action of the neuro-protective plant derived tastants may be mediated by the brain TRs and ORs.

### Rezumat

Receptorii gustativi, precum și receptorii olfactivi, au fost recent descoperiți la nivelul creierului uman, dar rolurile lor în fiziologia nervoasă nu sunt complet elucidate. Expresia acestor receptori ectopici este dereglată la pacienții cu boli neurodegenerative, într-o măsură comparabilă cu stadiul bolii. Diverse substanțe aromatice de origine vegetală au demonstrat o activitate neuroprotectoare. În medicina tradițională chineză, activitățile plantelor medicinale depind de aroma lor, care este rezultatul proprietăților lor gustative și olfactive, combinate. Conform acestei vechi teorii, diferitele arome au efecte terapeutice sistemice specifice, mediate de aromă. Plantele medicinale amare, dulci și picante sunt utilizate pentru tratarea bolilor neurodegenerative în medicina tradițională chineză. Scopul acestei lucrări este de a integra cunoștințele tradiționale și moderne cu privire la bolile neurodegenerative și de a elabora o nouă ipoteză (etno) farmacologică conform căreia unul dintre mecanismele multiple de acțiune ale substanțelor aromatice neuroprotectoare de origine vegetală poate fi mediată de receptorii olfactivi și gustativi.

**Keywords:** neurodegenerative, medicinal plants, taste receptors, olfactory receptors, Traditional Chinese Medicine

### Introduction

Taste and olfaction belong to the class of chemical senses. Unexpectedly, various taste receptors (TRs), as well as olfactory receptors (ORs), have been recently detected in non-sensorial organs, including human brain [5, 23, 60, 68]. Their physiological roles in the brain are still unknown. The expression of these “ectopic” receptors is dysregulated in human subjects with neuro-degenerative diseases, in a gradient compatible with disease staging [5, 24]. Despite recent advances in understanding the complex pathogenesis of these pathologies, the efficacy of the available therapies remains suboptimal [53]. The use of phytochemicals (plant derived agents) represents a new research trend in neurology research. More and more studies are suggesting that certain medicinal plants or isolated phytochemicals may promote neurogenesis and prevent neuronal loss, emerging as potential

therapeutic agents to improve structural and functional recovery in neurodegenerative diseases [17]. Various plant-derived tastants or odorants proved neuroprotective and neuroregenerative activity, *in vitro*, *in vivo* or even in clinical studies. Whether the cerebral taste and olfactory receptors are involved or not in their mechanism of action is not yet studied.

Interestingly, in Traditional Chinese Medicine, medicinal plants activities are dependent on their flavour [9], which is considered to be, by the modern scientists, a multi-sensorial modality, resulted from blending of all the three basic chemosensations (taste, odour, irritative orosensations). According to the Chinese ancient theory, various flavours have specific systemic therapeutic effects, mediated by the flavour itself [9, 88]. This traditional concept of flavour as descriptor and mediator of the ethnopharmacological activities is also found in

other ethnomedical systems in Asia, America, and Europe [25, 43], and recent studies suggested that it may not be completely devoid of a biological basis [20, 26].

The purpose of the present paper is to suggest an alternative therapeutic approach in neurodegenerative diseases (e.g. Alzheimer's disease (AD)), which was inspired by the flavour theory of traditional Chinese medicine (TCM) and the new discovery of TRs and ORs in brain.

This new integrative (ethno)pharmacological paradigm hypothesizes that one of the multiple mechanisms of action of the neuroprotective phytoconstituents may be mediated by the brain TRs and ORs.

### **Taste receptors and olfactory receptors**

Bitter, sweet and umami taste receptors share a common transduction mechanism, being G protein-coupled receptors [87]. Sweet taste receptors are T1R2/T1R3 heterodimers coupled with G protein. Umami taste receptors are also heterodimers (T1R1/T1R3) that bind L-amino acids (e.g. glutamate, aspartate). Bitter taste receptors belong to the T2R family of receptor proteins [87]. Amiloride-sensitive epithelial sodium channels (ENaC) play the major role in salty taste perception [30]. Although the molecular identity of sour receptor is still unknown, 2-pore-domain potassium channel (K2P) is considered to be the best candidate [45]. The key transducers of pungency are several members of the transient receptor potential (TRP) channels family: TRP vanilloid type 1, 3 and 4 (TRPV1, TRPV3 and TRPV4), TRP ankyrin type 1 (TRPA1), TRP melastatin type 8 (TRPM8) [61].

Scientists estimated that approximately 400 different functional ORs are expressed in humans [85]. ORs are G-protein coupled receptors, the corresponding genes representing 3-5% of all genes in mammals [82].

### **“Ectopic” expression of taste and olfactory receptors**

“Ectopic” localization of TRs and ORs has been recently shown in several non-gustative and non-olfactory tissues, respectively. TRs and orosensations transducers have been detected in gastrointestinal tract, liver, pancreas, respiratory system, heart, kidney, urinary bladder, adipose tissue, testis, spermatozoa, lymphocytes, endocrine glands and brain [8, 26], while ORs and various components of olfactory signalling pathways in germinal cells, testis, kidney, heart, developing muscle, lung, prostate, skin, gastrointestinal tract, pancreas, spleen, liver, adipose tissue, brain and retina [27, 54]. Interestingly, some of the ectopically expressed OR

genes were not expressed in olfactory epithelium [85], and in contrast to the olfactory epithelial cells, a single neuron in the brain may express several ORs [23].

These discoveries have raised questions about putative non-sensorial functions of TRs and ORs in various non-sensorial organs.

Scientists discovered many extra-gustative roles of the “ectopic” TRs: relaxation/contraction of muscles in bronchia, urinary bladder, and vessels, control of appetite, innate immunity, microbial infection, cell proliferation, inflammation, and heart activity [42, 63]. There is extensive evidence regarding non-olfactory functions of OR genes. They are involved in skeletal muscle regeneration [27], angiogenesis [41], apoptosis, cell proliferation and migration [38], wound healing, glucose homeostasis [15], oxygen homeostasis through hypoxic ventilator responses [15], regulation of glomerular filtration rate [23]. Taking into account all these facts, we could conclude that TRs and ORs play a pivotal role in maintaining body homeostasis

### **TRs and ORs expression in brain and their potential function**

Highly significant for our topic is that several types of TRs, orosensation transducers and ORs have been detected in the brain, including human brain: T2R (bitter taste receptors) [18], T1R (sweet taste receptors) [60], T2P (sour) [52], ENaC (salty taste transducer) [71], TRP (pungency transducer), OR (olfaction receptors) [28, 54].

TRs and ORs are also expressed in the choroid plexus [58, 60], highly vascularized branched structures located in the cerebral ventricles, which have several functions relevant in neurodegenerative diseases (production of cerebrospinal fluid, neural stem cell renewal, neuro-protection, clearance of toxic compounds and metabolites from the brain, repair processes following brain damage) [3].

Both TRs and ORs are clearly involved in nutrient and other chemical sensing in the brain, such as detection of soluble molecules in the cerebrospinal fluid (e.g. glucose by T1R, bitter noxious compounds by T2R, polyamines such as cadaverine, putrescine, spermine and spermidine by ORs) [60, 72]. The scientists even suggested that “tasting” and “smelling” the cerebro-spinal fluid is a newly discovered function of the choroid plexus. OR also contribute to the growth of axonal cones, axonal convergence, neural connectivity modulation and sensory map formation [48].

A recent transcriptome study has shown that TR and OR transduction pathways are among the top-five pathways which are significantly regulated by the sex hormones in choroid plexus [58]. Moreover, endogenous sexual steroid hormones (e.g.

androstenedione) also activate some ORs (e.g. OR51E2, OR7D4) [39].

Taking into account the neuroprotective potential of sex hormones and their benefits in neurodegenerative disease [12], it is expected that the TR and OR transduction pathways in the brain might play a key role in the nervous system physiology and pathophysiology, which may have relevance for the therapy.

### **Neurodegenerative diseases and dysregulation of taste and olfactory receptor expression in the brain**

The most accepted theory of neurodegeneration in AD is the excitotoxicity mediated by a subtype of glutamatergic receptors called N-methyl-D-aspartate receptors (NMDAR). Both excessive and insufficient synaptic NMDAR signalling compromises neuronal cell survival and plasticity [77]. Interestingly, glutamate is the most abundant excitatory neurotransmitter in the mammalian brain [77], but also the most important umami tastant. However, NMDAR seems not to have a dominant role in umami taste transduction [70].

Nevertheless, significant dysregulation of TRs and ORs has been found in specific cortical areas of human subjects with neurodegenerative diseases: entorhinal cortex in Alzheimer's disease (AD) [5], frontal cortex in PD [24]. Altered OR expression with disease progression has also been found in transgenic mice used as an AD model.

The degree of TR expression alteration in the entorhinal cortex of AD subjects was compatible with their disease staging: increased expression of bitter taste receptor T2R13 was found at stages III-IV, and T2R5 and T2R10 at stages V-VI, without any change of these TRs in frontal cortex at any stage of AD [5].

Scientists suggested that the complex alterations of brain TR and OR gene expression, either down- or up-regulation, is an argument for the fact that these abnormalities are not caused by the neuronal loss in AD [5]. This variability of patterns is rather similar with a modulated pathological response, an idea which lends weight to our hypothesis on the therapeutic potential of herbal tastants and odorants in neuro-degenerative diseases. A potential explanation lies in the hormonal regulation of TR and OR gene expression. It is well known that AD is often associated with a decrease in sex hormone levels [62]. An animal study on gonadectomized female and male rats showed that the decline of sex hormone induced up-regulation of the bitter taste receptor (T2R) genes and phospholipase C beta2 involved in taste transduction in females, but not in males, and a more complex regulation of OR genes (102 up-regulated and 282 down-regulated genes in

female rats and 42 up-regulated genes in male rats) [58].

Olfactory receptors OR2L13, OR1E1, OR2J3, OR52L1 and OR11H1 and taste receptors T2R5 and T2R50 were down-regulated, but T2R10 and T2R13 were up-regulated at relatively early stages in the frontal cortex area 8 in PD patient brains [24]. Scientists concluded that down-regulation of human ORs in the brain of PD subjects cannot be only due to the loss of neurons since in the same samples various pattern of TRs level were detected (either unchanged or up-regulated levels of some TRs) [24].

Another interesting fact is that olfactory bulbectomy was proposed as an animal model of agitated depression, causing behavioural changes, alterations of glutamatergic transmission through the NMDA receptor, and even neuronal degeneration [29]. These aspects suggest a potential link between olfaction and neuroprotection that is worthy to be further investigated.

### **Neurodegenerative diseases in Traditional Chinese Medicine**

Brain is an extra-ordinary organ in TCM, having ambivalent characteristics (hollowness, similarly to the Yang organs, and capacity to store the vital fluid called Essence, similarly to the Yin organs). It is nourished by the Kidney, which stores Essence. Essence produces marrow, including cerebral marrow. If the Kidney Essence is deficient, the nourishment of brain is impaired, and various neurological diseases appear. These may be prevented or treated by use of Kidney tonics, many of them having a component of sweet flavour.

TCM classifies senile dementia into six categories: (1) the Marrow deficiency syndrome, (2) the Liver and Kidney Yin deficiency syndrome, (3) the Spleen and Kidney Yang deficiency syndrome, (4) the Qi stagnation and Blood stasis syndrome, (5) the Turbid Phlegm blocking Orifice syndrome, and (6) the Heart and Liver Fire syndrome [32]. One of the key factors in AD pathogenesis is "phlegm turbidity obstructing the orifices". Phlegm is derived from excessive Dampness, leading to development of Heat, drying of Fluids. In this way, Dampness eventually congeals to form Phlegm. We suggest that a possible biological basis for "phlegm turbidity obstructing the orifices" may be the accumulation of beta-amyloid and neurofibrillary tangles containing phosphorylated tau protein in the brain, which is responsible for the appearance of senile plaques ("turbid Phlegm"), and the substantial loss of synaptic profiles ("obstructed orifices").

### Flavour based therapy in Traditional Chinese Medicine: Flavour is not just about the flavour

The Five Flavour theory, an essential part of TCM system, describes the function of drugs with five tasting modalities: bitter, sweet, pungent, sour and salty [9, 88]. The flavour signifies in TCM more

than the orosensation. Each TCM flavour has specific actions on the body. More and more studies found that these associations between flavours and ethnopharmacological activities may have a biological basis (e.g. see Table I for bitter flavour example).

**Table I**

Bitter taste non-sensorial activities: TCM *versus* modern science

Bitter flavour in TCM	Bitter taste receptors in modern medicine
reverse the upward motion of Qi in lung [9]	reversing obstruction in airway smooth muscle, bronchodilator effect, anti-allergic asthma [65]
activate Qi and blood motion [9]	anti-inflammatory [4, 44, 65], endothelium-dependent relaxation <i>via</i> T2R3, T2R4, T2R10 and T2R14 [47]
anti-diabetic [14]	Reducing blood glucose, modulating carbohydrate metabolism [19]
indications: coughs, stagnant blood syndrome, vomiting, diabetes	potential therapeutic effects: asthma, inflammatory states, nutrient sensing in the stomach, diabetes

### Integrative therapeutic approach in neurodegenerative diseases

According to TCM flavour theory, sweet taste tonifies (deficient tissues), and moistens (the tissues, including brain, dried by Heat). Bitter taste drains and dries (Dampness, the precursor of Phlegm), clears Heat. Pungent taste disperses (obstructions) and moves (stagnant Phlegm). Aromatic flavour (specific to volatile oils, which are associated with a peculiar pungency and odorant properties) penetrates through turbidity and revives the intellectual functions [9]. Therefore all these flavours (sweet, bitter, pungent) are helpful in “resolving phlegm to open the orifices”, one of the therapeutic TCM strategies for treating AD [32].

Interestingly, an *in silico* study showed that neuroprotective TCM phytochemicals, which bound to orthosteric sites of metabotropic glutamate receptors (mGluRs), related to umami taste receptors, key factors involved in AD pathogenesis, are highly correlated with a sweet flavour, while the allosteric site corresponds to a bitter flavour, and less to a pungent flavour [86]. Therefore sweet, bitter, pungent TCM compounds, which target mGluRs, may be considered, also on a scientific basis, as primary sources for developing new drugs for AD [86]. It is worth mentioning that the modern umami taste was proposed to belong to the “sweet” ethno-taste for several reasons [26].

Another recent study using *in silico* modelling method, validated *via* literature mining, found that there is a strong correlation between T2Rs and traditional bitter flavour property [88]. Among 2173 phytochemicals derived from 206 Chinese medicinal plants which were hit as T2R agonists, 71.84% were derived from medicinal herbs showing bitter flavour [88].

Since bitter TRs seem to modulate inflammation in certain organs (e.g. respiratory system) [65], we suggest that the up-regulated T2Rs in neurodegenerative diseases may be used as potential therapeutic targets possibly involved in the regulation of neuroinflammation. Anti-inflammatory agents, either synthetic or natural (e.g. non-steroidal anti-inflammatory drugs, terpenoids, phenolic derivatives, alkaloids, glycosides, and steroidal saponins) are mentioned as preventive tools in neuro-degenerative diseases (e.g. AD) [64]. Interestingly, several bitter phytochemicals showed anti-inflammatory activity in the nervous tissue (e.g. berberine, tangeretin, luteolin, iso- $\alpha$ -acids, sulfuraphane) [4, 10, 73, 74] (see Table II), and were proposed as therapeutic agents against neurodegenerative diseases. Moreover, it is known that bitter taste dysfunction, which is often present in patients with AD, may contribute to a chronic inflammatory state through mechanisms mediated by tumour necrosis factor (TNF), a potent pro-inflammatory cytokine [21].

**Table II**

Examples of evidence based neuroprotective phytochemicals, their organoleptic properties and brain bioavailability

Tastants/odorants (plant source)	TASTE/ODOR (OR)	CHEMICAL CLASS/ Bioavailability in brain	Evidence of potential benefits in neurodegenerative diseases
6-shogaol (ginger)	Pungent /trigeminal odorant	phenolic compound/BBB (+) very low penetration	anti-amyloidogenic activity <i>in vitro</i> and <i>in vivo</i> [51]
Apigenin (chamomile)	Bitter	flavone/BBB (+)	anti-amyloidogenic, neuroprotective, anti-neuroinflammatory, neurotrophic in AD and PD animal model [55,75]
Berberine (barberry)	Bitter	alkaloid/BBB (+)	anti-inflammatory, antioxidant, AChE ↓ [35], ↑ GLP-1 secretion in human enteroendocrine NCI-H716 cells through activation of bitter taste receptor T2R38 [83]

<b>Tastants/odorants (plant source)</b>	<b>TASTE/ODOR (OR)</b>	<b>CHEMICAL CLASS/ Bioavailability in brain</b>	<b>Evidence of potential benefits in neurodegenerative diseases</b>
Carvone (spearmint, caraway)	Pungent/minty odor (TRPM8, OR)	monoterpene ketone/BBB high penetration (+)	binding to OR dopaminergic neurons with potential benefits in PD [28]
Cinnamaldehyde (cinnamon)	Pungent, bitter, sweet/trigeminal odorant (TRPA1, OR)	phenylpropanoid aromatic aldehyde/BBB (+)	anti-inflammatory, neuroprotective in AD animal model [50]
Clerodane diterpenoids (Casearia graveolens)	Bitter	diterpenoids/BBB n.s.	Stimulation of NGF-mediated neurite outgrowth <i>in vitro</i> [80]
Curcumin (turmeric)	Bitter	diarylheptanoid polyphenol/BBB (+)	↓ Aβ oligomer formation, fibrilisation, oxidative stress, neuroinflammation in AD animal model [75], ↑ working memory in healthy older adults [16]
Epigallocatechin-3-galate (green tea)	Bitter, astringent	polyphenol/BBB (+)	binding to OR dopaminergic neurons with potential benefits in PD [28]
Galanthamine (snowdrop)	Bitter	alkaloid/BBB (+)	anti-inflammatory, neuroprotective in AD animal model [50]
Ginkgolide B (Ginkgo biloba)	Sweet, bitter	terpenoid lactone/BBB (+)	Stimulation of NGF-mediated neurite outgrowth <i>in vitro</i> [80]
Ginsenosides (Panax ginseng)	Bitter, astringent, sweet	triterpenoid saponin	↓ Aβ oligomer formation, fibrilisation, oxidative stress, neuroinflammation in AD animal model [75], ↑ working memory in healthy older adults [16]
Luteolin (many plants)	Bitter	flavone/BBB (+)	binding to OR dopaminergic neurons with potential benefits in PD [28]
Nobiletin	Bitter	Flavone/BBB (+) [69]	anti-inflammatory, neuroprotective in AD animal model [50]
Oleuropein (olive tree leaves)	Bitter	Secoiridoid/BBB (+) for its metabolite hydroxytyrosol	Stimulation of NGF-mediated neurite outgrowth <i>in vitro</i> [80]
Quercetin (onion, citrus)	Astringent, bitter	flavonol/BBB (+) low penetration	anti-amyloidogenic, ↓ tauopathy, ↑ cognitive performance in AD animal models [7]
Resveratrol (red grapes)	Bitter	stilbene/BBB (+)	improved brain glucose metabolism, cerebral blood flow <i>via</i> NO dependent vasorelaxation in healthy older humans [40, 78], neuroprotective <i>via</i> activation of sirtuin-1 [31], ↓ neuroinflammation [2]
Rosmarinic acid (sage, rosemary)	Bitter, pungent	phenolic acid/n.s.	inhibition of amyloid aggregation [59], ↓ amyloid-β peptide-induced neurotoxicity <i>in vitro</i> [36]
Silibin (milk thistle)	Bitter	flavonoid/n.s.	↓ Aβ <sub>25-35</sub> -induced memory deficit, ↑ autophagy, ↓ neuroinflammation in AD animal models [37]
Tangeretin (citrus fruits peel)	Bitter	flavone/BBB (+)	anti-inflammatory, attenuated cholinergic deficits, anti-amyloidogenic, reverse N-methyl- D-aspartate (NMDA) receptor hypofunction [11]
Thymoquinone (thyme)	Pungent /odorant (OR)	Quinone/BBB ↓	anti-brain insulin resistance and anti-amyloidogenic activities [6]
Xanthohumol (hops)	Bitter	prenylflavonoid/BBB n.s.	modulation of pathogenic pathways involved in ER stress, oxidative stress, proteasome molecular systems, and the neuronal cytoskeleton [34]
Isohumulone (hops)	Bitter	cyclopentanone/BBB (+)	Neuroinflammation ↓ (IL-1β, macrophage inflammatory protein-1α ↓) in the cerebral cortex, cognitive function ↑ [4]

AD- Alzheimer's disease, BBB (+)- penetrates the blood-brain barrier, n.s.- not specified, OR- olfactory receptor, TR- taste receptor, PD- Parkinson disease, ↓- reduced/inhibited/low, ↑- increased/activated/high

It is also significant that various bitter chemicals showed the ability to cross the blood-brain barrier,

being detectable in the brain (e.g. berberine, quinine, Ginkgo biloba terpenolactones, luteolin

and its metabolites) (Table II) [13, 56, 67]. Their cerebral level may be increased by various ways: glycoprotein P inhibitors, lecithin based liposomes, intranasal route of administration [1, 17, 57]. In certain neurodegenerative diseases (e.g. Parkinson disease (PD)) associated with disruption of the blood-brain barrier, the cerebral bioavailability seems not to be a big concern. On the contrary, certain phytochemicals may also ameliorate the integrity of the barrier [84]. Nonetheless, data on pharmacokinetics and cerebral bioavailability are still relatively rare. Despite their neuroprotective potential proven by *in vitro* and even *in vivo* experiments, more studies are required to elucidate whether these phytochemicals may reach the concentrations needed to activate brain TRs.

Bitter phytochemicals (e.g. berberine) may regulate glucose metabolism and GPL-1 secretion via TRs [19, 81]. The connection between diabetes/insulin resistance state and AD is now supported by a growing body of evidence [76]. Regulation of glucose metabolism may be a key in the prevention and treatment of AD, and bitter tastants may contribute via TR dependent mechanisms of action.

### Conclusions

The physiological roles of the orphan TRs and ORs located in the brain are not fully understood, but they are probably mediated by endogenous ligands, some of them already identified (e.g. glucose, polyamines).

We suggest that modulation of the various TR and OR signalling pathways in the brain may be a new therapeutic strategy in neurodegenerative diseases. It will be interesting assaying more systematically the TR and OR agonists isolated from medicinal plants traditionally used for treatment of neurodegenerative disease, to evaluate their activities on human nervous cells *in vitro* and *in vivo*. Phyto-tastants and phyto-odorants may represent new opportunities for developing neuroactive drugs. Moreover, the olfactory route seems to be a better way of neuroactive drug administration, regarding the accessibility into the brain [1].

Even though phytochemicals are a promising therapeutic alternative, there is a shortage of human evidence, and further studies are required to provide solid basis to understand their TR/OR-dependent or independent mechanisms of action, and to justify their use in the treatment of neurodegenerative diseases.

### Conflicts of Interest

The authors declare no conflicts of interest.

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