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Functional neuromodulation of chemosensation in vertebrates

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Abstract

Neuromodulation can be defined as a biophysical process that serves to modify – or modulate - the computation performed by a neuron or network as a function of task demands and behavioral state of the animal. These modulatory effects often involve substances extrinsic to the network under observation, such as acetylcholine (ACh), norepinephrine (NE), histamine, serotonin (5-HT), dopamine (DA), and a variety of neuropeptides. Olfactory and gustatory processes especially need to be adaptive and respond flexibly to changing environments, availability of resources and physiological needs. It is therefore crucial to understand the neuromodulatory processes that regulate the function of these systems.

Introduction

Neuromodulatory systems such as noradrenaline (NE), acetylcholine (ACh), serotonin (5HT) and dopamine (DA) serve important functions not only in cognitive processing, but also in sensory perception. Sensory perception, as much as other brain functions, needs to be modulated according to task demands, signal-to-noise ratio of the sensory environment as well as the animal's goals and physiological state. Each neuromodulator acts upon neurons in a variety of brain regions through a host of specific receptors with mechanisms including, but not limited to, membrane depolarization, modulation of network properties, changes in oscillatory dynamics, changes in synchronization, signal-to-noise ratio, network excitability and plasticity (reviewed in [1]). In sensory systems, these effects can be linked to alterations in sensory response magnitudes via altered signal to noise ratios, changes in the temporal precision between afferent input and postsynaptic responses, or regulation of contrast among neural representations. We will here review the major known functions of neuromodulatory inputs on olfactory and gustatory computations. We will focus our review on extrinsic

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neuromodulators in adult vertebrate animals, excluding peptides and hormonal modulation. Rather than giving an exhaustive enumeration of neuromodulatory effects in the structures reviewed, we will focus on the computations achieved by each system and the role of neuromodulation therein.

Olfactory and gustatory processing

Olfactory stimuli are transduced by olfactory sensory neurons, which project directly to the first processing center in the brain, the olfactory bulb. Here, they interact with OB principal cells, the mitral cells, and a number of local interneurons which form the glomerular microcircuits (described in [2]). Neural circuits at this stage have been proposed to regulate contrast and create concentration invariant representations of olfactory stimuli. Mitral cells project further to a second stage of processing with a second group of local interneurons, among which granule cells are the most prominent. Neural circuits at this stage are thought to create synchronous representations of olfactory stimuli, processed for optimal read-out by downstream centers (reviewed in [3]). The processed information from the OB is then projected to a number of diverse secondary olfactory structures including, among others, the anterior olfactory nucleus, piriform cortex, olfactory tubercle, hippocampal continuation, indusium griseum and tenia tecta; among these secondary structures, piriform cortex is the best studied. Piriform cortex has classically been associated with the learning of odor stimuli and the creation of quality information from complex mixtures [4]. Neuromodulator inputs to both structures have been well described and studied electrophysiologically and behaviorally (see Figures 1&2A for summary; reviewed in [5]). Neuromodulator inputs to the OB include ACh from the horizontal limb of the diagonal band of Broca (HDB), NE from the locus coeruleus (LC) and 5HT from the raphe nucleus. Unlike other sensory structures, the OB does not receive extrinsic DA inputs from the ventral tegmental area (VTA). Piriform cortex receives the same inputs as OB, as well as extrinsic DA inputs from the VTA. Physiological effects of these modulators in both structures have been relatively well characterized, with the exception of 5HT and DA in piriform cortex. In the OB and PC, a laminar organization of receptor distributions have been described, for example NE $\alpha 1$ receptors are mainly localized on mitral and granule cells whereas β receptors are mainly found in the glomerular layer (see Figure 2).

Unlike olfactory signals, which reach the piriform cortex in few steps, gustatory information travels through long multisynaptic routes before reaching the cortex (Figure 1). Tastants are detected by taste receptor cells in the oral cavity which activate first order neurons belonging to three cranial nerves. Gustatory signals then enter the brainstem, where they are processed by the nucleus of solitary tract (NST) first and the parabrachial nucleus (PbN) after (in primates gustatory signals bypass the PbN). Brainstem circuits are responsible for coding the physiochemical properties of tastants [6]. In alert animals neurons in both the nuclei encode for more than one tastant, with neurons in the PbN carrying a larger information load and relying more on a temporal coding strategy compared to NTS. Recent recordings from alert animals also emphasized the strong relationship between licking and neural activity in the NTS and PbN. From the brainstem, information can reach the gustatory portion of the insular cortex (GC) via two routes, a thalamic pathway and an amygdalar pathway. Neurons in GC are responsible for encoding taste quality, novelty, hedonic value

and anticipation [7], in addition, GC plays a crucial role in mediating aversive learning. Despite the richness of potential targets, little is known on the anatomical organization of inputs from neuromodulatory nuclei to gustatory nuclei and areas. Evidence shows that extrinsic cholinergic, noradrenergic, serotonergic or dopaminergic inputs can reach the NST, the PbN and the GC (see for example [8, 9],[10], summarized in Figure 1). Compared to olfaction, our understanding of the function of neuromodulation in the gustatory system is limited. Most of what we know comes from studies on the role of neuromodulation in taste learning [11, 12], with only a handful of articles directly investigating how gustatory computations are affected by neuromodulators.

Regulation of computation by neuromodulators

Neuromodulation can be defined as a process refining and/or adapting ongoing computation in neurons and networks (for review see Fellous [13]). Classically, neuromodulators have been associated with specific cognitive functions: ACh has been associated with attentional processes, NE with signal to noise modulation, DA with reward learning and 5HT with sleep-wake transitions and motor activity. In sensory systems, neuromodulation is often linked to the tuning of receptive fields, the regulation of signal-to-noise ratio and the regulation of plasticity and network dynamics. In the following sections we will review the computational roles of modulatory inputs in the olfactory and gustatory pathways. The correlation between cellular and perceptual effects of neuromodulators has been comparatively more extensively investigated in the OB; as a consequence, more detail about the role of neuromodulators in the OB will be provided compared to other structures. Neonatal olfactory learning in rodents, for which neuromodulatory systems are especially crucial, has been extensively reviewed elsewhere and will not be included in the present review [14, 15].

Here we will review evidence for the effects of the four major neuromodulatory systems on specific computations performed by the olfactory and the gustatory system in the adult.

Olfactory processing

Signal-to-noise modulation—Signal-to-noise modulation is often ascribed to noradrenergic inputs, and evidence suggests that this is a putative role of NE in olfactory processing (reviewed in [16]). In the olfactory bulb, infusions of noradrenaline substantially decreased olfactory detection thresholds in rats, without impacting odor discrimination. Computationally, this effect was shown to be due to a simultaneous increase in mitral cell responsiveness to odor input (increasing the signal) and increase in mitral cell inhibition mediated by granule cells (decreasing noise). In the piriform cortex, stimulation of NE inputs increased pyramidal cell odor responses, enhancing odor perception [17]. In cortical slices, NE was shown to modulate pyramidal cell excitability to OB inputs (increase in signal) but decrease the synaptic strength among activated pyramidal cells, the net result of which is a decrease in noise, as confirmed by computational modeling [18]. As a consequence, common NE inputs to OB and PC would increase signal and decrease noise in both structures, enabling the detection and processing of lower concentration stimuli. Serotonergic inputs to a strongly bursting class of bulbar interneurons, external tufted (ET) cells could presumably enhance signal-to-noise ratio in the glomerular layer by creating

stronger coupling between odor responsive mitral cells [19]; however the network or perceptual effects of 5HT in the OB are yet to be tested. Similarly, 5HT excites cortical pyramidal and inhibitory cells, putatively also contributing to enhance the incoming signal and decreasing noise in a fashion similar to NE. 5HT may play a similar role in the NTS, where it has been shown to excite TH positive neurons, possibly modulating the balance of excitation and inhibition in this system.

Contrast enhancement—Attentional processes have often been associated with cholinergic modulation. In sensory processing, attentional processes can modulate the organism's ability to identify odorants and discriminate them from background or other odorants. In the olfactory bulb, ACh modulation has been shown to regulate the discrimination between chemically and perceptually similar odorants, a phenomenon also called contrast enhancement. Briefly, ACh acting on nicotinic receptors on inhibitory interneurons narrows the receptive fields of mitral cells, while simultaneously depolarizing responsive mitral cells; together these seemingly contradictory actions result in higher contrast between odor representations. Behaviorally this translates to increased discrimination between odorants in the presence of ACh, and decreased discrimination otherwise (reviewed in [20]). Serotonine has similar effects on neurons in the OB: while it increases presynaptic inhibition by activating inhibitory interneurons, it also depolarizes mitral cells; as with ACh, this should result in modulation of contrast [5] but remains to be tested behaviorally.

Pro-active interference—Cholinergic modulation in the piriform cortex has been proposed to modulate pro-active interference, i.e. the interference of previously learned information with new information [21-23]. At the cellular level, while ACh depolarizes pyramidal cells and interneurons, thus changing the dynamics of cortical processing, ACh also suppresses the transmission of information between pyramidal cells. Information transfer between pyramidal cells serves to recall previously learned information; hence, in the presence of ACh, this information is suppressed and less likely to interfere with new learning. Numerous computational models have shown that cholinergic modulation increases memory capacity and prevents interference, and behavioral results have confirmed this theory in rodents [23].

Short term memory—The role of neuromodulators in short term memory has been assessed using a non-associative habituation task or an olfactory delayed-match to sample task. Blockade of muscarinic bulbar receptors can impair delayed-match to sample performance in rats, potentially by decreasing synchronized activity and plasticity [24]. Direct bulbar infusions of NE were shown to decrease the duration of habituation memory, a counterintuitive result not easily explained by known cellular phenomena. A separate form of short term memory, mediated by PC rather than OB, rapid olfactory habituation (on a 30 second time scale), has been shown to be mediated by presynaptic metabotropic glutamate receptors on the OB inputs to piriform cortex. While the memory formation itself is not dependent on extrinsic neuromodulators, the specificity of this memory has been shown to depend on working muscarinic receptors in PC (reviewed in [25]).

Cortical Learning and associative memory—In piriform cortex, learning is modulated by ACh through facilitation of LTP (reviewed in [23]). Modulation of cortical dynamics by ACh has long been thought necessary to allow the formation of associative odor memories in olfactory cortex. In the olfactory bulb, action of ACh on muscarinic receptors is thought to increase synchronization between responsive mitral cells, resulting in better readout of pyramidal cells which also increases learning. Hence, the action of ACh in both OB and PC would increase cortical learning [26] via separate, but well coordinated mechanisms. A study in mice showed that when all bulbar NE receptors were blocked, mice acquired a novel difficult odor discrimination task less efficiently [27], an effect that could also result from the desynchronization of bulbar outputs described above.

Gustatory processing

Shift between sparse and dense coding—Historically, the nature of gustatory coding has been highly debated, with two views (one relying on sparse representations and one on dense representations) confronting each other [6]. Recent ideas, based on electrophysiological recordings across multiple structures, no longer advocate for one or another theory and suggest the possible presence of both types of coding schemes in a flexible and context-dependent manner. Evidence from GC recordings showing that ACh can decrease a cell's best response to a tastant while increasing its non-best responses to other tastants is consistent with such a rearrangement of taste coding [28] in response to behavioral state. This modulation could involve rearrangements of the balance between excitation and inhibition by cholinergic inputs: ACh reduces inhibitory transmission onto pyramidal cells and had mixed effects on connections between inhibitory interneurons in GC [29]. The final results of these changes would be a shift away from sparse taste representations (typically observed in anesthetized states) to dense, population-based, representations characteristic of wakefulness.

Novelty and familiarity detection—Neurons in GC are known to encode novelty and familiarity of a tastant [30]. Repeated exposition to the same tastant leads to changes in neural responses in GC which parallel behavioral modifications of taste consumption (i.e. increase of taste consumption due to attenuation of neophobia). Processing of taste novelty in GC has been shown to depend upon several neuromodulators [11, 12], including ACh [31]. Direct measurements of extracellular levels of ACh revealed an inverse relationship between familiarity and ACh: novel stimuli associate with higher levels of ACh than familiar stimuli [32]. Data directly linking the levels of ACh with changes in the spiking signature of familiarity are missing, however it is reasonable to expect a direct link between the two.

Hedonic value—The increase of consumption due to familiarization with a tastant is related to an increase in its perceived hedonic value [33]. The role of GC in processing hedonic signals has been established with imaging, electrophysiological and behavioral experiments [34]. Analysis of the time course of firing responses to different tastants revealed that GC neurons can encode hedonic value in the late part of their response. The mechanisms underlying hedonic coding depend on inputs from limbic areas, including BLA [35]. Whether neuromodulatory inputs are necessary for coding of hedonic value is not known, however their role in hedonic learning is well established: neuromodulators are

known to be necessary to establish aversive memories [11, 12]. In the case of Ach, its role is believed to involve a modulation of plasticity at amygdalo-cortical synapses. Given the importance of this connection in mediating palatability coding in GC, it is reasonable to expect that Ach-dependent changes in the functional connectivity between these two areas would result in modulation of hedonic coding.

Anticipatory coding—Neurons in the gustatory system are also known to encode anticipatory cues predicting the availability of gustatory stimuli. GC neurons that respond to anticipatory cues prime the cortex in a way similar to unexpected tastants. Expression of instrumentally conditioned cue responses depends on inputs from BLA. While the involvement of neuromodulators in this phenomenon has not been investigated yet, data from the literature provide hints at a potential role for Ach, NE and DA. Classical studies on dopaminergic and noradrenergic neurons unveiled their ability to respond to anticipatory cues [17, 36] and suggest the possibility that such signals in GC (or BLA) might also be tuned to respond to anticipatory cues. More recently, results from studies in the visual cortex indicate the importance of Ach in mediating changes in neural activity associated with reward timing expectation [37].

Conclusions

In summary, neuromodulation provides the chemosensory systems with the flexibility to adapt to behavioral demands, behavioral states and stimulus fluctuations. At early stages of chemosensory processing, neuromodulators regulate important computations such as signal-to-noise modulation or contrast enhancement. Neuromodulation also enhances mechanisms of oscillations and synchrony, thereby enhancing plasticity processes in later stages of processing. At cortical stages of processing, while still acting on signal-to-noise modulation and tuning curves, neuromodulators allow the system to switch between the processing of learned and novel information, to create new representations and to modify coding, thereby providing the system with a means to optimize the learning of chemosensory information and regulate novelty and hedonic value. Overall, neuromodulators provide a means for cortical processing to be context dependent rather than strictly feedforward process.

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Glossary

OB	Olfactory bulb
PC	Piriform cortex
NTS	Nucleus of solitary tract
PbN	Parabrachial nucleus
GC	Gustatory (Insular) cortex
ACh	Acetylcholine
NE	noradrenaline

HDB	Horizontal limb of the diagonal band of Broca
LC	Locus coeruleus
RN	Raphe nucleus
VTA	ventral tegmental area

Highlights

We lay out olfactory and gustatory information processing

We summarize neuromodulatory inputs to olfactory and gustatory pathways

We describe neuromodulation in olfaction and taste from a computational point of view

Known cellular effects of neuromodulators and their functional relevance are summarized

Figure 1.

Schematic depiction of major olfactory and gustatory pathways and their modulatory inputs. Neuromodulatory inputs to structures specifically associated with olfaction or gustation and discussed in this review are depicted. See main text for a description of computations in these pathways. The list of structures is not exhaustive and is meant to show the route that information takes before it reaches the primary sensory cortex of each modality.

Figure 2.

Illustration of laminar distribution of receptors in the olfactory bulb and cortex with respect to computational functions in these networks. **A.** Olfactory bulb. Sensory information, transduced by olfactory sensory neurons in the olfactory epithelium (OE) is projected to target neurons in the glomerular layer (GL) of the OB. Local microcircuits, comprised of periglomerular (PG), external tufted (ET) and short axon (SA) cells process the incoming information. This layer of bulbar processing is thought to be involved in contrast and normalization processes. The resulting activity of mitral cells (Mi) is then further processed in the external plexiform layer (EPL), where Mi cells interact with granule cells (Gr). The mutual interactions between these groups of cells and additional interneurons not depicted here are thought to create oscillatory dynamics that serve to synchronize Mi cell outputs towards olfactory secondary cortices. Receptors for ACh, NE and 5HT are numerous and organized in a laminar fashion through out the bulbar layers including GL, EPL, internal plexiform layer (IPL) and granule cell layer (GCL) (nACh: nicotinic, mACh: muscarinic). Bulbar outputs project, among several other structures, to the piriform cortex (PC), where they connect with pyramidal cells (Pyr) and local interneurons (Ff) in a widely distributed and non-topographical fashion. A second major class of inhibitory interneurons (Fb) provides additional computational power to this structure. Presynaptic inhibition by metabotropic glutamate receptors in layer Ia mediates a form of short term memory, rapid habituation, whose specificity is dependent on mACh receptors in layers Ia and II. The dense network of association fibers between cortical pyramidal cells has been suggested to form an auto-associative memory capable of storing olfactory information. The modulation of synaptic transmission in this layer by NE and ACh has been shown to be a crucial component of this associative memory function.