Humidity sensation, cockroaches, worms, and humans: are common sensory mechanisms for hygrosensation shared across species?

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THE ABILITY TO SENSE the surrounding environment represents one of the most important attributes that any animal species requires to ensure survival. For this reason, animals (including humans) present a variety of sensory systems (e.g., visual, somatic, auditory) which, by transducing distinctive physical properties of external stimuli (e.g., light, temperature, touch, sound) into biological signals (e.g., action potential generated at afferent nerve endings), provide the living organism with awareness of the characteristics of its surrounding environment. Ultimately, the ability to encode sensory information is used across the animal kingdom to initiate or adjust specific behaviors, which are aimed to maintain homeostasis, regulate growth and reproduction, and ensure survival (Shelford 1918).

One such sensory ability, which has been shown to be a critical sensory feature of many terrestrial animals (including humans), is that of humidity sensation or hygrosensation, i.e., the ability to discriminate between moisture levels (Montell 2008). Specifically, the main distinctive feature between species is whether the organism is or is not provided with a specific sensory organ to detect humidity (i.e., hygoreceptors). The presence of specific hygoreceptors has been primarily observed in insects. For instance, the American cockroach, Periplaneta americana L., is provided with hygoreceptors located in the antenna (i.e., hygroreceptive sensillum), whose neural substrates (i.e., moist and dry sensitive neural cells) selectively respond to changes in ambient humidity and air pressure (Tichy and Kallina 2010). The transduction mechanisms of the cockroach’s hygroreceptive sensillum are activated by the hygroscopic behavior of this sensory organ: swelling or shrinking of the hygroreceptive sensillum (as a result of changes in ambient humidity and air pressure) compresses or expands the dendrites surrounding the sensillum wall, thus increasing or decreasing the activity of mechanosensitive moist and dry neurons (Fig. 1A) (Tichy and Kallina 2010).

Similar specific dry- and moist-sensing receptors have also been identified in the common fruit fly, Drosophila melanogaster (Fig. 1B) (Liu et al. 2007). Interestingly, the molecular bases of these hygoreceptors have been identified in the expression of specific transient receptor potential (TRP) cation channels that are involved in mechano- as well as temperature-dependent transduction (Liu et al. 2007). The fact that the common fruit fly detects changes in ambient humidity and air pressure via mechano- as well as temperature-dependent sensory inputs (Liu et al. 2007), provides evidence for the possibility that insects hygoreceptors could also operate as psychometers. These hygroreceptive organs could provide information on the humidity (or the dryness) of the air by sensing temperature changes resulting from the degree of cooling due to evaporation of moisture from the hygroreceptive sensillum surface (Tichy and Kallina 2010), a process that is determined by the vapor pressure gradient between moisture on the sensillum’s surface and in the air.
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The discovery that humidity sensation in animals provided with hygroreceptors appears to rely on mechanoo- and temperature-dependent transduction mechanisms provides insights into the potential biological strategies adopted by those animals which, on the contrary, are not provided with specific hygroreceptors. Indeed, hygroreceptor-lacking animals (including humans) could also rely on mechanoo- and temperature-dependent sensory mechanisms to detect humidity and wetness (Filingeri et al. 2014b). However, until recently most of the research on hygrosensation has focused on organisms provided with specific hygroreceptors, and still little is known about the underlying molecular, neuronal, and behavioral mechanisms that underpin hygrosensation in species lacking specific humidity detectors.

In this respect, the recent work of Russell et al. (2014) has provided the first neuromolecular evidence for the existence of a specific hygrosensation strategy in an animal lacking hygroreceptors, namely, the free-living roundworm, Caenorhabditis elegans. In their study, Russell et al. (2014) investigated how C. elegans responds to humidity gradients. This free-living roundworm was hypothesized to be sensitive to humidity because of its small volume and hydrostatic skeleton, a fact that makes it vulnerable to desiccation and overhydration, and therefore potentially attracted by particular humidity levels deemed optimal for survival. To determine whether this animal could migrate to a preferred level of ambient humidity, a specific hygrotaxis assay (which allowed testing of the directed response of a motile organism to moisture) was designed. Worms (n = 20–200) were placed in a box with an elevated central area bordered by two troughs containing distilled water and desiccant. The two troughs generated a controlled humidity gradient ranging from 10% (i.e., desiccant side) to 95% (i.e., water side). At this point, the humidity sensation of C. elegans was assessed by recording whether the worms migrated toward a specific side of the box (i.e., dry or humid) over a 60-min time period. To quantify the worms’ hygrotaxis, a behavioral index was derived, which indicated whether a behavioral index was derived, which indicated whether the specific genes, cation channels, and sensory transduction molecules, to identify the neuromolecular bases of the sensory pathways used by C. elegans to detect humidity.

Initially, molecular disruption of olfaction, taste, and osmosensation did not result in changes in hygrotaxis in mutant worms. However, when hygrotaxis was tested in mutants lacking mec-10 and asic-1 genes (well-known transcription factors for those DEG/ENaC/ASIC cation channels which are essential for mechanosensation in animals) (Tsuzuki and Bautista 2009), hygrotaxis was found to be significantly impaired. Furthermore, ablation of the touch neurons in which mec-10 and asic-1 genes are expressed also abolished hygrotaxis. These results indicated that the genes and neurons that underpin mechanosensation in C. elegans were therefore essential for hygrosensation.

Having appraised the role of mechanosensitive neurons, Russell et al. (2014) further investigated whether thermosensitive neurons could also play a role in hygrosensation. The reason for testing whether thermal cues were also required for hygrosensation was based on previous evidence which had indicated the involvement of thermosensitive TRP channels in humidity detection in hygroreceptor-provided animals such as the fruit fly (Liu et al. 2007), as well as on human psychophysical experiments of wetness perception [e.g., Bentley (1900) was the first scientist to report that the blend of light mechanical pressure and coldness could be responsible for evoking the perception of skin wetness in humans]. When humidity detection was assessed in mutants lacking TAX-4 (i.e., a cation channel expressed on thermosensitive neurons), worms showed impaired hygrotaxis, a fact which indicated that thermosensitive pathways were also essential for hygrosensation in C. elegans.

All in all, the neuromolecular results of Russell et al. (2014) indicated that the specific genes, cation channels, and sensory neurons that underpin the ability of C. elegans to sense me-
mechanical and temperature-related stimuli are functionally essential for this organism’s ability to sense humidity. When paired with the behavioral results, these findings highlight that the ability of these worms to sense humidity is specifically centered on the sensory integration of humidity-dependent thermal and mechanical inputs. The authors concluded that the remarkable ability of *C. elegans* to sense humidity could rely on the central integration of sensory cues generated by changes in the mechanical (i.e., skin hydration) and thermal properties (i.e., skin temperature) of the worms’ skin when this is exposed to different humidity levels. These mechanical and thermal sensory cues could be related to humidity-dependent changes in skin hydration (which in turn could activate mechanosensitive neurons via a stretch-induced mechanism) and skin temperature (which in turn could activate thermosensitive neurons due to the evaporative cooling resulting from moving along different humidity gradients) (Fig. 1C).

In clarifying the molecular bases for the hygrosensation of *C. elegans*, Russell et al. (2014) have provided the first neuromolecular and behavioral evidence for a hygrosensation strategy in an animal lacking branched organs for humidity detection. In this respect, the authors proposed the intriguing possibility that the *C. elegans* mechano- and temperature-dependent hygrosensitivity represents an adaptive hygrosensation strategy that could be shared by other hygroreceptor-lacking animals provided with orthologous mechano- and temperature-sensitive proteins in their somatosensory organs. Among these animals, humans could be a notable example (Russell et al. 2014).

Remarkably, the comparative hypothesis proposed by Russell et al. (2014) seems to have found preliminary support in the recent work performed by our group (see Filingeri et al. 2014a). In this recent work, the sensory pathways for human cutaneous wetness perception were identified, and the first neuropsychological model that explains how humans sense humidity and skin wetness was developed (Filingeri et al. 2014a).

In line with what was observed in *C. elegans*, the hygrosensation strategy that we have identified in humans is based on the sensory integration of mechanical and thermal inputs occurring at the skin’s surface when wet (Filingeri et al. 2014a). Not having been provided with specific skin hygroreceptors, humans have been proposed to “learn” to perceive skin wetness through a complex multisensory integration of thermal (i.e., heat transfer) and tactile (i.e., mechanical pressure and friction) inputs generated by the interaction between skin and moisture (Fig. 1D). Starting from this assumption, our group has for the first time demonstrated that humans rely on cutaneous thermal and mechanical sensory inputs (as primarily subserved by peripheral A-nerve fibers) in their ability to sense skin wetness. Indeed, when cutaneous cold and tactile sensitivity were diminished by a reduction in the activity of A-nerve afferents (performed through a modified local compression ischemia protocol), our participants showed a significantly reduced ability to perceive skin wetness (Filingeri et al. 2014a).

Taken together, the findings of Russell et al. (2014) are therefore of particular significance for three main reasons. First, these findings provide the first neuromolecular evidence for the mechanisms underpinning the hygrosensation strategy of a living organism lacking specific hygroreceptive organs (see Fig. 1C). Second, this newly discovered hygrosensation strategy seems to be shared by another notable hygroreceptor-lacking species, i.e., humans (compare Fig. 1, C and D). Third, the thermo- and mechanosensory pathways underpinning humidity sensation in species lacking hygroreceptors (e.g., *C. elegans* and humans; Fig. 1, C and D) appear to be similar to the transduction mechanisms for hygrosensitivity observed in those species provided with specific hygroreceptors (e.g., cockroach and fruit fly; Fig. 1, A and B). In light of the above, it could therefore be suggested that, whether underpinned by the presence of a branched sensory receptor (i.e., hygroreceptor) or by the central integration of sensory inputs coded by different receptors (i.e., thermal and tactile), animal hygrosensation seems to rely on potentially universal mechanisms of mechanical and temperature-related sensory transduction, which could be shared across a wide range of species, including humans.

The identification of molecular candidates for nonspecific hygrosensation represents an important advancement in our understanding of mammalian and nonmammalian hygrosensation. However, numerous questions still remain unanswered, particularly with regard to human hygrosensation. Although the work of Russell et al. (2014) has identified molecular mechanisms for nonspecific hygrosensation in an animal model, the same mechanisms remain entirely unexplored in humans. Indeed, our understanding of the molecular bases of peripheral temperature-dependent and mechanotransduction in humans has only recently started to be uncovered (for an extensive review, see Vriens et al. 2014), and whether both temperature-gated TRP channels and mechanically activated DEG/ENaC/ASIC channels could be functionally essential for human hygrosensation remains a matter of speculation. Future investigations should therefore deal with the question of whether pharmacological manipulation of these temperature- and mechanically activated channels could disrupt/rescue human ability to sense humidity and wetness.

Increasing the knowledge on the molecular bases of human hygrosensation is relevant for its clinical significance. For instance, undesired symptoms such as spontaneous sensations of cold wetness are often experienced across the body by individuals suffering from multiple sclerosis or polynuropathies. Hence, understanding the molecular mechanisms of human hygrosensation and wetness perception could provide insights into the pathological mechanisms involved in the altered somatosensory function observed in these patients. This knowledge could then be used to develop specific treatment strategies targeting rescue and/or amelioration of sensory function in these pathological conditions. The fact that such an approach has already been used in other research areas (e.g., investigation of the role of temperature-sensitive TRP channels in the development of acute and chronic pain and development of specific analgesic drugs targeting these channels) (Vriens et al. 2014) represents a promising avenue for future research aiming to elucidate the molecular mechanisms of human hygrosensation.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author.
AUTHOR CONTRIBUTIONS
D.F. conception and design of research; D.F. analyzed data; D.F. interpreted results of experiments; D.F. prepared figures; D.F. drafted manuscript; D.F. edited and revised manuscript; D.F. approved final version of manuscript.

REFERENCES