CellPress

Review

Emerging Role of Sensory Perception in Aging and Metabolism

Celine E. Riera[1,2,3] and Andrew Dillin[1,2,3,*]

Sensory perception comprises gustatory (taste) and olfactory (smell) modalities as well as somatosensory (pain, heat, and tactile mechanosensory) inputs, which are detected by a multitude of sensory receptors. These sensory receptors are contained in specialized ciliated neurons where they detect changes in environmental conditions and participate in behavioral decisions ranging from food choice to avoiding harmful conditions, thus insuring basic survival in metazoans. Recent genetic studies, however, indicate that sensory perception plays additional physiological functions, notably influencing energy homeostatic processes and longevity through neuronal circuits originating from sensory tissues. Here we review how these findings are redefining metabolic signaling and establish a prominent role of sensory neuroendocrine processes in controlling health span and lifespan, with a goal of translating this knowledge towards managing age-associated diseases.

Trends

The fine-tuning of smell (olfactory) and taste (gustatory) sensitivities is tightly regulated by endocrine signals involved in energy balance, due to the presence of many endocrine receptors on these neurons.

Not much is known about the effect of upstream sensory inputs in the hypothalamus on regulatory mechanisms governing whole-body energy homeostasis. In addition to the obvious role of olfaction and taste in influencing behavioral decisions about food choice, recent studies suggest that olfactory stimuli may contribute to the regulation of energy homeostasis.

Neuroendocrine processes, engaged by sensory afferent neurons expressing transient receptor potential vanilloid 1 (TRPV1), are tightly involved in the maintenance of metabolic homeostasis and play a role in regulating longevity.

Sensory Cues and Hypothalamic Hunger Circuits

The regulation of whole-body energy homeostasis relies on a tight balance between food intake and energy expenditure. To adapt quickly to variations in environmental conditions and maintain global body energy homeostasis, mammalian systems have developed a neurocircuitry within the hypothalamus that integrates external signals into an autonomic response via the sympathetic nervous system. The melanocortin system, namely melanocortin 3 and 4 receptors (MC3R and MC4R), in the arcuate nucleus (ARC) controls feeding in response to circulating insulin ghrelin and leptin levels and relays information to pre-autonomic neurons in the paraventricular nucleus (PVN). In particular, ARC neurons coexpressing the orexigenic neuropeptides agouti-related proteins (AgRPs) (inverse agonists of MC3R and MC4R) and neuropeptide Y (NPY) (agonist of NPY receptor) along with neurons coexpressing anorexigenic pro-opiomelanocortin (POMC) precursor, a precursor of α-MSH that activates MC4R, and cocaine- and amphetamine-related transcript (CART), have been identified as key players in controlling energy balance [1–6]. The ARC and PVN circuits also communicate with the lateral parabrachial nucleus (PBN), which sends anorexigenic projections to the central amygdala (CeA) [7]. The CeA, located in the forebrain region, integrates homeostatic and motivational aspects of feeding in addition to receiving taste sensory input from the brainstem [8]. Bilateral lesion of the CeA induces hyperphagia and obesity in rats [9] and is required for hedonic perception of food as demonstrated in conditioned taste aversion assays [10]. Yamamoto *et al.* demonstrated that both the CeA and the basolateral amygdala (BLA) are required for this behavioral change, which associates the ingestion of a pleasant food to a malaise and promotes enhanced taste sensitivity towards the conditioned stimulus. Inhibitory synaptic inputs from the BLA preferentially innervate and suppress the activity of lateral hypothalamus (LH) glutamatergic neurons to control food intake [11]. The amygdala also communicates taste information to the reward centers of the

[1]Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA 94720, USA
[2]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
[3]Glenn Center for Research on Aging, University of California, Berkeley, Berkeley, CA, USA

*Correspondence: dillin@berkeley.edu (A. Dillin).

mesolimbic dopaminergic system center, comprising the ventral tegmental area (VTA), the nucleus accumbens (NAc), the medial prefrontal cortex (mPFC), and the orbitofrontal cortex (OFC), which is essential for motivated feeding behaviors with palatable food (Figure 1).

Interestingly, recent technological advances have allowed the natural recording of orexigenic AgRP and anorexigenic POMC neuron activity in awake, behaving animals using an optical method called fiber photometry [12]. The presence of food, without its ingestion, is sufficient to rapidly switch the activation state of these neurons on hunger and can be immediately reversed by removing the food cues. The intensity of the response depends on the palatability of the food presented, revealing that the ARC can rapidly associate food hedonic or energetic value to sensory stimuli and obtain real-time information about food availability and palatability in addition to endocrine signals regulating the nutritional state of the animal. What is the reason for this rapid sensory regulation? It is possible that this mechanism allows an immediate means to inhibit food scavenging or other appetitive behaviors once food has been encountered. More work is required to understand the neuronal circuitry for transmission of these sensory inputs to the ARC.

Olfaction and Energy Balance

Olfactory stimuli are absorbed by the mucosal surfaces lining the main olfactory epithelium (MOE) and septal organ present in many nonhuman mammals [13]. Each molecule is detected

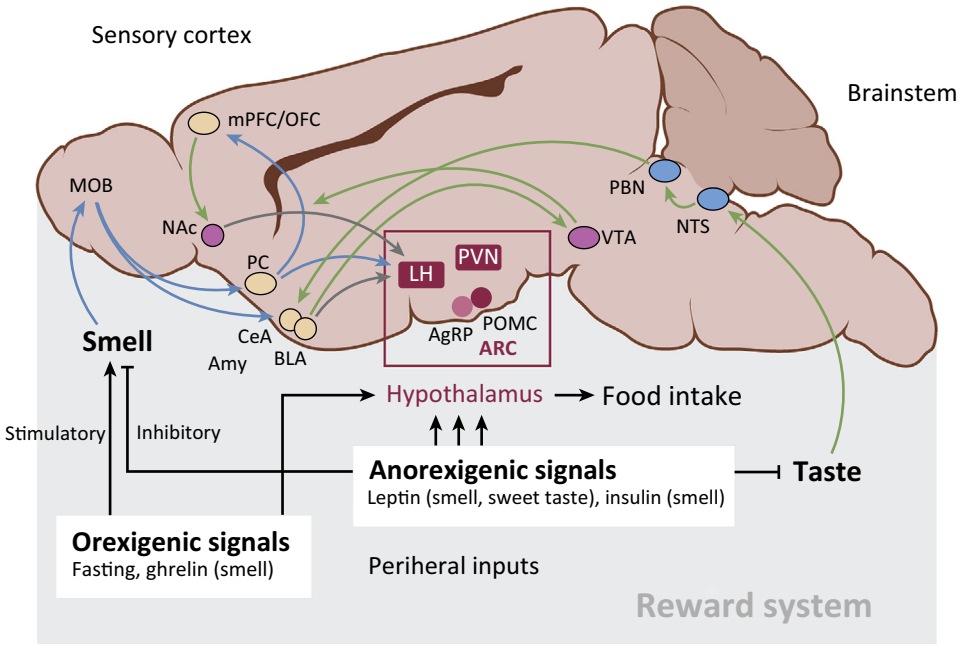

Figure 1. Integrated Model of the Sensory Inputs in the Central Nervous System Regulating Homeostatic and Hedonic Feeding. Taste signals (green) are transmitted via cranial nerves to the nucleus of the tractus solitarius (NTS) and the parabrachial nucleus of the pons (PBN) and further transmitted to the amygdala (Amy) and the cortex. These centers activate the mesolimbic dopamine system, an essential interface between palatability and eating behavior that comprises the ventral tegmental area (VTA) of the midbrain (the major source of dopamine), the nucleus accumbens (NAc), the medial prefrontal cortex (mPFC), and the orbitofrontal cortex (OFC). This system integrates external stimuli through the mPFC and OFC and stimulates the lateral hypothalamus (LH). Olfactory signals (blue) arise from the main olfactory bulb (MOB) and are integrated by the piriform cortex (PC) and the cortical Amy, which transmit the olfactory information to the OFC and the LH. In the hypothalamus, LH GABAergic inputs promote food intake by stimulating the paraventricular nucleus (PVN). Sensory inputs also induce arcuate nucleus (ARC) neuron activity through rapid of orexigenic agouti-related protein (AgRP) neurons and activation of neurons coexpressing anorexigenic pro-opiomelanocortin (POMC), which signal to pre-autonomic neurons of the PVN to initiate a satiety response.