ARTICLE ADDENDUM

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# The sensory system: More than just a window to the external world

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**While the traditional importance of the sensory system lies in its ability to perceive external information about the world, emerging discoveries suggest that sensory perception has a greater impact on health and longevity than was previously appreciated. These effects are conserved across species. In this mini-review, we discuss the specific sensory cues that have been identified to significantly impact organismal physiology and lifespan. Ongoing work in the aging field has begun to identify the downstream molecules that mediate the broad effects of sensory signals. Candidates include FOXO, neuropeptide F (NPF), adipokinetic hormone (AKH), dopamine, serotonin, and octopamine. We then discuss the many implications that arise from our current understanding of the effects of sensory perception on health and longevity.**

**Keywords:** AKH, lifespan, aging, model systems, NPF, pheromones, sensory perception

**Abbreviations:** AKH, adipokinetic hormone; NPF, neuropeptide F.



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Life depends on the ability of an organism to correctly assess its environment and respond accordingly. To illustrate, migratory animals such as birds utilize environmental cues, including temperature and sunlight, to inform them when it is time to relocate. Failure to identify and/or respond to these cues appropriately would ultimately result in death due to cold exposure and hunger.

Emerging research demonstrates that the sensory system does not simply report the status of the environment. Rather, the cues themselves can have significant effects on organismal health and longevity. In the worm *Caenorhabditis elegans*, functional manipulation of discrete sensory neurons caused differential effects on lifespan.[1,2] Subsequent studies performed using the fruit fly *Drosophila melanogaster* not only established that the effects of manipulating the sensory system on lifespan were evolutionarily conserved but also identified a repertoire of sensory cues that have a direct impact on aging. Genetic manipulations that render flies broadly anosmic caused significant increases in lifespan.[3] Food cues, such as sweet (via the receptor Gr5a) or bitter (via the receptor Gr66a) tastes, had opposite, yet significant effects on lifespan.[4] Ablation of water sensing via the water receptor Ppk28 caused significant increases in both fat levels and lifespan.[5] Loss of the ability to sense danger cues via the $CO_2$ receptor, Gr63a, also resulted in significantly increased fat levels and in extended lifespan.[6] Conversely, pheromonal cues, sensed in male flies via the receptor Ppk23, caused significant decreases in fat levels and longevity.[7]

While we are beginning to understand the types of environmental cues that significantly impact health and longevity, the mechanisms by which a few specific sensory neurons affect the lifespan of cells and tissues throughout the animal remain poorly understood. Neurotransmitter release is likely involved in this process since these molecules are responsible for direct communication between neighboring neurons, propagating sensory information from the initial site of sensory stimulation to deeper regions of the nervous system. An understanding of which neurotransmitters are important in transmitting longevity signals from sensory neurons may provide clues about the types of neural circuits that are critical for controlling lifespan. In *C. elegans*, serotonin receptor mutants exhibited significant alterations in lifespan.[8] Overexpression of BAS-1 (a dopa decarboxylase responsible for the synthesis of both serotonin and dopamine) in serotonergic neurons caused

improved behavioral performance with age as well as increased overall lifespan of the worms.[9] A separate study demonstrated that lifespan can be extended in *C. elegans* by pharmacologically altering adrenoceptor, histamine, serotonin, dopamine, or octopamine signaling.[10-12] Dopamine has also been implicated in mammalian longevity; mice fed the drug levodopa (L-DOPA), which is expected to potentiate dopamine levels, had significantly longer lives (up to 50% longer),[13] whereas Dopamine Receptor 4 (*DRD4*) mutants show reduced lifespan when the animals were kept in an enriched environment.[14] Interestingly, the 7R allele of *DRD4* in humans is associated with longevity.[14] Knowing the types of neural transmission and the specific neurotransmitters involved in propagating "longevity signals" may help identify target molecules for the development of therapies that maximize the benefits of sensory perception.

In addition to neurotransmitters, which are responsible for short distance communication between neurons, it is of interest to identify the molecules that are responsible for propagating sensory information through broader neuronal and cellular networks that affect the aging process. One candidate neuropeptide that appears to fulfill this role is neuropeptide F (NPF). When male flies were exposed to female pheromones, levels of *NPF* mRNA and protein were increased in the brain (**Fig. 1**).[7] Furthermore, silencing of NPF-expressing neurons rendered male flies insensitive to the effects of female pheromones.[7] Together these data suggest that NPF may be a key molecule in transmitting one or more sensory cues to different neuronal populations within the nervous system or even to other target tissues, such as the gut.[15] Of note, the NPF homolog in mammals, called neuropeptide Y (NPY), also has significant effector roles in a variety of physiological outcomes such as feeding, metabolism, reproduction, and stress.[16] A second neuropeptide involved in communicating sensory information across tissues is the glucagon-like adipokinetic hormone (AKH). Ablation of the water-sensing receptor *ppk28* increased AKH levels in *D. melanogaster* while mutation of the *AKH* receptor abrogated *ppk28*-mediated lifespan extension, implicating a role for AKH in water sensing and establishing a potential link between this peptide hormone and aging.[5] Importantly, FOXO, a transcription factor in the insulin-signaling pathway that is known to influence lifespan across species, is also required for *ppk28* loss of function to extend lifespan. While the specific cues and/or the neuronal circuitry of one species may not be directly translatable to another species, the ways in which the sensory system orchestrates significant physiological changes in complex outcomes, such as aging, are likely conserved across species. New evidence supports this view; sensory perturbations in mice, similar to what have been demonstrated in worms and flies, significantly increased their lifespan and promoted more "youthful" physiologies and behaviors.[17]

What are the implications that can be made from our current understanding of the effect of sensory systems on organismal physiology? Firstly, and perhaps the most obvious, sensory experiences may have more significant effects on human health than are currently realized. This can be inferred from the fact that sensory manipulations in species separated in evolutionary time by millions of years of have equally dramatic effects on health and lifespan, reaffirming that the effects of sensory perception on organismal physiology is evolutionary conserved. Just which specific sensory cues are relevant to us, how they are integrated, and in what ways they impact our health and lifespan remain to be addressed. Secondly, data from our laboratory indicate that the perception of one

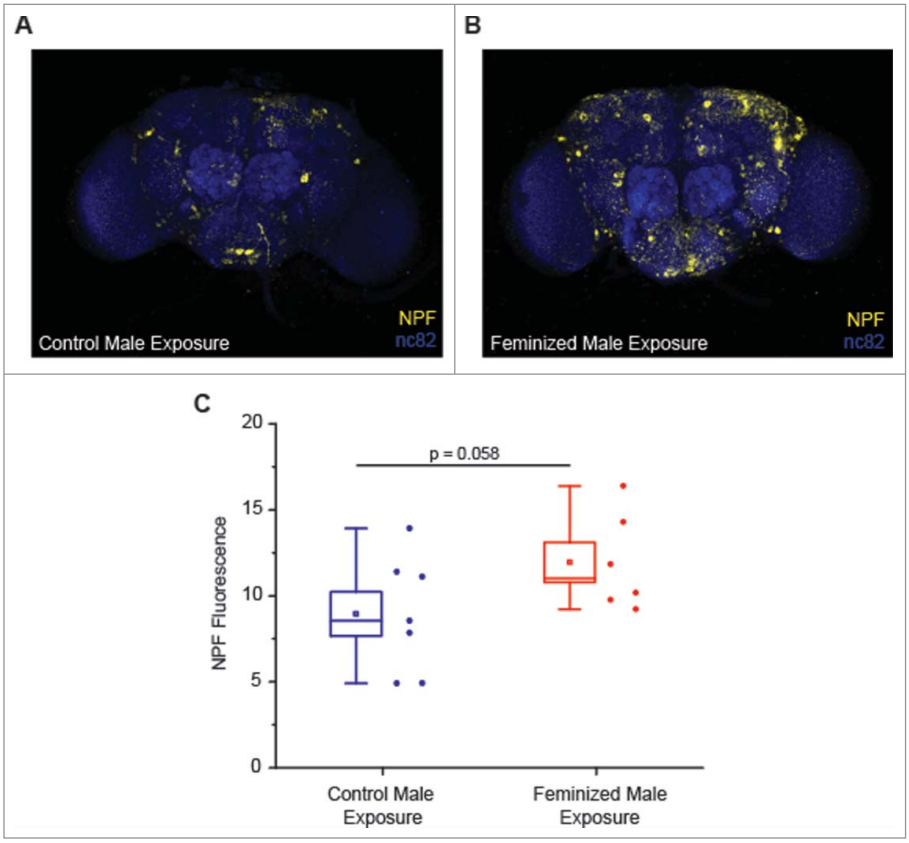


**Figure 1.** Pheromone Exposure Enhances NPF Levels in the Adult Fly Brain. Brains isolated from adult male flies exposed to either (**A**) control males or (**B**) males genetically engineered to express female pheromones were immunostained against NPF (yellow) and the nc82 neuronal cell marker (blue). (**C**) Quantification of total NPF fluorescence. The total NPF immunostaining normalized to nc82 area ($n = 7$ for male adult brain samples exposed to male flies; $n = 6$ for male adult brain samples exposed to feminized males; $p = 0.058$ as measured by Student's t-test). The NPF antibody used in this experiment was kindly provided by Ping Shen.

sense leads to the drastic down-regulation in the expression of genes involved in sensing other, seemingly dissimilar environmental cues.[7] This observation suggests the hypothesis that organisms have evolved mechanisms to modulate their sensitivity to a certain amount of environmental input(s) in response to the perception of others. Sensory overload may therefore be counterproductive, or even stressful. It will therefore be of interest to test whether exposing an organism to one type of environmental cue modifies its ability to either detect or enact an appropriate physiological response to other types of environmental cues, as would be predicted from our RNA sequencing data.[7] Thirdly, the effects of pheromone perception may directly impact evolutionary dynamics. While our recent work demonstrates that pheromone perception of the opposite gender significantly shortened fly lifespan, we also observed that mating after pheromone exposure partially rescued the pheromone-induced lifespan effects.[7] Thus, weaker males that sense females but are not allowed to mate are more likely to die earlier than stronger males that successfully mate. Perhaps this is a mechanism through which females manipulate males to increase the probability of mating with those that are more robust, thereby ensuring that the "strongest genes" are incorporated in future generations.[18] Lastly, our laboratory has shown that pathways important for modulating aging in an organism, such as insulin and target of rapamycin signaling, can also affect pheromone production and its overall attractiveness.[19,20] It is therefore plausible that the sensory system may be a conduit through which the genome of one individual can impact the health and lifespan of another.[7]

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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