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Neuronal Mechanisms that Drive Organismal Aging Through the Lens of Perception

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Abstract

Sensory neurons provide organisms with data about the world in which they live, for the purpose of successfully exploiting their environment. The consequences of sensory perception are not simply limited to decision-making behaviors; evidence suggests that sensory perception directly influences physiology and aging, a phenomenon that has been observed in animals across taxa. Therefore, understanding the neural mechanisms by which sensory input influences aging may uncover novel therapeutic targets for aging-related physiologies. In this review, we examine different perceptive experiences that have been most clearly linked to aging or age-related disease: food perception, social perception, time perception, and threat perception. For each, the sensory cues, receptors, and/or pathways that influence aging as well as the individual or groups of neurons involved, if known, are discussed. We conclude with general thoughts about the potential impact of this line of research on human health and aging.

Keywords

sensory perception; model systems; diet; social isolation; threat perception; time perception

INTRODUCTION

Aging is a phenomenon that impacts nearly all organisms. The aging process is generally characterized by a continuous health decline that results in diminished vitality and increased morbidity that, in humans, is typically associated with negative feelings. According to the writings of the nineteenth-century Italian philosopher, Giacomo Leopardi, “Old age is the supreme evil, because it deprives us of all pleasures, leaving us only the appetite for them, and it brings with it all sufferings.” Stories about the search for ways to slow down or even halt the aging process are found in historical tales from around the world: in Russia through

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the legends of Alexander the Great, in ancient Greece through the writings of the fifth-century historian Herodotus, in the stories of the indigenous people of the Caribbean, and in the sixteenth-century tales (now considered myth) of the exploits of the Spaniard Juan Ponce de León in his search for the Fountain of Youth. It is clear from the prevalence of such stories that the fear of growing old is a universal concern as we continue to look for ways to mitigate its effects.

Today, the scientific method rather than oral history is used to guide our investigations on aging. However, it was not always clear that modern science would be able to generate impactful insights into how organisms age given the complexity associated with the aging phenotype. Early work by Pearl's and McCay's groups (1, 2) showed that systematic experimental manipulation can alter life span in different species, and in some cases, extend it. A genetic screen for mutations that extended life span in the nematode worm, *Caenorhabditis elegans*, further demonstrated that aging is genetically influenced, although the specific genes responsible were not identified (3). Kenyon and colleagues (4) identified one such gene, the insulin-growth factor receptor *daf-2*, providing seminal evidence that life span can be significantly increased by mutating a single gene. Since then, many genes have been discovered that, when altered, directly affect how organisms age. These studies have revealed evolutionarily conserved molecular events and pathways that modulate life span in different species, some of which include insulin/insulin-like growth factor signaling (IIS), target of rapamycin signaling, the unfolded protein response, genomic instabilities, epigenetic drift, mitochondrial dysfunction, and cellular senescence (5). While extended discussions on the theories of aging in light of each of these pathways are beyond the scope of this review and are examined in detail elsewhere (5), the fact that these cellular pathways can be manipulated in a manner that slows aging and extends life span clearly demonstrates that the phenotypic complexities associated with aging may have simpler, common causes.

The goal of aging research is not to simply prolong life. Biologists who study aging believe that by understanding the details of how we age, important strides will be made toward delaying or eliminating the onset of many age-related diseases such as cancer, cardiovascular disease, and dementia. There are data that suggest this to be true. For example, mice that lived longer as a result of diet restriction (6) or the loss of growth hormone receptor/binding protein (7) experienced lower cancer incidence, and monkeys given a low-calorie diet exhibited decreased overall morbidity as well as decreased incidences of cancer, diabetes, and brain atrophy (8). Modulating the activity of genes and pathways that determine the rate of aging and that delay many age-associated pathologies, with the objective of identifying those that also minimize negative side effects, would therefore have significant therapeutic benefit. This is particularly important because the population structures of many countries are shifting toward an increasing percentage of older individuals. Hence, the primary goal of aging research today is to slow aging and to extend meaningful, healthy life span.

Arguably, however, a conceptual shift has occurred in recent years with respect to the nature of the specific molecular and environmental influences that impact life span. While long considered a process that animals experience passively, through the accumulation of molecular damage or use of a finite amount of energy, it is now clear that aging is modulated

by specific pathways. It is acutely malleable, susceptible to sensory influences, and strictly controlled, non-autonomously, by specific cells and tissues, including coordinated sets of neurons. In this view, organisms continuously perceive and evaluate key biological states, such as nutrient availability and demand, and they react, physiologically, in ways that promote individual survival or reproduction.

This perspective serves to focus the content of our review, in which we present evidence that sensory perception influences energy homeostasis, tissue physiology, and organism aging through neuronal circuits that emanate from sensory tissues and that interface with deeper regions of the central nervous system (CNS). The molecular study of these relationships is often traced back to the work of Apfeld & Kenyon (9) who used *C. elegans* to show that mutants with absent or defective sensory cilia lived longer. In the years since, sensory effects on health and aging have been observed across the phylogeny of invertebrate and vertebrate animals. Functional manipulation of discrete sensory neurons in *C. elegans* either shortened or extended life span depending on the specific neurons involved (10). Genetic manipulations that rendered *Drosophila melanogaster* broadly anosmic significantly affected life span, as did environmental cues such as sweet taste, water, danger, and pheromones (11). Manipulation of the sensory system also influenced life span in mammals, as loss of the pain receptor TRPV1 significantly extended mouse life span (12).

The understanding of how sensory perception affects aging and age-related disease is rudimentary, and much of what is currently known is derived from experiments using invertebrate model systems, specifically the fruit fly, *Drosophila*, and the nematode worm, *C. elegans*. Genetic and neuronal manipulations are straightforward in these animals, and life span assays take a few weeks or a few months, which has allowed researchers to establish causal links between sensory circuits and aging. This review therefore focuses on progress in these systems, although relevant examples are provided in vertebrates when possible to illustrate evolutionary conservation of the phenotypes as well as to highlight areas that merit investigation in species more closely related to humans. The body of the review is divided into four main sections based on different types of perceptive experiences that have been most clearly linked to aging or age-related disease: food perception, social perception, time perception, and threat perception. Each section details findings that describe how specific sensory cues, receptors, and/or pathways influence aging as well as the individual or groups of neurons involved, if known. General thoughts about the future of this line of research are then provided at the end of this perspective.

FOOD PERCEPTION

Diet is one of the most potent, and arguably the most well-known, modulator of health, behavior, and life span. To our knowledge, the earliest published observation in which aging was shown to be modulated by diet was made by Kopec in 1928 (13), who discovered that intermittent starvation of adult *Drosophila* extended life span. Soon after, McKay and colleagues (1) reported that feeding rats a calorically restricted diet also significantly extended life span. Since this time, similar manipulations, most of which were designed to reduce caloric availability in the diet, have been shown to extend life span in a range of different species and to improve metabolic health measures in humans (14). However, recent

results, many of which have utilized the Geometric Framework for Nutrition, have established that the composition and availability of specific nutrients within the diet are more influential in modulating life span than caloric content alone (15). Even the way in which individual nutrients are presented may be important; simply separating the sugar and yeast components of the *Drosophila* diet, thereby allowing the animals to decide on the pattern and amount of nutrient uptake, modulates life span independent of the amount of each nutrient consumed (16). These studies provide compelling evidence that aging is influenced not only by caloric intake, but also by the type, quantity, consumption, and presentation of individual dietary components.

The mechanisms by which diet imposes changes in physiology and life span remain unclear. Cell-autonomous changes in metabolic and storage tissues as a direct result of nutrient availability are clearly influential, but the nervous system also orchestrates cell non-autonomous changes throughout the organism in response to various forms of nutrient perception. In *Drosophila*, protein deprivation induced synaptic remodeling and altered firing properties of a specific dopaminergic circuit (17). Such changes were required for compensatory protein feeding after deprivation, and they were reversed by reintroducing the amino acids glutamine or tryptophan. In mice, fatty acid feeding modulated markers of sympathetic nervous system output to adipose tissue, implicating neuronal function regulation by fatty acids as an important determinant of metabolic health (18).

Perception of dietary components is sufficient to modulate aging and metabolic health independent of food intake in a variety of model systems, including *C. elegans* (10), *Drosophila* (19), and mice (20). In *C. elegans*, food-derived odors were sufficient to increase insulin-like peptide 6 and decrease life span, effects that required sensory neurons that are lost in *tax-2*/*tax-4* mutants (21). In flies, food odors partially reversed the longevity-extending benefits of dietary restriction, and olfactory-deficient flies lived up to 50% longer than control animals (22). Taste-blind flies lived longer than control flies, despite eating more (19). Ablation of mature olfactory sensory neurons in mice stimulated sympathetic nerve activity that resulted in β-adrenergic receptor activation in adipocytes to promote fat degradation, suggesting a possible neuronal mechanism by which mice were resistant to diet-induced obesity (20). The environmental cues that elicit effects on life span are often species specific and ecologically relevant. For example, olive flies (*Bactrocera oleae*) exposed to alpha-pinene, a common plant compound that is present in both olive fruit and leaves, exhibited increased life span and reproduction (23).

These examples highlight a growing realization of the link that exists between dietary cues and specific neural or endocrine circuits that modulate healthy aging, which are summarized in the next section and include the dietary cues themselves as well as the intracellular molecules that bridge diet perception with aging effects. For discussion purposes, different aspects of nutrient perception are considered (Figure 1), although in practice, they are almost surely not mutually exclusive in mechanism or effect. The first is closely related to canonical sensory perception in which peripheral sensory circuits, driven often by the sight, taste, or smell of specific nutrients, transduce external information to higher brain regions. Aging effects are therefore orchestrated by the CNS and mediated through cell non-autonomous mechanisms. The second involves internal nutrient-sensing mechanisms that are responsive

to unmetabolized nutrients (nutrient sensing) or their catabolized molecular byproducts (metabolic sensing), independent of external sensory input. These molecules are often sensed by cells both inside and outside of the nervous system, and they may provoke actions that are cell autonomous or non-autonomous.

Sugar Perception

Sugar overconsumption is generally detrimental to animals, and it is associated with increased energy storage and declining metabolic health, which leads to excessive body weight, metabolic disorders (e.g., diabetes and hyperphagia), and reduced life span (24–27). Indeed, flies on high sugar diets store more triglycerides and become obese (28), whereas mice on Western-style diets high in sugar and fat develop diabetes and obesity (29). One possible mechanism of action driving these effects involves increased cellular respiration that results from increased glucose consumption and leads to increased energy production in the form of ATP, which is classically associated with excess energy storage and declining metabolic health.

The consequences of increased energy storage on health and aging are broad and may be inter-twined with other, independent effects. For example, glucose metabolism increases intracellular levels of acetyl-CoA. Similar to protein phosphorylation, this metabolite is used for the posttranslational modification of many proteins that influence cell function, including mechanistic target of rapamycin (mTOR) regulatory proteins that are associated with aging. Acetyl-CoA has been well studied in the context of gene expression regulation (see 30 for a review). These data suggest that dietary sugar may influence healthy aging via a combination of changes in energy storage, protein posttranslational modifications that modulate life span, and altered gene regulation. Importantly for this review, however, is that the perception of sugar alone can influence behavior and aging. For instance, perceiving dietary sugar through taste receptors in *Drosophila* was both necessary and sufficient to suppress starvation-induced sleep loss when animals encountered nutrient-poor food sources (31). Loss of the *Drosophila* trehalose receptor, *Gr5a*, significantly decreased life span without altering feeding (32). Data such as these demonstrate an important role for the perceptual effects of dietary sugar, and they indicate that the physiological effects of sugar are modulated by a complex interaction between sugar metabolism and its perception.

Sugar sensation regulates intracellular signaling pathways that are implicated in aging. The most well studied is arguably the IIS pathway, which is glucose responsive and highly conserved across species. This pathway regulates biological processes such as growth, development, and behavior in addition to aging. Direct manipulation of IIS has been shown to significantly modulate life span in *C. elegans*, *Drosophila*, and mice (see 33, 34 and references therein). Some of the downstream molecular components of this pathway are known; *Drosophila* express a single member of the FoxO family of transcription factors, and it is a key effector of the IIS pathway on aging and aging-related pathologies (35). Ablation of neuroendocrine cells that express insulin-like peptides in the *Drosophila* brain are sufficient to extend life span (36), but the direct effect of *Drosophila* FoxO on aging has been observed primarily in the peripheral tissues, including the peripheral and head fat bodies (37, 38), suggesting that glucose stimulation of the IIS pathway exerts life span

effects through tissue non-autonomous processes. In *C. elegans*, a large body of literature supports the notion that FoxO/daf-16 is a critical mediator of the links between diet and aging, including evidence for its involvement in food perception. FoxO/daf-16 was found to be required for life span extension by dietary restriction (39) and has been reviewed in great detail elsewhere (40). Of note, ablation of some (but not all) *C. elegans* sensory neurons extends life span in a FoxO-dependent manner (10). Furthermore, optogenetic activation of a subset of chemosensory neurons decreases the mRNA abundance of FoxO/daf-16 target genes independent of food consumption and shortens life span (21). These data support a role for FoxO in food perception and as a critical component of nutrient-signaling pathways.

ChREBP/Mondo/Mlx are a second group of transcription factors with defined roles in metabolic glucose sensation and aging. In *C. elegans*, the ChREBP/Mondo/Mlx complex promotes life span, as loss of *mml-1* or *mxl-2* (the worm homologs of mammalian ChREBP and Mlx) reduced life span in wild-type worms as well as long-lived worms with reduced insulin signaling (41). Furthermore, *mxl-2* was required for life span extension in a dietary restriction worm model (i.e., mutation of *eat-2*). Activation of the Mondo/Mlx transcription factors in *Drosophila* modulated the metabolism of lipids, carbohydrates, and amino acids through the transcription factor, *sugarbabe*, and other downstream effector genes (42). The fly homolog of ChREBP, *mio*, has been shown to function in neurons to regulate feeding and energy storage (43), but its effects on life span have yet to be determined. Glucose stimulation of ChREBP in rat hepatocytes increased fibroblast growth factor 21 (FGF21) mRNA (44), a hormone-like member of the FGF family that controls tissue cross talk to enhance organismal energy usage and that controls stress responses by modulating both the somatotropic and hypothalamic-pituitary-adrenal axes (45). Interestingly, FGF21 is thought to protect against age-related disorders in humans, such as atherosclerosis, cardiovascular disease, and metabolic syndrome (46). Furthermore, transgenic FGF21 expression in mice significantly increases mouse life span, regardless of sex (47). These data together suggest that glucose-sensing transcriptional networks modulate aging and aging-related disease in multiple model organisms through conserved components of the nutrient perception network.

Attractive directions for future research into the effects of sugar perception on aging include manipulation of known sugar taste receptors as well as specific neuronal populations that have been shown to be involved in carbohydrate and metabolic sensing pathways. Sugar taste receptors of interest in *Drosophila* include the Gr64 family of receptors (48), which influence fly choice behavior toward a variety of different sugars (e.g., trehalose, maltose, sucrose, and glucose). In mammals, the sweet taste T1R2/T1R3 receptor dimer (49) is particularly interesting because it has been shown to regulate mTORC1 activity and autophagy, both of which are known to affect aging (50). Neuronal sensors of internal nutrient availability are also intriguing candidates to be studied for their potential effects on aging. For example, *Drosophila* neurons that express the sodium/solute cotransporter-like *SLC5A11* (or *cupcake*) are required for glucose-regulated feeding in flies (51); for directing fly choice toward nutritive, rather than non-nutritive, sugars; and for enhancing the excitability of these neurons in response to starvation (52, 53). Neurons that express diuretic hormone 44 (*Dh44*, the *Drosophila* homolog of mammalian corticotrophin-releasing hormone) require a functional hexokinase C for their activation by glucose, and a subset of

these neurons also expresses insulin-like peptides, which themselves influence aging, as mentioned above. This type of metabolic sensing is conserved in mammals; the activity of appetite-regulating neurons in the mammalian hypothalamus and brainstem are altered by rising glucose levels and require a functional glucokinase (54). Lastly, biogenic amines (e.g., serotonin and octopamine) and neuropeptides (e.g., NPF/NPY and leucokinin) have documented roles in regulating sugar feeding in response to internal states and are emerging as conserved modulators of aging in other contexts.

Protein Perception

Similar to sugar, manipulation of dietary protein alters life span (15). There is a large established literature on the metabolic effects of protein intake and an emerging literature on the neuronal effects of protein sensing (55). Many animals will seek and ingest a protein source when starved of it, suggesting they have dedicated protein sensors (16), although there is little known about the molecular details behind this perception. In mammals, the T1R1- and T1R3-type receptors are found on taste cells and form a complex that is responsible for amino acid sensing. In invertebrates, the ionotropic receptor Ir76b was recently identified to mediate responses to amino acids (56). It is not currently known what role, if any, these receptors have in aging.

Most of what is known about the impact of neuronal protein sensing on aging comes from research using *Drosophila*. Flies deprived of amino acids or starved of all nutrients switch from a diet comprised primarily of sugar to one primarily of protein (57). This behavioral switch in feeding preference requires both serotonin signaling through the 5-HT2A receptor and plasticity of a dopaminergic circuit (16, 17). While it is known that tryptophan or glutamine supplementation suppresses the dopaminergic plasticity that occurs during starvation (17), the precise molecular intermediate(s) that signal protein starvation as well as the mechanism through which serotonin and dopaminergic circuits drive starvation-induced behaviors are unknown. When the two primary macronutrients in the diet, sugar and protein, are presented separately to flies so that they behaviorally construct the composition of their own diet, they live shorter than when presented with a single, complete diet (16). This effect also requires serotonin signaling through the serotonin receptor 5-HT2A (16).

There is an extensive literature detailing how dietary protein influences aging via the highly conserved, internal protein-sensing molecules TOR and GCN2, the mammalian homologs of mTOR and EIF2AK4, respectively (58). Briefly, TOR and GCN2 are both serine-threonine kinases that function as amino acid sensors and regulate a wide range of downstream biological processes that modulate growth, metabolism, and life span (59, 60). Repressing TOR signaling through rapamycin treatment increased life span in worms (61), fruit flies (62), and mice (63). TOR signaling has also been implicated in the development of age-related neurodegenerative disease (64). GCN2 is required for life span extension in worms due to TOR inhibition (65). In flies, GCN2 is at least partially required for the life span extension effect of dietary restriction, likely through transcriptional induction of translation initiation factor 4E-binding protein (4E-BP) (60).

Little is known about how the perception or consumption of specific amino acids modulate aging, and this area is ripe for further study. Both methionine and tryptophan restriction

reduced food intake and extended life span in different animal models, but the mechanism and neuronal populations involved in these behavioral changes are currently unknown (66). Branched-chain amino acids (BCAAs), which are isoleucine, leucine, and valine, have been reported to have health effects; however, the data are conflicted. Decreased consumption of BCAAs was associated with reduced TOR signaling, reduced insulin signaling, and improved glucose tolerance in mice (67), all of which have been linked to increased life span, suggesting that decreased consumption of BCAA may slow aging. This seems to be the case, although the effects of BCAA reduction were similar to those resulting from general amino acid restriction (68). Others have reported that increases in dietary BCAAs extend life span in mice and worms (69). Such inconsistency may be due to differences in the method of BCAA manipulation (e.g., either added to food or administered separately through drinking water), which can differentially affect body weight and behavior, highlighting the need for standardized diets.

Interestingly, the products of BCAA metabolism regulate feeding behavior and neuropeptide expression in the brain, indicating that BCAAs may be part of a metabolic-sensing network (69–71). For example, BCAAs are catabolized to the neurotransmitter glutamate or acetyl-CoA, a sub-strate used for posttranslational modifications. Notably, metabolic flux experiments have revealed that oxidation of BCAAs in the mouse brain occurs within minutes, supporting the argument that it is the BCAA metabolites that may be key messenger molecules used by nutrient-processing networks to modulate neuronal function and potentially aging itself (72). Of the three BCAAs, leucine is the only one that has been shown to directly activate a neuronal population (73). Leucine is sensed by *Drosophila* insulin-producing cells via two proteins, Minidiscs (related to mammalian solute carrier proteins) and JhI-21 (a leucine transporter) (74). Leucine sensing via Minidiscs is dependent on glutamate dehydrogenase and leads to *Drosophila* insulin-like peptide release, suggesting that it is part of the metabolic sensing system (73). Intriguingly, *JhI-21* mutants have extended life span, reinforcing the notion that internal protein-sensing pathways are important regulators of longevity (16).

Fatty Acid Perception

Sensing of lipids and free fatty acids influence neural circuits that control energy state-dependent feeding in mammals, and studies of conserved processes in invertebrates suggest they may influence aging. Fatty acid oxidation occurs in astrocytes via the production of ketone bodies that are thought to be exported and subsequently taken up by neurons. This process represents the metabolic basis of brain fatty acid sensing, and it is an important regulator of state-dependent feeding (75, 76). It is generally believed that dysregulated fatty acid sensing in the mammalian brain contributes to aging-related metabolic disease (see 75 for a review). In mammals, starvation-dependent increases in free fatty acids encouraged feeding by driving the upregulation of agouti-related peptide (*Agrp*) gene transcription, a key driver of food intake. *Agrp* is co-expressed in *Npy*-expressing neurons, which are involved in feeding behaviors, motivation, energy balance, and age-dependent metabolic phenotypes (77–80). Neurons that express the fly homolog of mammalian *Npy* neuropeptide F (*NPF*) are sensitive to fat-derived metabolites and are involved in the regulation of both feeding and life span (81–83). *NPF*-expressing neurons also respond indirectly to nutrients

through the ligand Upd1, the fly analog of the mammalian protein leptin, that binds to its receptor, Domeless, to decrease feeding. Although the *upd1*-expressing cells in the fly brain are able to detect a decline in circulating nutrients, the identity of those nutrients is not known (84).

Other Metabolic Sensors

AMP-activated kinase (AMPK) and the sirtuins deserve attention here as neuronal metabolic sensors that have been extensively studied in the context of aging (59, 85, 86). AMPK is activated by binding AMP or ADP and, in turn, regulates a host of metabolic pathways that increase energy supplies and reduce energy demand. The sirtuin proteins are NAD^+-dependent deacetylases that modulate a wide range of downstream targets to influence physiology and aging (85, 87). AMPK activation extended life span in *C. elegans* in a manner that required functional, neuronal CREB-regulated transcription coactivator 1 (CRTC-1) (88). AMPK is also required for the effect of dietary restriction to increase worm life span (88). In *Drosophila*, brain-specific AMPK overexpression induced autophagy in both the brain and gut tissues and was sufficient to increase life span (86). Sirtuins were first identified as potential modulators of longevity in the brewer's yeast, *Saccharomyces cerevisiae* (89) and subsequently in *C. elegans*, where increased dosage of *sir-2.1* (the homolog of mammalian *Sirtuin 1*) increased life span (90). In *Drosophila*, *Sir2* expression in neurons significantly increased both male and female life span (91). A similar finding was made using mice, where brain-specific overexpression of *Sirtuin 1* extended the life span of both male and female mice (92). In addition to their role in aging itself, sirtuins have implicated roles in age-related diseases such as cancer (93), Alzheimer's, and Huntington disease (94). One possible hypothesis by which sirtuins affect aging and age-related phenotypes is through neuroepigenetic changes caused by histone deacetylation, the details of which can be found elsewhere (95).

Perception of Internal Hunger States

In humans, sensory perception influences motivation, arousal, drive, and emotion. These states are encoded in our brains, and they subsequently control, in a causal sense, behavior, physiology, and conscious experience. Given that sensory perception of nutrients is sufficient to alter life span, it seems reasonable to speculate that the related neural states, such as those of hunger or satiety, also modulate aging. There are, to our knowledge, no direct tests of this hypothesis, but molecular mechanisms and neuronal populations that have recently been identified to respond to starvation and direct adaptive feeding behaviors are promising candidates for further study.

In *Drosophila*, a few different neuronal populations have been implicated in evaluating nutrient availability and influencing the hunger state. Inactivation of four GABAergic interneurons resulted in voracious eating regardless of prior feeding, indicating that they are involved in hunger or the motivation to feed (96). An additional set of cholinergic interneurons increased their activity in response to sucrose during the starvation state (97), suggesting that they are part of a complex, multi-input circuitry. In line with this, 12 pairs of *SLC5A11*-expressing neurons in the central fly brain responded to starvation by increasing their excitability via regulation of a potassium channel (53). Second-order sweet taste

neurons became more sensitive to sucrose following starvation, indicating that they may also be hunger sensors (98). Other neurons that regulate the activity of dopaminergic protocerebral posterior lateral region 1 (PPL1) "punishment neurons" have been proposed to mediate motivational states, including appetitive memory (99, 100). Taotie neurons encode an apparent hunger-like state that is independent of energy state, and their activation or inhibition influences feeding behavior regardless of whether a fly is fully fed or starved (101, 102). They also regulate insulin secretion (102). Lastly, serotonergic neurons have been directly implicated in encoding hunger (101). Future research investigating how these neural populations influence aging should address whether the hunger-like state is responsible for influencing life span while also controlling for potential confounding effects such as changes in behavior or food intake.

SOCIAL PERCEPTION

The influence that social surroundings have on overall health is well documented, as both clinical and epidemiological findings support associations connecting favorable social experiences, increased well-being, and healthy aging (103). Strong social support networks have been shown to reduce mortality and morbidity rates in the elderly through a variety of means, including increased resistance to cardiovascular disease (104), decreased incidence of risk factors contributing to coronary disease (105), improved rehabilitation from incidence of stroke (106), and enhanced protection from cognitive decline (107). Psychosocial stress and low socioeconomic status also confer increased vulnerability to morbidity and mortality (108, 109). Similar social effects on behavior and physiology have been observed in various animal models, where increasing social exposure can delay disease progression and strengthen immune function (110, 111), improve physiological function, and reduce cellular stress response (112). Social stress and low social status reduced life span and increased the risk of cardiovascular disease in mice (113). Together these data support the overarching hypothesis that enhancing social well-being slows the aging process across taxa.

Consistent with how humans approach social situations, many animals are capable of engaging others and forming interpersonal relationships within their social construct by relying on physical senses to identify those who they consider acceptable (e.g., for the purpose of courtship and mating) or those they perceive as aversive (e.g., territorial opponents). Studies using model systems have revealed that social perception mechanisms involved with the interpretation of conspecific sex are largely driven by smell- and taste-dependent pheromonal cues, whose composition differs across sexes and species (114, 115). For example, a highly discrete, sexually dimorphic circuit in *Drosophila* involves a single peripheral olfactory receptor, Or67d, that responds specifically to the male pheromone *cis*-vaccenyl acetate (116, 117). Also in *Drosophila*, nonvolatile cuticular hydrocarbons, which are detected by specific taste receptors such as the cation channel *ppk23*, are sex specific and influenced by diet, age, and molecular pathways that modulate life span (114, 118, 119). The behavioral switch between mating and aggressive tendencies in mice is defined by the interplay of pheromone inputs received by the main olfactory epithelium and vomeronasal organ as well as CNS modulation of sex-driven behavioral circuits by testosterone and estrogen (120). Consistent with these observations, primate species not only rely on

olfactory cues to determine outgroup individuals who pose a threat (121) but also to evaluate reproductive worthiness of favorable mates (122).

Recent work indicates that perception of the opposite sex has significant effects on aging and age-related traits in several species. In *C. elegans*, hermaphrodites exhibited accelerated aging and shortened life span when exposed to a specific blend of pheromonal cues, called ascarosides, that are secreted by males and promote sexual maturation (123, 124). Similarly, in *Drosophila*, general loss of olfactory receptor function increased life span (22), and genetic reprogramming of male or female flies to produce the pheromone profile of the opposite sex demonstrated that perception of the opposite sex alone was sufficient to significantly alter fat metabolism, stress resistance, and life span (81). These effects scaled with increased exposure to pheromones, led to general changes in the metabolic profile of the brain, and required specific neuropeptidergic pathways, such as NPF/NPY and CRZ/GNRH (81, 125).

The notion that perception of the opposite sex modulates aging has challenged the long-standing hypothesis that the act of reproduction incurs a survival cost. In fitness trade-off models, reproduction places demand on limited energetic resources, thereby causing somatic functions to receive less energy to sustain long-term function, thus compromising future health and survival. However, in male *Drosophila*, mating partially reversed the deleterious effects and increased the life span of flies that were exposed to opposite sex pheromones (81), suggesting that energetic costs do not underlie reduced life span and that successful copulation can be viewed as a beneficial reward in some situations. Moreover, neither the degree of courtship received nor the number of eggs produced correlated with declines in the survival of mated females (125, 126). Given these observations, the costs of reproduction associated with aging may arise not from physical damage, but instead from the animal's motivation to court or mate, both of which are driven by exposure to sex-specific sensory cues.

Contrary to the social fulfillment and emotional reward achieved through successful social interactions, social isolation, whether through the lack of social cues or the perceived loss of social connectivity, elicits changes in behavior and physiology that can be largely construed as harmful to overall health, promoting higher mortality rates (103, 127). The negative effects of chronic isolation on behavior, health, and longevity have been observed when subjecting social animal model systems to solitary confinement. Socially isolated animals display erratic behavior indicative of an elevated anxiety state, including heightened aggressive tendencies (128, 129). Collectively, physical isolation is associated with a system-wide stress on physiological homeostasis and cellular function, ultimately affecting age-related dysfunction and disease. For example, prolonged social isolation promotes weight gain and increased lipid content (130). Socially isolated animals exhibited elevated tumor progression in cancer models (131), increased cardiovascular incidences (132), and age-associated disease progression (111, 133), suggestive of compromised immune function and diminished cellular control. Life span data from *Drosophila* indicate that social enrichment can protect animals from molecular stress and age-associated disease (134, 135), supporting a potential role for social enrichment as a mitigator of accelerated aging.

Work with animals kept in different social situations have started to illuminate the neural networks and associated neuronal molecules that modulate the effects of social perception. Many of these pathways have been shown in different experimental contexts to influence aging. In mammals, social perception converges upon two central neuroendocrine stress response systems: the hypothalamic-pituitary-adrenal and the sympathetic adrenomedullary axes, whose functions with respect to social isolation effects on health have been extensively covered elsewhere (136). In flies, similar mechanisms are in place to respond to social stress and perceived reward pathways, such as neurotransmission from dopamine, neuropeptidergic signaling from NPF, and protein-dependent sensory pathways described earlier (137, 138). Increased serotonergic signaling caused heightened aggression behavior (139, 140), in part through specific synaptic connections made with inhibitory 5-HT1A expressing neurons in higher-ordered social processing centers of the *Drosophila* brain (139). Conversely, loss of octopamine signaling (the *Drosophila* homolog of mammalian norepinephrine) caused a general decrease in aggression metrics (141). Interestingly, both 5-HT1A and the octopamine receptor Oamb were found to be expressed in *Drosophila* insulin-producing cells in the fly brain, a metabolic homeostatic sensor known to regulate aging (142).

TIME PERCEPTION

An organism's ability to predict daily events, such as sunrise and sunset, is important for the employment of optimal survival strategies. The body's ability to sense and organize time relies on circadian clocks, the workings of which utilize a transcriptional-translational negative feedback loop that is similar across species (143, 144). It can be set and reset by the perception of specific environmental cues, or zeitgebers, such as light and temperature, through a process known as entrainment. Molecular rhythms are coordinated between circadian neurons and communicated to control downstream physiological rhythms. Circadian clocks exhibit a period of approximately 24 h that persists even in the absence of time cues, which is thought to ensure that behavioral, physiologic, and metabolic processes align with environmental conditions. Much like food odors that induce physiological changes in anticipation of nutrient intake, circadian rhythms allow organisms to perceive time and to anticipate meal times, periods of predator activity, and seasonal changes.

Disruptions of the circadian system are associated with an increased risk of age-related conditions such as cancer, diabetes, and neurodegeneration (145). Nighttime shift work is correlated with these poorer health outcomes, potentially because the body incorrectly anticipates the meal times or other time-dependent behaviors (146). On the other hand, well-timed manipulation of sensory inputs or environmental cues can increase the strength of organismal rhythms and improve health-related outcomes. For example, temperature cycles reinforced rhythms in *Drosophila* and restored rhythmicity to arrhythmic flies (147). Time-restricted feeding has been used to prevent obesity in mouse models of chronic shift work (148). In humans, bright light exposure at specific times of day has been used effectively to improve sleep and cognitive performance, particularly during the winter months and in patients with neurodegenerative diseases (149). These manipulations indicate that improving circadian function, and thus restoring proper time perception, may be capable of improving age-related disorders.

It is well established that aging affects the function of the circadian clock. Sleep-wake cycles break down as animals age, which are detected as weakened, fragmented sleep cycles and changes in circadian-affected behavioral outputs. Such changes have been documented in *Drosophila* (150), rodents (151), and humans (152). In *Drosophila*, transcriptional oscillations of clock genes in peripheral tissues were reduced with age (153). The effect of age on clock gene oscillations in the brain is not as clear; one study reported an age-related decline in the strength of neuronal oscillations (154), whereas another reported strong rhythms that were largely unchanged in brains but declined in peripheral clocks with age (153). Aging has also been reported to reduce the strength of circadian clock gene cycling in the suprachiasmatic nucleus (SCN), the region of the mammalian brain where the master pacemaker resides (155). Neural activity rhythms in the SCN are also degraded with age (151). Combating circadian declines accompanying aging via an SCN transplant derived from fetal tissue was shown to restore rhythms in rats and increase longevity in the golden hamster (156, 157).

Altering the way in which organisms perceive time through genetic and environmental manipulation of clock molecules influences life span. In *Drosophila*, mutations in the *period* (*per*) gene, which abolished endogenous rhythms, reduced life span (158). *Per* mutant flies also exhibited increased neurodegeneration and decreased oxidative stress resistance (159). Conversely, *per* overexpression has been reported to increase fly life span, although this observation was dependent on both sex and diet (160). *Timeless* (*tim*), the binding partner of *per* that forms the repressive limb of the feedback loop, was reported to be required for extended life span through diet restriction (161), although this result has been contested (162). Peripheral *tim* overexpression specifically in the fly fat body increased life span (160). *Cycle* is a transcription factor target of the PER/TIM complex, and *cyc* deficiency in male flies significantly shortened life span (163). Increasing *cyc* expression in the fly fat body significantly increased life span when flies were aged on a protein-rich diet (160). *Bmal1* is the mammalian ortholog of *cyc*, and *Bmal1* deficiency in mice caused significant increases in physiologies associated with aging, such as sarcopenia, cataracts, decreased hair growth, and reduced life span (164). Brain-specific *Bmal1* rescue of circadian clock function was sufficient to restore peripheral transcriptional rhythms in the liver and increase survival (165, 166). Finally, overexpressing the *Drosophila cryptochrome-1* gene (*cry*), which is a blue light photoreceptor that modulates TIM degradation, was shown to increase rhythmicity with age, increase oxidative stress, and extend life span (167). These studies further suggest that manipulation of circadian system holds potential for improving health and longevity.

THREAT PERCEPTION

A key adaptive capability found in every organism is the ability to detect and respond appropriately to potential threats for survival, including predators, parasites, disease, and even death. Ants, zebrafish, scrub jays, elephants, and nonhuman primates all behaviorally respond to sick or dead conspecifics (168, 169). There is also evidence of behavioral effects associated with exposure to sick and dead conspecifics in humans, where stressful stimuli have been associated with depression, anxiety, and broader physiological issues that may potentially influence life span (170, 171). In *C. elegans*, exposure to media containing excretions from starved, predatory *Pristionchus pacificus* elicited immediate avoidance

behaviors that require ASI, ASJ, ASH, and ADL sensory neurons (172). *C. elegans* also avoid environmental threats such as media containing homogenized worm extract; this response requires cGMP signaling in ASI and ASK sensory neurons (173). Interestingly, many of these specific sensory neurons have also been implicated in the regulation of *C. elegans* life span. ASI neurons are required for the life span extension following dietary restriction (174), ASJ neurons modulate life span in response to food and temperature cues (21, 175), and G protein signaling in the nociceptive ASH/ADL neurons modulates life span (10). It is therefore attractive to speculate that these neurons may also modulate life span in response to perceived environmental threats.

Links between potential threats, behavior, and life span have also been established in *Drosophila*. Flies are capable of socially transmitting information about perceived threats. When housed with a parasitic wasp species, female *Drosophila* reduced their egg laying, and they communicated threat presence to naïve flies using wing movements, who also suppressed their egg laying (176). Behavioral and physiological responses to threats may also have long-term effects, including changes in life span. For example, when healthy flies were exposed to dead conspecifics, they became leaner, experienced reduced climbing ability, were aversive to naïve flies, and had reduced life span. The effects of exposure to dead conspecifics on aversiveness and life span required visual and olfactory function in the exposed flies, and the sight of dead flies produced changes in the head metabolome. Genetic and pharmacologic attenuation of serotonergic signaling eliminated these effects, providing evidence for an evolutionarily conserved neural mechanism that links threat perception with changes in behavior and aging (169).

Whether threat perception influences mammalian aging has yet to be tested. However, several avenues of research toward addressing this question may be of interest. Olfactory and vomeronasal threat cues detected by rodents signal the presence of a predator through connections from the main and accessory olfactory bulbs to the posteroventral medial amygdala (177, 178). Rats with lesions in this area exhibit a reduced fear response to cats and their odors (179). Rodent exposure to live predators also activated two other amygdala nuclei, the lateral amygdala and the posterior accessory basal amygdaloid nucleus (180), which receive inputs from visual and auditory association areas that are required for normal fear responses to feline predators (181). It would be of interest to determine whether predator exposure in rats or mice influences life span in a manner that is dependent on vomeronasal cues or on neural processing in key areas of the amygdala. In humans, elevations in stress hormones such as glucocorticoids are associated with increased age-related cognitive declines in humans, such as Alzheimer's and Parkinson's disease (182), providing a potential mechanistic link between general stress perception and age-related pathology.

SUMMARY AND FUTURE DIRECTIONS

The continual growth in the number of elderly in our society will result in an increased prevalence of age-related diseases that will have dramatic economic and health-related consequences over the coming decades. Although the causes and consequences of many diseases, including cancer and dementia, are slowly being unraveled, the mechanisms that

underlie aging as the most significant risk factor associated with these disease states are relatively unknown. Interventions that impact the basic mechanisms of aging are expected to ameliorate or eliminate multiple pathologies and diseases.

This review focused on examining the role of specific perceptive experiences on age and age-related disease in four areas: food perception, social perception, time perception, and threat perception (Figure 2). The most progress has been made in linking food cues to aging, likely due to the early discovery of the relationship between diet and life span. Nevertheless, more recent work has expanded to include the effects of other perceptive cues. As noted throughout this review, the ability of sensory perception to affect aging in both *C. elegans* and *Drosophila* is both strong and highly nuanced; sensory perception of food, danger, and mates can double or halve an organism's life span depending on the context and the specific neurons involved. All indications are that these effects are conserved in mice, which bodes well for future investigation into the effects of perceptive experiences on human health and aging.

One emerging trend is the extent to which highly conserved neuromodulators, including biogenic amines and neuropeptides, are important determinants of the sensory modulation of aging. These signaling molecules are known determinants of neural states in a range of animal models, but only recently have they been directly linked to aging. Serotonin modulates sensory integration in mammals (183) and, as discussed above, has been linked to the longevity effects of sensory perception in *C. elegans* as well as protein perception, food odors, and threat perception affect aging in *Drosophila*. Additionally, feeding serotonin receptor antagonists extended life span in worms by putatively mimicking dietary restriction (184). Similar roles are emerging for dopamine and octopamine (the analog of vertebrate norepinephrine) (185). Although these are some of the most well-studied and influential neurotransmitters in multiple organisms, including humans, an important challenge going forward will be to isolate the specific mechanisms through which they modulate aging per se.

Is sensory perception really a potential target for the treatment of human aging? We believe the answer is yes. All organisms share similar goals, such as the need for food and mates and the desire to avoid danger. While the cues associated with these needs may be different across species, the biological responses to what those cues represent are much the same. The same neural circuits that evaluate internal and external nutritional status to determine what and when to eat also interact with conserved major hormone axes, such as leptin signaling in mice as well as insulin-like and TGF-β signaling in flies and worms (52, 186, 187). The preprandial response to food cues can alter insulin release, appetite, and exercise performance (188). Putative reward systems have significant effects on human aging, and disrupting the physiological feedback to the brain that is normally associated with protein consumption can increase *Drosophila* life span up to 50% (16). Social interactions among humans influence the progression of aging and disease, much like what is observed in flies. The observations that obesity clusters in social networks and that social interaction can slow the decline in cognitive function in older populations suggest that sensory cues from the social world directly influence physiology and can therefore be a key target for intervention (189). Together, these studies support the notion that, in addition to providing an opportunity

to discover basic mechanisms of aging, understanding how sensory perception modulates life span in model systems may also lead to creative intervention strategies that form the basis of a simple yet powerful program of disease prevention and healthy aging.

In humans, sensory perception influences motivation, arousal, drive, and emotions. These states are encoded in our brains, and they subsequently control, in a causal sense, behavior, physiology, and conscious experience. One conjecture presented in this review is that these states are also important modulators of aging. We are naturally inclined to associate neural states with subjective feelings, such as hunger, fear, or longing. As important as these feelings are to our lives, however, they are almost surely not the functions that were favored by natural selection. More likely targets were the behavioral and physiological outcomes that those states promote (190). Even today, sub-liminal sensory information (e.g., rapid flashing of smiling faces) can influence human behavior (e.g., promote positive reviews of neutral taste) in the absence of subjective experience. The use of model systems to test this conjecture will be important to provide direct, hypothesis-driven tests of how sensory perception defines neural states that influence aging and age-related behaviors.

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LITERATURE CITED

1. McCay CM, Crowell MF, Maynard LA. 1935 The effect of retarded growth upon the length of life span and upon the ultimate body size: one figure. J. Nutr 10:63–79
2. Pearl R, Parker SL. 1922 Experimental studies on the duration of life. II. Hereditary differences in duration of life in line-bred strains of *Drosophila*. Am. Nat 56:174–87
3. Johnson TE, Friedman DB, Fitzpatrick PA, Conley WL. 1987 Mutant genes that extend life span. Basic Life Sci 42:91–100 [PubMed: 3435398]
4. Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R. 1993 A *C. elegans* mutant that lives twice as long as wild type. Nature 366:461–64 [PubMed: 8247153]
5. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. 2013 The hallmarks of aging. Cell 153:1194–217 [PubMed: 23746838]
6. Weindruch R, Walford RL. 1982 Dietary restriction in mice beginning at 1 year of age: effect on lifespan and spontaneous cancer incidence. Science 215:1415–18 [PubMed: 7063854]
7. Ikeno Y, Hubbard GB, Lee S, Cortez LA, Lew CM, et al. 2009 Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. J. Gerontol. A Biol. Sci. Med. Sci 64:522–29 [PubMed: 19228785]
8. Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, et al. 2009 Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 325:201–4 [PubMed: 19590001]
9. Apfeld J, Kenyon C. 1999 Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. Nature 402:804–9 [PubMed: 10617200]
10. Alcedo J, Kenyon C. 2004 Regulation of *C. elegans* longevity by specific gustatory and olfactory neurons. Neuron 41:45–55 [PubMed: 14715134]
11. Linford NJ, Kuo TH, Chan TP, Pletcher SD. 2011 Sensory perception and aging in model systems: from the outside in. Annu. Rev. Cell Dev. Biol 27:759–85 [PubMed: 21756108]

12. Riera CE, Huising MO, Follett P, Leblanc M, Halloran J, et al. 2014 TRPV1 pain receptors regulate longevity and metabolism by neuropeptide signaling. Cell 157:1023–36 [PubMed: 24855942]
13. Kopec S 1928 On the influence of intermittent starvation on the longevity of the imaginal stage of *Drosophila melanogaster*. J. Exp. Biol 5:204–11
14. Fontana L, Partridge L, Longo VD. 2010 Extending healthy life span—from yeast to humans. Science 328:321–26 [PubMed: 20395504]
15. Simpson SJ, Le Couteur DG, Raubenheimer D, Solon-Biet SM, Cooney GJ, et al. 2017 Dietary protein, aging and nutritional geometry. Ageing Res. Rev 39:78–86 [PubMed: 28274839]
16. Ro J, Pak G, Malec PA, Lyu Y, Allison DB, et al. 2016 Serotonin signaling mediates protein valuation and aging. eLife 5:e16843 [PubMed: 27572262]
17. Liu Q, Tabuchi M, Liu S, Kodama L, Horiuchi W, et al. 2017 Branch-specific plasticity of a bifunctional dopamine circuit encodes protein hunger. Science 356:534–39 [PubMed: 28473588]
18. Guilherme A, Pedersen DJ, Henchey E, Henriques FS, Danai LV, et al. 2017 Adipocyte lipid synthesis coupled to neuronal control of thermogenic programming. Mol. Metab 6:781–96 [PubMed: 28752043]
19. Ostojic I, Boll W, Waterson MJ, Chan T, Chandra R, et al. 2014 Positive and negative gustatory inputs affect *Drosophila* lifespan partly in parallel to dFOXO signaling. PNAS 111:8143–48 [PubMed: 24847072]
20. Riera CE, Tsaousidou E, Halloran J, Follett P, Hahn O, et al. 2017 The sense of smell impacts metabolic health and obesity. Cell Metab. 26:198–211.e5 [PubMed: 28683287]
21. Artan M, Jeong DE, Lee D, Kim YI, Son HG, et al. 2016 Food-derived sensory cues modulate longevity via distinct neuroendocrine insulin-like peptides. Genes Dev. 30:1047–57 [PubMed: 27125673]
22. Libert S, Zwiener J, Chu X, Vanvoorhies W, Roman G, Pletcher SD. 2007 Regulation of *Drosophila* life span by olfaction and food-derived odors. Science 315:1133–37 [PubMed: 17272684]
23. Gerofotis CD, Ioannou CS, Nakas CT, Papadopoulos NT. 2016 The odor of a plant metabolite affects life history traits in dietary restricted adult olive flies. Sci. Rep 6:28540 [PubMed: 27339862]
24. Skorupa DA, Dervisefendic A, Zwiener J, Pletcher SD. 2008 Dietary composition specifies consumption, obesity, and lifespan in *Drosophila melanogaster*. Aging Cell 7:478–90 [PubMed: 18485125]
25. Solon-Biet SM, McMahon AC, Ballard JW, Ruohonen K, Wu LE, et al. 2014 The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. Cell Metab. 19:418–30 [PubMed: 24606899]
26. Schlotterer A, Kukudov G, Bozorgmehr F, Hutter H, Du X, et al. 2009 *C. elegans* as model for the study of high glucose-mediated life span reduction. Diabetes 58:2450–56 [PubMed: 19675139]
27. May CE, Vaziri A, Lin YQ, Grushko O, Khabiri M, et al. 2019 High dietary sugar reshapes sweet taste to promote feeding behavior in *Drosophila melanogaster*. Cell Rep. 27:1675–85.e7 [PubMed: 31067455]
28. Musselman LP, Fink JL, Narzinski K, Ramachandran PV, Hathiramani SS, et al. 2011 A high-sugar diet produces obesity and insulin resistance in wild-type *Drosophila*. Dis. Model. Mech 4:842–49 [PubMed: 21719444]
29. Winzell MS, Ahren B. 2004 The high-fat diet-fed mouse: a model for studying mechanisms and treatment of impaired glucose tolerance and type 2 diabetes. Diabetes 53(Suppl. 3):S215–19 [PubMed: 15561913]
30. Narita T, Weinert BT, Choudhary C. 2019 Functions and mechanisms of non-histone protein acetylation. Nat. Rev. Mol. Cell Biol 20:156–74 [PubMed: 30467427]
31. Linford NJ, Ro J, Chung BY, Pletcher SD. 2015 Gustatory and metabolic perception of nutrient stress in *Drosophila*. PNAS 112:2587–92 [PubMed: 25675472]
32. Waterson MJ, Chan TP, Pletcher SD. 2015 Adaptive physiological response to perceived scarcity as a mechanism of sensory modulation of life span. J. Gerontol. Ser. A 70:1088–91

33. Altintas O, Park S, Lee SJ. 2016 The role of insulin/IGF-1 signaling in the longevity of model invertebrates, *C. elegans* and *D. melanogaster*. BMB Rep. 49:81–92 [PubMed: 26698870]
34. Gems D, Partridge L. 2013 Genetics of longevity in model organisms: debates and paradigm shifts. Annu. Rev. Physiol 75:621–44 [PubMed: 23190075]
35. Murtaza G, Khan AK, Rashid R, Muneer S, Hasan SMF, Chen J. 2017 FOXO transcriptional factors and long-term living. Oxid. Med. Cell. Longev 2017:3494289 [PubMed: 28894507]
36. Broughton SJ, Piper MD, Ikeya T, Bass TM, Jacobson J, et al. 2005 Longer lifespan, altered metabolism, and stress resistance in Drosophila from ablation of cells making insulin-like ligands. PNAS 102:3105–10 [PubMed: 15708981]
37. Hwangbo DS, Gersham B, Tu M-P, Palmer M, Tatar M. 2004 *Drosophila* dFOXO controls lifespan and regulates insulin signalling in brain and fat body. Nature 429:562–66 [PubMed: 15175753]
38. Alic N, Tullet JM, Niccoli T, Broughton S, Hoddinott MP, et al. 2014 Cell non-autonomous effects of dFOXO/DAF-16 in aging. Cell Rep. 6:608–16 [PubMed: 24508462]
39. Greer EL, Dowlatshahi D, Banko MR, Villen J, Hoang K, et al. 2007 An AMPK-FOXO pathway mediates longevity induced by a novel method of dietary restriction in *C. elegans*. Curr. Biol 17:1646–56 [PubMed: 17900900]
40. Tullet JM. 2015 DAF-16 target identification in *C. elegans*: past, present and future. Biogerontology 16:221–34 [PubMed: 25156270]
41. Johnson DW, Llop JR, Farrell SF, Yuan J, Stolzenburg LR, Samuelson AV. 2014 The *Caenorhabditis elegans* Myc-Mondo/Mad complexes integrate diverse longevity signals. PLOS Genet. 10:e1004278 [PubMed: 24699255]
42. Mattila J, Havula E, Suominen E, Teesalu M, Surakka I, et al. 2015 Mondo-Mlx mediates organismal sugar sensing through the Gli-similar transcription factor Sugarbabe. Cell Rep. 13:350–64 [PubMed: 26440885]
43. Docherty JEB, Manno JE, McDermott JE, DiAngelo JR. 2015 Mio acts in the *Drosophila* brain to control nutrient storage and feeding. Gene 568:190–95 [PubMed: 26024590]
44. Iizuka K, Takeda J, Horikawa Y. 2009 Glucose induces FGF21 mRNA expression through ChREBP activation in rat hepatocytes. FEBS Lett. 583:2882–86 [PubMed: 19660458]
45. Fisher FM, Maratos-Flier E. 2016 Understanding the physiology of FGF21. Annu. Rev. Physiol 78:223–41 [PubMed: 26654352]
46. Salminen A, Kaarniranta K, Kauppinen A. 2017 Regulation of longevity by FGF21: interaction between energy metabolism and stress responses. Ageing Res. Rev 37:79–93 [PubMed: 28552719]
47. Zhang Y, Xie Y, Berglund ED, Coate KC, He TT, et al. 2012 The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. eLife 1:e00065 [PubMed: 23066506]
48. Jiao Y, Moon SJ, Wang X, Ren Q, Montell C. 2008 Gr64f is required in combination with other gustatory receptors for sugar detection in *Drosophila*. Curr. Biol 18:1797–801 [PubMed: 19026541]
49. Murovets VO, Bachmanov AA, Zolotarev VA. 2015 Impaired glucose metabolism in mice lacking the Tas1r3 taste receptor gene. PLOS ONE 10:e0130997 [PubMed: 26107521]
50. Wauson EM, Zaganjor E, Lee AY, Guerra ML, Ghosh AB, et al. 2012 The G protein-coupled taste receptor T1R1/T1R3 regulates mTORC1 and autophagy. Mol. Cell 47:851–62 [PubMed: 22959271]
51. Ugrankar R, Theodoropoulos P, Akdemir F, Henne WM, Graff JM. 2018 Circulating glucose levels inversely correlate with *Drosophila* larval feeding through insulin signaling and SLC5A11. Commun. Biol 1:110 [PubMed: 30271990]
52. Dus M, Ai M, Suh GSB. 2013 Taste-independent nutrient selection is mediated by a brain-specific Na^+/solute co-transporter in *Drosophila*. Nat. Neurosci 16:526–28 [PubMed: 23542692]
53. Park JY, Dus M, Kim S, Abu F, Kanai MI, et al. 2016 *Drosophila* SLC5A11 mediates hunger by regulating K^+ channel activity. Curr. Biol 26:1965–74 [PubMed: 27397890]
54. De Backer I, Hussain SS, Bloom SR, Gardiner JV. 2016 Insights into the role of neuronal glucokinase. Am. J. Physiol. Endocrinol. Metab 311:E42–55 [PubMed: 27189932]
55. Journel M, Chaumontet C, Darcel N, Fromentin G, Tome D. 2012 Brain responses to high-protein diets. Adv. Nutr 3:322–29 [PubMed: 22585905]

56. Croset V, Schleyer M, Arguello JR, Gerber B, Benton R. 2016 A molecular and neuronal basis for amino acid sensing in the *Drosophila* larva. Sci. Rep 6:34871 [PubMed: 27982028]
57. Steck K, Walker SJ, Itskov PM, Baltazar C, Moreira JM, Ribeiro C. 2018 Internal amino acid state modulates yeast taste neurons to support protein homeostasis in *Drosophila*. eLife 7:e31625 [PubMed: 29393045]
58. Weichhart T 2018 mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. Gerontology 64:127–34 [PubMed: 29190625]
59. Johnson SC, Rabinovitch PS, Kaeberlein M. 2013 mTOR is a key modulator of ageing and age-related disease. Nature 493:338–45 [PubMed: 23325216]
60. Kang MJ, Vasudevan D, Kang K, Kim K, Park JE, et al. 2017 4E-BP is a target of the GCN2-ATF4 pathway during *Drosophila* development and aging. J. Cell Biol 216:115–29 [PubMed: 27979906]
61. Robida-Stubbs S, Glover-Cutter K, Lamming DW, Mizunuma M, Narasimhan SD, et al. 2012 TOR signaling and rapamycin influence longevity by regulating SKN-1/Nrf and DAF-16/FoxO. Cell Metab. 15:713–24 [PubMed: 22560223]
62. Bjedov I, Toivonen JM, Kerr F, Slack C, Jacobson J, et al. 2010 Mechanisms of life span extension by rapamycin in the fruit fly *Drosophila melanogaster*. Cell Metab. 11:35–46 [PubMed: 20074526]
63. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, et al. 2009 Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature 460:392–95 [PubMed: 19587680]
64. Mazucanti CH, Cabral-Costa JV, Vasconcelos AR, Andreotti DZ, Scavone C, Kawamoto EM. 2015 Longevity pathways (mTOR, SIRT, Insulin/IGF-1) as key modulatory targets on aging and neurodegeneration. Curr. Top. Med. Chem 15:2116–38 [PubMed: 26059361]
65. Rousakis A, Vlassis A, Vlanti A, Patera S, Thireos G, Syntichaki P. 2013 The general control nonderepressible-2 kinase mediates stress response and longevity induced by target of rapamycin inactivation in *Caenorhabditis elegans*. Aging Cell 12:742–51 [PubMed: 23692540]
66. Mirzaei H, Suarez JA, Longo VD. 2014 Protein and amino acid restriction, aging and disease: from yeast to humans. Trends Endocrinol. Metab 25:558–66 [PubMed: 25153840]
67. Antikainen H, Driscoll M, Haspel G, Dobrowolski R. 2017 TOR-mediated regulation of metabolism in aging. Aging Cell 16:1219–33 [PubMed: 28971552]
68. Juricic P, Grönke S, Partridge L. 2019 Branched-chain amino acids have equivalent effects to other essential amino acids on lifespan and ageing-related traits in *Drosophila*. J. Gerontol. A Biol. Sci. Med. Sci
69. Mansfeld J, Urban N, Priebe S, Groth M, Frahm C, et al. 2015 Branched-chain amino acid catabolism is a conserved regulator of physiological ageing. Nat. Commun 6:10043 [PubMed: 26620638]
70. Purpera MN, Shen L, Taghavi M, Münzberg H, Martin RJ, et al. 2012 Impaired branched chain amino acid metabolism alters feeding behavior and increases orexigenic neuropeptide expression in the hypothalamus. J. Endocrinol 212:85–94 [PubMed: 21969404]
71. She P, Reid TM, Bronson SK, Vary TC, Hajnal A, et al. 2007 Disruption of BCATm in mice leads to increased energy expenditure associated with the activation of a futile protein turnover cycle. Cell Metab. 6:181–94 [PubMed: 17767905]
72. Neinast MD, Jang C, Hui S, Murashige DS, Chu Q, et al. 2018 Quantitative analysis of the whole-body metabolic fate of branched-chain amino acids. Cell Metab. 29:417–29.e4 [PubMed: 30449684]
73. Manière G, Ziegler AB, Geillon F, Featherstone DE, Grosjean Y. 2016 Direct sensing of nutrients via a LAT1-like transporter in *Drosophila* insulin-producing cells. Cell Rep. 17:137–48 [PubMed: 27681427]
74. Ziegler AB, Manière G, Grosjean Y. 2018 JhI-21 plays a role in *Drosophila* insulin-like peptide release from larval IPCs via leucine transport. Sci. Rep 8:1908 [PubMed: 29382949]
75. Magnan C, Levin BE, Luquet S. 2015 Brain lipid sensing and the neural control of energy balance. Mol. Cell. Endocrinol 418:3–8 [PubMed: 26415589]
76. Le Foll C, Levin BE. 2016 Fatty acid-induced astrocyte ketone production and the control of food intake. Am. J. Physiol. Regul. Integr. Comp. Physiol 310:R1186–92 [PubMed: 27122369]

77. Wortley KE, Anderson KD, Yasenchak J, Murphy A, Valenzuela D, et al. 2005 Agouti-related protein-deficient mice display an age-related lean phenotype. Cell Metab. 2:421–27 [PubMed: 16330327]

78. Füredi N, Mikó A, Gaszner B, Feller D, Rostás I, et al. 2018 Activity of the hypothalamic melanocortin system decreases in middle-aged and increases in old rats. J. Gerontol. A 73:438–45

79. Sternson SM. 2013 Hypothalamic survival circuits: blueprints for purposive behaviors. Neuron 77:810–24 [PubMed: 23473313]

80. Kaushik S, Rodriguez-Navarro Jose A, Arias E, Kiffin R, Sahu S, et al. 2011 Autophagy in hypothalamic AgRP neurons regulates food intake and energy balance. Cell Metab. 14:173–83 [PubMed: 21803288]

81. Gendron CM, Kuo TH, Harvanek ZM, Chung BY, Yew JY, et al. 2014 *Drosophila* life span and physiology are modulated by sexual perception and reward. Science 343:544–48 [PubMed: 24292624]

82. Itskov PM, Ribeiro C. 2013 The dilemmas of the gourmet fly: the molecular and neuronal mechanisms of feeding and nutrient decision making in *Drosophila*. Front. Neurosci 7:12 [PubMed: 23407678]

83. Kim DH, Shin M, Jung SH, Kim YJ, Jones WD. 2017 A fat-derived metabolite regulates a peptidergic feeding circuit in *Drosophila*. PLOS Biol. 15:e2000532 [PubMed: 28350856]

84. Beshel J, Dubnau J, Zhong Y. 2017 A leptin analog locally produced in the brain acts via a conserved neural circuit to modulate obesity-linked behaviors in *Drosophila*. Cell Metab. 25:208–17 [PubMed: 28076762]

85. Satoh A, Imai SI, Guarente L. 2017 The brain, sirtuins, and ageing. Nat. Rev. Neurosci 18:362–74 [PubMed: 28515492]

86. Ulgherait M, Rana A, Rera M, Graniel J, Walker DW. 2014 AMPK modulates tissue and organismal aging in a non-cell-autonomous manner. Cell Rep. 8:1767–80 [PubMed: 25199830]

87. Blander G, Guarente L. 2004 The Sir2 family of protein deacetylases. Annu. Rev. Biochem 73:417–35 88. [PubMed: 15189148]

88. Burkewitz K, Morantte I, Weir HJ, Yeo R, Zhang Y, et al. 2015 Neuronal CRTC-1 governs systemic mitochondrial metabolism and lifespan via a catecholamine signal. Cell 160:842–55 [PubMed: 25723162]

89. Kaeberlein M, McVey M, Guarente L. 1999 The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. Genes Dev. 13:2570–80 [PubMed: 10521401]

90. Tissenbaum HA, Guarente L. 2001 Increased dosage of a *sir-2* gene extends lifespan in *Caenorhabditis elegans*. Nature 410:227–30 [PubMed: 11242085]

91. Rogina B, Helfand SL. 2004 Sir2 mediates longevity in the fly through a pathway related to calorie restriction. PNAS 101:15998–6003 [PubMed: 15520384]

92. Satoh A, Brace CS, Rensing N, Cliften P, Wozniak DF, et al. 2013 Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. Cell Metab. 18:416–30 [PubMed: 24011076]

93. O'Callaghan C, Vassilopoulos A. 2017 Sirtuins at the crossroads of stemness, aging, and cancer. Aging Cell 16:1208–18 [PubMed: 28994177]

94. Herskovits AZ, Guarente L. 2014 SIRT1 in neurodevelopment and brain senescence. Neuron 81:471–83 [PubMed: 24507186]

95. Watroba M, Dudek I, Skoda M, Stangret A, Rzodkiewicz P, Szukiewicz D. 2017 Sirtuins, epigenetics and longevity. Ageing Res. Rev 40:11–19 [PubMed: 28789901]

96. Pool AH, Kvello P, Mann K, Cheung SK, Gordon MD, et al. 2014 Four GABAergic interneurons impose feeding restraint in *Drosophila*. Neuron 83:164–77 [PubMed: 24991960]

97. Yapici N, Cohn R, Schusterreiter C, Ruta V, Vosshall LB. 2016 A taste circuit that regulates ingestion by integrating food and hunger signals. Cell 165:715–29 [PubMed: 27040496]

98. Kain P, Dahanukar A. 2015 Secondary taste neurons that convey sweet taste and starvation in the *Drosophila* brain. Neuron 85:819–32 [PubMed: 25661186]

99. White KE, Humphrey DM, Hirth F. 2010 The dopaminergic system in the aging brain of *Drosophila*. Front. Neurosci 4:205 [PubMed: 21165178]
100. Krashes MJ, DasGupta S, Vreede A, White B, Armstrong JD, Waddell S. 2009 A neural circuit mechanism integrating motivational state with memory expression in *Drosophila*. Cell 139:416–27 [PubMed: 19837040]
101. Albin SD, Kaun KR, Knapp J-M, Chung P, Heberlein U, Simpson JH. 2015 A subset of serotonergic neurons evokes hunger in adult *Drosophila*. Curr. Biol 25:2435–40 [PubMed: 26344091]
102. Zhan YP, Liu L, Zhu Y. 2016 Taotie neurons regulate appetite in *Drosophila*. Nat. Commun 7:13633 [PubMed: 27924813]
103. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. 2015 Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect. Psychol. Sci 10:227–37 [PubMed: 25910392]
104. Ong AD, Allaire JC. 2005 Cardiovascular intraindividual variability in later life: the influence of social connectedness and positive emotions. Psychol. Aging 20:476–85 [PubMed: 16248706]
105. Brummett BH, Barefoot JC, Siegler IC, Clapp-Channing NE, Lytle BL, et al. 2001 Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. Psychosom. Med 63:267–72 [PubMed: 11292274]
106. Glass TA, Matchar DB, Belyea M, Feussner JR. 1993 Impact of social support on outcome in first stroke. Stroke 24:64–70 [PubMed: 8418553]
107. Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B. 2000 Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 355:1315–19 [PubMed: 10776744]
108. Epel ES, Lithgow GJ. 2014 Stress biology and aging mechanisms: toward understanding the deep connection between adaptation to stress and longevity. J. Gerontol. A Biol. Sci. Med. Sci 69(Suppl. 1):S10–16 [PubMed: 24833580]
109. Chetty R, Stepner M, Abraham S, Lin S, Scuderi B, et al. 2016 The association between income and life expectancy in the United States, 2001–2014. JAMA 315:1750–66 [PubMed: 27063997]
110. Dawson EH, Bailly TPM, Dos Santos J, Moreno C, Devilliers M, et al. 2018 Social environment mediates cancer progression in *Drosophila*. Nat. Commun 9:3574 [PubMed: 30177703]
111. Huang H, Wang L, Cao M, Marshall C, Gao J, et al. 2015 Isolation housing exacerbates Alzheimer's disease-like pathophysiology in aged APP/PS1 mice. Int. J. Neuropsychopharmacol 18:pyu116 [PubMed: 25568286]
112. Mumtaz F, Khan MI, Zubair M, Dehpour AR. 2018 Neurobiology and consequences of social isolation stress in animal model—a comprehensive review. Biomed. Pharmacother 105:1205–22 [PubMed: 30021357]
113. Razzoli M, Nyuyki-Dufe K, Gurney A, Erickson C, McCallum J, et al. 2018 Social stress shortens lifespan in mice. Aging Cell 17:e12778 [PubMed: 29806171]
114. Kuo TH, Yew JY, Fedina TY, Dreisewerd K, Dierick HA, Pletcher SD. 2012 Aging modulates cuticular hydrocarbons and sexual attractiveness in *Drosophila* melanogaster. J. Exp. Biol 215:814–21 [PubMed: 22323204]
115. Brennan PA, Kendrick KM. 2006 Mammalian social odours: attraction and individual recognition. Philos. Trans. R. Soc. B 361:2061–78
116. Wang L, Anderson DJ. 2010 Identification of an aggression-promoting pheromone and its receptor neurons in *Drosophila*. Nature 463:227–31 [PubMed: 19966787]
117. Kurtovic A, Widmer A, Dickson BJ. 2007 A single class of olfactory neurons mediates behavioural responses to a *Drosophila* sex pheromone. Nature 446:542–46 [PubMed: 17392786]
118. Fedina TY, Kuo TH, Dreisewerd K, Dierick HA, Yew JY, Pletcher SD. 2012 Dietary effects on cuticular hydrocarbons and sexual attractiveness in *Drosophila*. PLOS ONE 7:e49799 [PubMed: 23227150]
119. Kuo TH, Fedina TY, Hansen I, Dreisewerd K, Dierick HA, et al. 2012 Insulin signaling mediates sexual attractiveness in *Drosophila*. PLOS Genet 8:e1002684 [PubMed: 22570625]
120. Yang CF, Shah NM. 2014 Representing sex in the brain, one module at a time. Neuron 82:261–78 [PubMed: 24742456]

121. Henkel S, Setchell JM. 2018 Group and kin recognition via olfactory cues in chimpanzees (Pan troglodytes). Proc. R. Soc. B 285 10.1098/rspb.2018.1527
122. Lazaro-Perea C, Snowdon CT, Arruda MF. 1999 Scent-making behavior in wild groups of common marmosets. Behav. Ecol. Sociobiol 46:313–24
123. Maures TJ, Booth LN, Benayoun BA, Izrayelit Y, Schroeder FC, Brunet A. 2014 Males shorten the life span of *C. elegans* hermaphrodites via secreted compounds. Science 343:541–44 [PubMed: 24292626]
124. Aprison EZ, Ruvinsky I. 2016 Sexually antagonistic male signals manipulate germline and soma of *C. elegans* hermaphrodites. Curr. Biol 26:2827–33 [PubMed: 27618262]
125. Harvanek ZM, Lyu Y, Gendron CM, Johnson JC, Kondo S, et al. 2017 Perceptive costs of reproduction drive ageing and physiology in male *Drosophila*. Nat. Ecol. Evol 1:0152
126. Flintham EO, Yoshida T, Smith S, Pavlou HJ, Goodwin SF, et al. 2018 Interactions between the sexual identity of the nervous system and the social environment mediate lifespan in *Drosophila melanogaster*. Proc. R. Soc. B 285 10.1098/rspb.2018.1450
127. Uchino BN. 2006 Social support and health: a review of physiological processes potentially underlying links to disease outcomes. J. Behav. Med 29:377–87 [PubMed: 16758315]
128. Chen S, Lee AY, Bowens NM, Huber R, Kravitz EA. 2002 Fighting fruit flies: a model system for the study of aggression. PNAS 99:5664–68 [PubMed: 11960020]
129. Zelikowsky M, Hui M, Karigo T, Choe A, Yang B, et al. 2018 The neuropeptide Tac2 controls a distributed brain state induced by chronic social isolation stress. Cell 173:1265–79.e19 [PubMed: 29775595]
130. Liu G, Nath T, Linneweber GA, Claeys A, Guo Z, et al. 2018 A simple computer vision pipeline reveals the effects of isolation on social interaction dynamics in *Drosophila*. PLOS Comput. Biol 14:e1006410 [PubMed: 30161262]
131. Liu H, Wang Z. 2005 Effects of social isolation stress on immune response and survival time of mouse with liver cancer. World J. Gastroenterol 11:5902–4 [PubMed: 16270407]
132. Karelina K, Norman GJ, Zhang N, Morris JS, Peng H, DeVries AC. 2009 Social isolation alters neu-roinflammatory response to stroke. PNAS 106:5895–900 [PubMed: 19307557]
133. Dong H, Goico B, Martin M, Csernansky CA, Bertchume A, Csernansky JG. 2004 Modulation of hip-pocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. Neuroscience 127:601–9 [PubMed: 15283960]
134. Ruan H, Wu CF. 2008 Social interaction-mediated lifespan extension of *Drosophila* Cu/Zn superoxide dismutase mutants. PNAS 105:7506–10 [PubMed: 18508973]
135. Ruland C, Berlandi J, Eikmeier K, Weinert T, Lin FJ, et al. 2018 Decreased cerebral Irp-1B limits impact of social isolation in wild type and Alzheimer's disease modeled in *Drosophila melanogaster*. Genes Brain Behav. 17:e12451 [PubMed: 29251829]
136. Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW. 2015 The neuroendocrinology of social isolation. Annu. Rev. Psychol 66:733–67 [PubMed: 25148851]
137. Ganguly-Fitzgerald I, Donlea J, Shaw PJ. 2006 Waking experience affects sleep need in *Drosophila*.Science 313:1775–81 [PubMed: 16990546]
138. Shohat-Ophir G, Kaun KR, Azanchi R, Mohammed H, Heberlein U. 2012 Sexual deprivation increases ethanol intake in *Drosophila*. Science 335:1351–55 [PubMed: 22422983]
139. Alekseyenko OV, Chan YB, Fernandez MP, Bulow T, Pankratz MJ, Kravitz EA. 2014 Single serotonergic neurons that modulate aggression in *Drosophila*. Curr. Biol 24:2700–7 [PubMed: 25447998]
140. Dierick HA, Greenspan RJ. 2007 Serotonin and neuropeptide F have opposite modulatory effects on fly aggression. Nat. Genet 39:678–82 [PubMed: 17450142]
141. Hoyer SC, Eckart A, Herrel A, Zars T, Fischer SA, et al. 2008 Octopamine in male aggression of *Drosophila*. Curr. Biol 18:159–67 [PubMed: 18249112]
142. Luo J, Lushchak OV, Goergen P, Williams MJ, Nassel DR. 2014 *Drosophila* insulin-producing cells are differentially modulated by serotonin and octopamine receptors and affect social behavior. PLOS ONE 9:e99732 [PubMed: 24923784]

143. Mohawk JA, Green CB, Takahashi JS. 2012 Central and peripheral circadian clocks in mammals. Annu. Rev. Neurosci 35:445–62 [PubMed: 22483041]

144. Tataroglu O, Emery P. 2015 The molecular ticks of the *Drosophila* circadian clock. Curr. Opin. Insect. Sci 7:51–57 [PubMed: 26120561]

145. Evans JA, Davidson AJ. 2013 Health consequences of circadian disruption in humans and animal models. Prog. Mol. Biol. Transl. Sci 119:283–323 [PubMed: 23899601]

146. James SM, Honn KA, Gaddameedhi S, Van Dongen HPA. 2017 Shift work: disrupted circadian rhythms and sleep-implications for health and well-being. Curr. Sleep Med. Rep 3:104–12 [PubMed: 29057204]

147. Yoshii T, Heshiki Y, Ibuki-Ishibashi T, Matsumoto A, Tanimura T, Tomioka K. 2005 Temperature cycles drive *Drosophila* circadian oscillation in constant light that otherwise induces behavioural arrhyth-micity. Eur. J. Neurosci 22:1176–84 [PubMed: 16176360]

148. Oike H, Sakurai M, Ippoushi K, Kobori M. 2015 Time-fixed feeding prevents obesity induced by chronic advances of light/dark cycles in mouse models of jet-lag/shift work. Biochem. Biophys. Res. Commun 465:556–61 [PubMed: 26297949]

149. Videnovic A, Klerman EB, Zee PC. 2017 Light therapy promoting dopamine release by stimulating retina in Parkinson disease-reply. JAMA Neurol. 74:1268–69 [PubMed: 28806434]

150. Koh K, Evans JM, Hendricks JC, Sehgal A. 2006 A *Drosophila* model for age-associated changes in sleep:wake cycles. PNAS 103:13843–47 [PubMed: 16938867]

151. Nakamura TJ, Nakamura W, Yamazaki S, Kudo T, Cutler T, et al. 2011 Age-related decline in circadian output. J. Neurosci 31:10201–5 [PubMed: 21752996]

152. Buysse DJ, Monk TH, Carrier J, Begley A. 2005 Circadian patterns of sleep, sleepiness, and performance in older and younger adults. Sleep 28:1365–76 [PubMed: 16335481]

153. Luo W, Chen WF, Yue Z, Chen D, Sowcik M, et al. 2012 Old flies have a robust central oscillator but weaker behavioral rhythms that can be improved by genetic and environmental manipulations. Aging Cell 11:428–38 [PubMed: 22268765]

154. Rakshit K, Krishnan N, Guzik EM, Pyza E, Giebultowicz JM. 2012 Effects of aging on the molecular circadian oscillations in *Drosophila*. Chronobiol. Int 29:5–14 [PubMed: 22217096]

155. Nakamura TJ, Nakamura W, Tokuda IT, Ishikawa T, Kudo T, et al. 2015 Age-related changes in the circadian system unmasked by constant conditions. eNeuro 2:e0064–15.2015

156. Li H, Satinoff E. 1998 Fetal tissue containing the suprachiasmatic nucleus restores multiple circadian rhythms in old rats. Am. J. Physiol 275:R1735–44 [PubMed: 9843862]

157. Hurd MW, Ralph MR. 1998 The significance of circadian organization for longevity in the golden hamster. J. Biol. Rhythms 13:430–36 [PubMed: 9783234]

158. Krishnan N, Kretzschmar D, Rakshit K, Chow E, Giebultowicz JM. 2009 The circadian clock gene period extends healthspan in aging *Drosophila melanogaster*. Aging 1:937–48 [PubMed: 20157575]

159. Krishnan N, Davis AJ, Giebultowicz JM. 2008 Circadian regulation of response to oxidative stress in *Drosophila melanogaster*. Biochem. Biophys. Res. Commun 374:299–303 [PubMed: 18627767]

160. Solovev I, Shegoleva E, Fedintsev A, Shaposhnikov M, Moskalev A. 2019 Circadian clock genes' overexpression in *Drosophila* alters diet impact on lifespan. Biogerontology 20:159–70 [PubMed: 30470951]

161. Katewa SD, Akagi K, Bose N, Rakshit K, Camarella T, et al. 2016 Peripheral circadian clocks mediate dietary restriction-dependent changes in lifespan and fat metabolism in *Drosophila*. Cell Metab 23:143–54 [PubMed: 26626459]

162. Ulgherait M, Chen A, Oliva MK, Kim HX, Canman JC, et al. 2016 Dietary restriction extends the lifespan of circadian mutants *tim* and *per*. Cell Metab. 24:763–64 [PubMed: 27916531]

163. Hendricks JC, Lu S, Kume K, Yin JC, Yang Z, Sehgal A. 2003 Gender dimorphism in the role of cycle (BMAL1) in rest, rest regulation, and longevity in *Drosophila melanogaster*. J. Biol. Rhythms 18:12–25 [PubMed: 12568241]

164. Kondratov RV, Kondratova AA, Gorbacheva VY, Vykhovanets OV, Antoch MP. 2006 Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock. Genes Dev 20:1868–73 [PubMed: 16847346]

165. McDearmon EL, Patel KN, Ko CH, Walisser JA, Schook AC, et al. 2006 Dissecting the functions of the mammalian clock protein BMAL1 by tissue-specific rescue in mice. Science 314:1304–8 [PubMed: 17124323]
166. Hughes ME, Hong HK, Chong JL, Indacochea AA, Lee SS, et al. 2012 Brain-specific rescue of Clock reveals system-driven transcriptional rhythms in peripheral tissue. PLOS Genet. 8:e1002835 [PubMed: 22844252]
167. Rakshit K, Giebultowicz JM. 2013 Cryptochrome restores dampened circadian rhythms and promotes healthspan in aging *Drosophila*. Aging Cell 12:752–62 [PubMed: 23692507]
168. Anderson JR. 2016 Comparative thanatology. Curr. Biol 26:R553–56 [PubMed: 27404245]
169. Chakraborty TS, Gendron CM, Lyu Y, Munneke AS, DeMarco MN, et al. 2019 Sensory perception of dead conspecifics induces aversive cues and modulates lifespan through serotonin in *Drosophila*. Nat. Commun 10:2365 [PubMed: 31147540]
170. Petrie K, Milligan-Saville J, Gayed A, Deady M, Phelps A, et al. 2018 Prevalence of PTSD and common mental disorders amongst ambulance personnel: a systematic review and meta-analysis. Soc. Psychiatry Psychiatr. Epidemiol 53:897–909 [PubMed: 29869691]
171. Smith TC, Ryan MA, Wingard DL, Slymen DJ, Sallis JF, et al. 2008 New onset and persistent symptoms of post-traumatic stress disorder self reported after deployment and combat exposures: prospective population based US military cohort study. BMJ 336:366–71 [PubMed: 18198395]
172. Liu Z, Kariya MJ, Chute CD, Pribadi AK, Leinwand SG, et al. 2018 Predator-secreted sulfolipids induce defensive responses in *C. elegans*. Nat. Commun 9:1128 [PubMed: 29555902]
173. Zhou Y, Loeza-Cabrera M, Liu Z, Aleman-Meza B, Nguyen JK, et al. 2017 Potential nematode alarm pheromone induces acute avoidance in *Caenorhabditis elegans*. Genetics 206:1469–78 [PubMed: 28495959]
174. Bishop NA, Guarente L. 2007 Two neurons mediate diet-restriction-induced longevity in *C. elegans*. Nature 447:545–49 [PubMed: 17538612]
175. Zhang B, Gong J, Zhang W, Xiao R, Liu J, Xu XZS. 2018 Brain-gut communications via distinct neuroendocrine signals bidirectionally regulate longevity in *C. elegans*. Genes Dev. 32:258–70 [PubMed: 29491136]
176. Kacsoh BZ, Bozler J, Ramaswami M, Bosco G. 2015 Social communication of predator-induced changes in Drosophila behavior and germ line physiology. eLife 4:e07423
177. Pereira AG, Moita MA. 2016 Is there anybody out there? Neural circuits of threat detection in vertebrates. Curr. Opin. Neurobiol 41:179–87 [PubMed: 27750206]
178. Perez-Gomez A, Bleymehl K, Stein B, Pyrski M, Birnbaumer L, et al. 2015 Innate predator odor aversion driven by parallel olfactory subsystems that converge in the ventromedial hypothalamus. Curr. Biol 25:1340–46 [PubMed: 25936549]
179. Gross CT, Canteras NS. 2012 The many paths to fear. Nat. Rev. Neurosci 13:651–58 [PubMed: 22850830]
180. Martinez RC, Carvalho-Netto EF, Ribeiro-Barbosa ER, Baldo MV, Canteras NS. 2011 Amygdalar roles during exposure to a live predator and to a predator-associated context. Neuroscience 172:314–28 [PubMed: 20955766]
181. McDonald AJ. 1998 Cortical pathways to the mammalian amygdala. Prog. Neurobiol 55:257–332 [PubMed: 9643556]
182. Vyas S, Rodrigues AJ, Silva JM, Tronche F, Almeida OF, et al. 2016 Chronic stress and glucocorticoids: from neuronal plasticity to neurodegeneration. Neural Plast. 2016:6391686 [PubMed: 27034847]
183. Hanson JL, Hurley LM. 2014 Context-dependent fluctuation of serotonin in the auditory midbrain: the influence of sex, reproductive state and experience. J. Exp. Biol 217:526–35 [PubMed: 24198252]
184. Petrascheck M, Ye X, Buck LB. 2007 An antidepressant that extends lifespan in adult *Caenorhabditis elegans*. Nature 450:553–56 [PubMed: 18033297]
185. Burkewitz K, Morantte I, Weir HJM, Yeo R, Zhang Y, et al. 2015 Neuronal CRTC-1 governs systemic mitochondrial metabolism and lifespan via a catecholamine signal. Cell 160:842–55 [PubMed: 25723162]

186. Domingos AI, Vaynshteyn J, Voss HU, Ren X, Gradinaru V, et al. 2011 Leptin regulates the reward value of nutrient. Nat. Neurosci 14:1562–68 [PubMed: 22081158]

187. You YJ, Kim J, Raizen DM, Avery L. 2008 Insulin, cGMP, and TGF-β signals regulate food intake and quiescence in *C. elegans*: a model for satiety. Cell Metab 7:249–57 [PubMed: 18316030]

188. Teff K 2000 Nutritional implications of the cephalic-phase reflexes: endocrine responses. Appetite 34:206–13 [PubMed: 10744911]

189. Christakis NA, Fowler JH. 2007 The spread of obesity in a large social network over 32 years. N. Engl. J. Med 357:370–79 [PubMed: 17652652]

190. Anderson DJ, Adolphs R. 2014 A framework for studying emotions across species. Cell 157:187–200 [PubMed: 24679535]

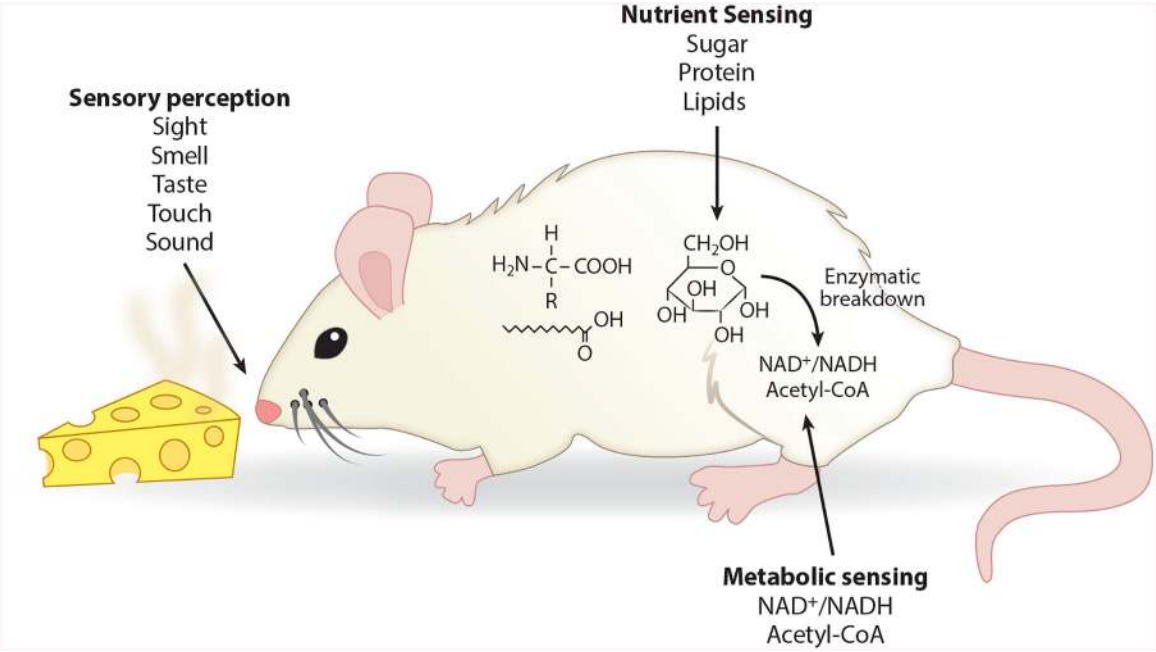

Figure 1.

Illustration of the different aspects of nutrient perception. The sensing of external cues by canonical sensing modalities is called sensory perception. Internalized nutrients are sensed via nutrient sensing pathways, whereas their metabolized products are sensed via metabolic sensing pathways.

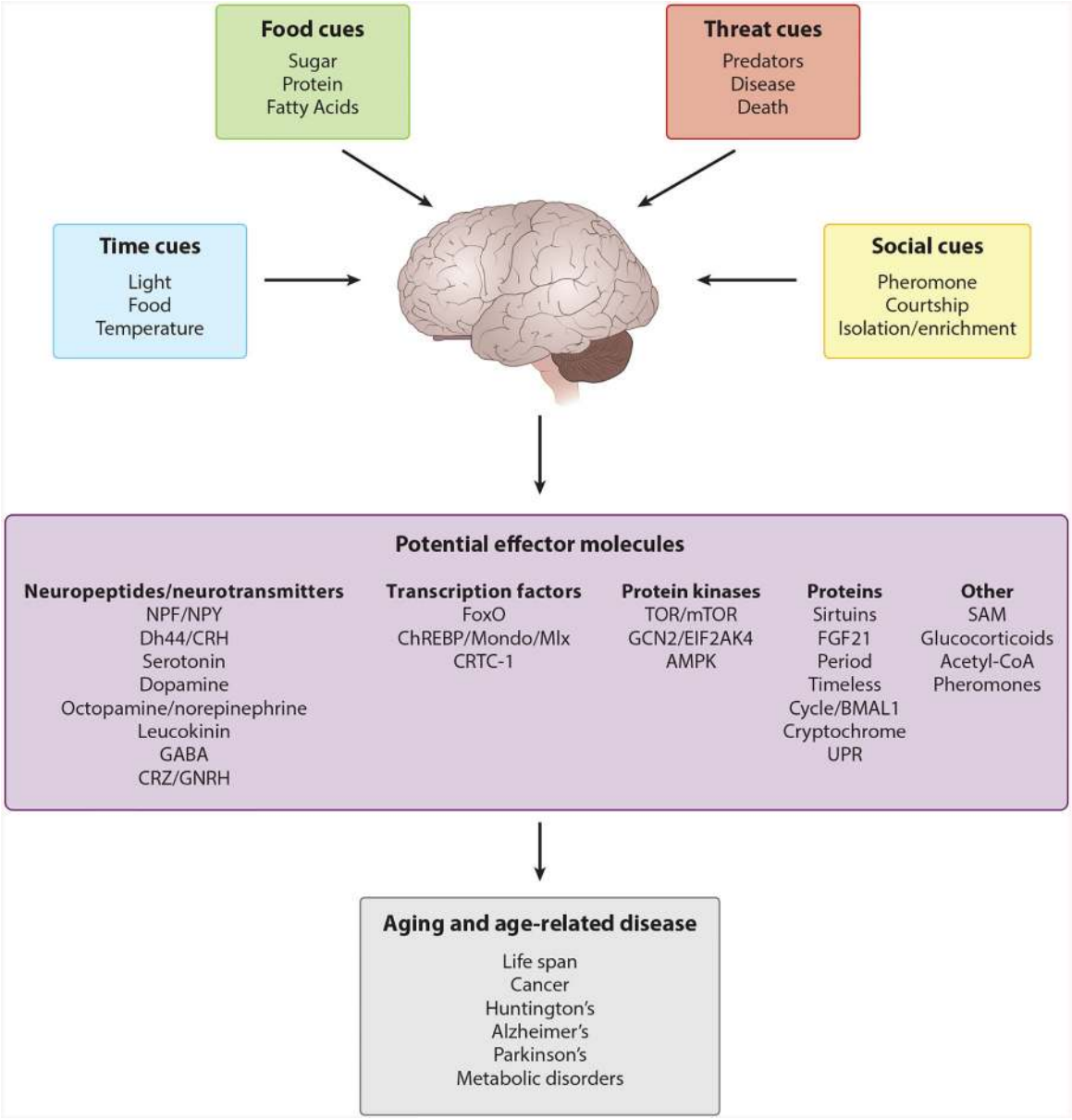

Figure 2.

Potential effector molecules that may mediate sensory perceptive experiences, thereby potentially impacting aging and age-related disease. Abbreviations: CRTC-1, CREB-regulated transcription coactivator 1; FGF21, fibroblast growth factor 21; mTOR, mechanistic target of rapamycin; NPF, neuropeptide F; NPY, neuropeptide Y; SAM, S-adenosyl methionine; UPR, unfolded protein response.