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Epidermal Keratinocyte Sensing and Processing of Environmental Information Together with the Brain's Simulation and Prediction Abilities Helped to Enable *Homo sapiens*' Evolutionary Success

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Abstract

Among terrestrial mammals, *Homo sapiens* has evolved a very specific anatomical feature—very little body hair—thus, the skin surface is exposed directly to the environment. We and others have demonstrated that skin epithelial cells, called keratinocytes, express not only functional sensory systems for a variety of environmental responses, but also a series of neurotransmitter receptors that play key roles in information processing in the brain. Furthermore, the brain cortex is particularly large in *Homo sapiens*, which has a higher ratio of brain to whole-body weight than any other mammalian species. Here we propose that the evolutionary success and global spread of *Homo sapiens* are due at least in part to the existence and interaction of these two systems; i.e. the epidermis and brain cortex. First, we discuss the role of the epidermis as a sophisticated organ with multiple sensory inputs and information-processing capabilities, and then we consider the putative requirement for a large brain to carry out simulations and predictions based on input from multiple epidermal systems. We also present some other examples where a functionally sophisticated epidermis is associated with a large brain size. Finally, we discuss possible reasons why *Homo sapiens* has emerged as the sole surviving human subspecies.

Keywords

Skin, Brain Cortex, Body Hair, Neurotransmitter

1. Introduction

Surface coverings of living things have generally evolved to offer a survival advantage in their natural environment; for example, reptiles have protective scales, birds have feathers that are used to control flight, and terrestrial mammals have insulating body hair. But among terrestrial mammals, *Homo sapiens* evolved certain unique anatomical features—including loss of body hair—which exposed the skin surface directly to the environment, leaving only a water-impermeable membrane, the stratum corneum, at the outermost layer of the skin, as protection. Furthermore, another unusual anatomical characteristic of *Homo sapiens* is a large brain, especially the cerebral cortex section of the brain. Indeed, the ratio of brain to whole body weight; i.e. the encephalization quotient, is higher than in any other mammalian species. Among more than 200 primate species, only *Homo sapiens* possesses this combination of exposed skin and a large brain. Several questions then logically arise. What special advantage(s) do humans derive from their hairless skin? Could the combination of hairless skin and a large brain account for the evolutionary success of *Homo sapiens*? Then, did this unique combination contribute to the successful spread of *Homo sapiens* across the globe into an enormous range of environments, from hot, ultraviolet-B-enriched deserts to arctic regions?

In this article, we propose possible answers to these questions. Specifically, we hypothesize that the coevolution of a hairless epidermis with an enlarged brain (perhaps the latter "driven" by the former) provides the basis for the unique capabilities of *Homo sapiens* to control, manipulate and theorize about the human environment. We suggest that denuded epidermis receives and processes environmental information in real time. This input initiates emergency action when required, while also being passed on to the brain, where it is utilized for simulation/prediction to guide future action, which in turn could be modified by sensory feedback. The number of keratinocytes at the human body surface is estimated to be 100 billion. Thus, it is plausible that the epidermis generates huge amounts of information about its environment.

2. Epidermal Keratinocytes as a Complex Sensory System

While it has long been recognized that nerve terminals in the dermis (that extend non-myelinated nerve fibers into the overlying epidermis) play key roles in cutaneous sensation, in the past two decades, an enormous range of sensory functions has been discovered in epidermal keratinocytes (**Table 1**).

For example, we and others have shown that keratinocytes express a series of functional thermal receptors, transient receptor potential channels (TRPs) (Inoue et al., 2002, Tsutsumi et al., 2010a; Tsutsumi et al., 2011b; Denda, 2016). TRPV1 is activated by temperature (>43˚C), capsaicin, and acidic conditions, and activation of TRPV1 induces a sensation of pain (Caterina et al., 1997). Mice with keratinocyte-specific knockout of TRPV1 do not show pain-related avoidance responses after topical applications of irritants like capsaicin (Pang et al., 2015).

Table 1. Physical and chemical factors sensed by keratinocytes.

Environmental factors	Receptors	Role in sensing	References
Visible radiation	RHO	Light and dark	Tsutsumi et al., 2009a
	OPN1LW	Red-green light	Tsutsumi et al., 2009a
	OPN1MW	Blue light	Tsutsumi et al., 2009a
Electric potential	L-type VGCC	Electric potential	Denda et al., 2006
Magnetic field	Unknown	Magnetic energy	Lisi et al., 2006
High-frequency sound	Unknown	10 - 30 kHz sound	Denda & Nakatani, 2010
Temperature	TRPV1	Temperature > 43˚C	Tsutsumi et al., 2011b
		Capsaicin, low pH < 6.6	Inoue et al., 2002
	TRPV2	Temperature > 52˚C	Tsutsumi et al., 2011b
	TRPV3	Temperature > 33˚C	Peier et al., 2002
		Thymol, eugenol	Xu et al., 2006
	TRPV4	Temperature > 34˚C	Chung et al., 2003
		Osmotic pressure	Liedtke, 2007
	TRPM8	Temperature < 22˚C	Tsutsumi et al., 2010a
		Menthol	Denda et al., 2010
	TRPA1	Temperature < 17˚C	Tsutsumi et al., 2010a
Atmospheric pressure	Unknown	Changes of pressure	Ikeyama et al., 2013
Mechanical stress	Unknown	Touch	Tsutsumi et al., 2009b
Oxygen	Unknown	Oxygen partial pressure	Boutin et al., 2008
Perfume	OR2AT4	Sandalwood	Busse et al., 2014

Mechanical stress also induces excitation of keratinocytes via elevation of intracellular calcium ion concentrations (Tsutsumi et al., 2009b). This information is transferred to the nervous system and recognized as tactile sensations (Tsutsumi et al., 2011a). Moehring et al. reported that ATP release, induced by mechanical stimulation of keratinocytes, is a critical component of baseline mammalian tactile sensation (Moehring et al., 2018). Osmotic pressure, atmospheric pressure, odorants, and changes in oxygen partial pressure also induce keratinocyte excitation (Denda & Denda, 2007; Ikeyama et al., 2007; Boutin et al., 2008).

The effects of infrared and ultraviolet light on the epidermis are well known, and we showed further that visible light influences epidermal permeability barrier homeostasis (Denda & Fuziwara, 2008). We also found that a series of photoreceptors expressed in the retina are also expressed in human epidermal keratinocytes (Tsutsumi et al., 2009a) (**Figure 1**).

We then demonstrated that both audible sounds and ultrasound influence epidermal permeability barrier homeostasis (Denda & Nakatani, 2010). Sound at 5 kHz did not influence barrier recovery, whereas 10 (audible), 20 and 30 (ultrasound) kHz sound accelerated barrier recovery. Thus, epidermal keratinocytes

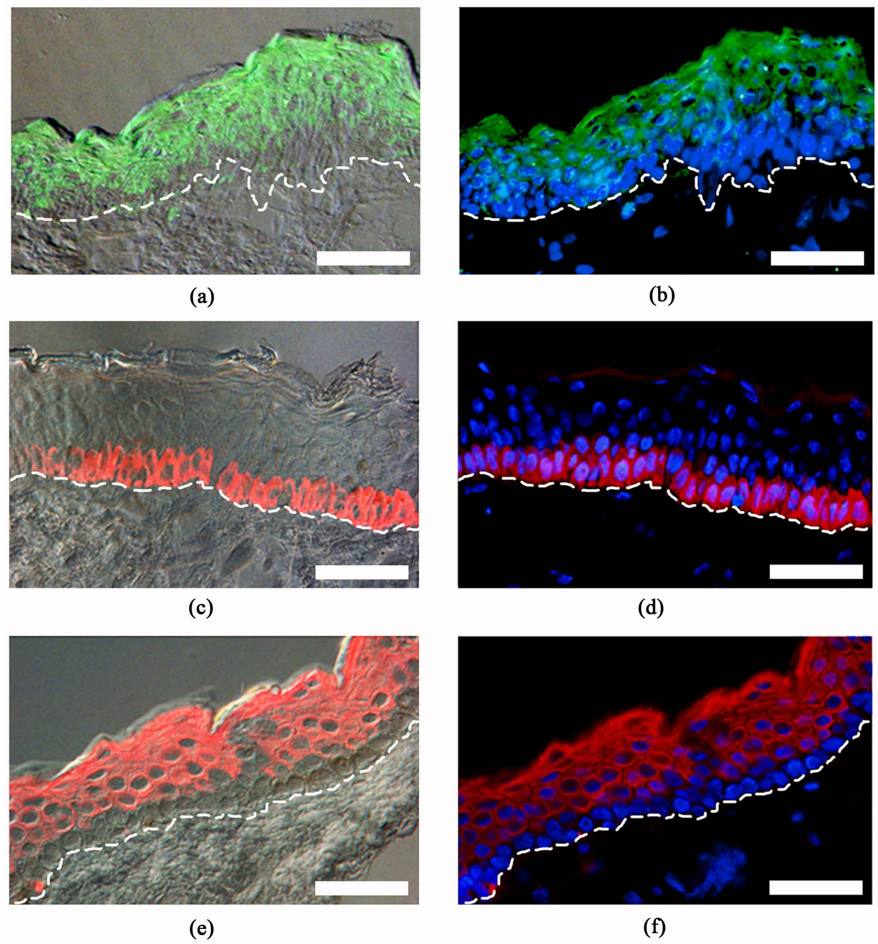

Figure 1. Photoreceptor expression in human epidermis. Human skin is studied immunohistochemically with the anti-rhodopsin (RHO) monoclonal antibody (RET-P1). Dotted lines indicate basal membrane at the epidermis/dermis. Marked immunoreactivity to RET-P1 was observed in the upper layer of the epidermis of human skin ((a) green color) Merged image with nuclear staining ((b) blue color). Immunohistochemical study of human skin with anti-Red Green-opsin (OPN1LW) ((c) red color) with nuclear staining ((d) blue color) and anti-Blue-opsin (OPN1MW) ((e) red color) with nuclear staining ((f) blue color). Marked immunoreactivity against anti-Red Green-opsin was observed at the basal layer of the epidermis of human skin, and immunoreactivity against anti-Blue-opsin was observed throughout the epidermis, except for the basal layer. It is possible a photoreceptor activated by longer-wavelength radiation (Red Green) would be localized in a deeper layer than receptors activated by shorter-wavelength radiation (Blue), because longer-wavelength radiation can penetrate deeper into the skin than shorter-wavelength radiation. Bar: 50 μm (Modified from Tsutsumi et al., 2009a).

appear to sense a wider range of light and sound than either the eyes or ears, albeit with lower definition. Keratinocytes also express olfactory receptors (Busse et al., 2014), and a wide variety of chemicals can alter these receptors' electrochemical properties (Inoue at al., 2005, 2015). Furthermore, a variety of moleculesoriginally recognized as olfactory or gustatory molecules can improve skin pathology. For example, activation of olfactory receptor OR2AT4 accelerated wound healing (Busse et al., 2014), and topical application of fructose or mannose accelerated the recovery of epidermal permeability barrier function after injury (Denda, 2011).

Other studies indicate that keratinocytes can sense magnetic fields (Lisi et al., 2006) and that epidermal homeostasis is influenced by the distribution of electrical potential (Denda & Kumazawa, 2010; Denda et al., 2006). It is conceivable that keratinocytes might even sense cosmic radiation, because these particles can induce electromagnetic phenomena. It has also been suggested that quantum-mechanical phenomena, such as tunneling, might influence biochemical reactions (Cha et al., 1989). Thus, keratinocytes appear torespond to an enormous range of environmental phenomena.

3. Epidermis as an Information-Processing System

We have shown that a series of neurotransmitter receptors, which play key roles in information processing in the brain, are also expressed in keratinocytes (Denda et al., 2002a, 2002b, 2003a, 2003b, 2004; Fuziwara et al., 2003, 2005; Deing et al., 2013; Stojadinovic et al., 2013; Slominski et al., 2001; Wakamatsu et al., 1997). In addition, keratinocytes express a variety of neurohormones and receptors that are produced in the brain or induced by messages from the brain (Denda et al., 2012; Takei et al., 2013; Slominski et al., 2000). Hence, we speculate that the epidermis might possess information/emotion-processing capability, independent of the brain (**Table 2**).

For example, when different-shaped molds were pressed on the fingertip, different electrophysiological patterns were observed in peripheral nerves of the forearm, suggesting that geometrical information may be recognized by the skin (Pruszynski & Johansson, 2014). Also, we have observed distinct spatiotemporal patterns of calcium concentration in monolayer-cultured human keratinocytes after physical or chemical stimulation (Tsutsumi et al., 2010b, 2013; Denda & Tsutsumi, 2014). The

Table 2. Neurotransmitters, neuropeptides, and hormones generated by keratinocytes, and receptors functionally expressed in keratinocytes.

Molecule	Receptor	References
ATP	P2X, Y receptors	Inoue et al., 2005; Denda et al., 2002a
Glycine	Glycine receptor	Inoue et al., 2015
GABA	GABA (A) receptor	Denda et al., 2002b
Adrenaline	Adrenergic β2 receptor	Denda et al., 2003a
Acetylcholine	Cholinergic receptors	Denda et al., 2003b
Dopamine	Dopamine 2-like receptor	Fuziwara et al., 2005
Glutamate	NMDA receptor	Fuziwara et al., 2003
Oxytocin	Oxytocin receptor (OXTR)	Denda et al., 2012; Deing et al., 2013
Cortisol	Glucocorticoid receptor (GR)	Stojadinovic et al., 2013
CRF, ACTH	CRH receptors	Slominski et al., 2000, 2001
	Melanocortin-1 receptor	Wakamatsu et al., 1997
Nitric Oxide		Ikeyama et al., 2007

fingertip can recognize micron-scale patterns (Nakatani et al., 2011), but the density of peripheral nerve fibers in healthy skin is quite low (Tsutsumi et al., 2016) and may be inadequate to provide such fine discrimination. Therefore, it seems likely that epidermal keratinocytes are involved in information processing related to tactile sensation in the skin.

Individual neurons in the brain and keratinocytes show considerable similarities, in that they express comparable receptors and endocrinological systems, as described above, though their cell-cell communication systems are quite different. Neurons are connected via large numbers of synapses, forming a very complex network. On the other hand, cell-to-cell communication in the epidermis is less extensive (Tsutsumi et al., 2009b). A possible evolutionary explanation for this tiered system is to enable a very rapid response to environmental danger signals. Thus, when we encounter high temperatures or harmful chemicals, we move away from them quickly via spinal reflex (Giszter et al., 1989). On the other hand, some environmental signals might be sent to the brain as experiences that would be helpful to avoid future potential danger.

4. The Brain as a System of Simulation and Prediction

It has been shown that episodic memories are stored within the hippocampal-entorhinal cortex, while long-lasting memories are stored in the cerebral cortex (Kitamura et al., 2017). Thus, it seems feasible that the cerebral cortex might serve as a kind of virtual space in which stimuli from the external environment are processed and integrated based on information received from the sensory system, including the epidermis, and then used to formulate long-term strategies for coping with the world. This epidermal sensory group should be considered distinct from emergency response systems that interpret danger and would be consistent with the human capability for scientific theory-building. For example, though Yukawa predicted the existence of the meson as an elemental particle in 1935 (Yukawa, 1935), it was not detected until 1947 (Lattes et al., 1947). Similarly, Einstein predicted the effect of gravity on light in 1911 (Einstein, 1911), but the effect was only confirmed by astronomical observation by Eddington during an eclipse in 1919 (Eddington, 2011). How did Yukawa and Einstein predict such completely new phenomena? Wolfgang Pauli described the recognition of order in nature as follows: "The process of understanding, that is, in the conscious realization of new knowledge, seems thus to be based on a correspondence, a 'matching' of inner images pre-existent in the human psyche with external objects and their behavior" (Pauli, 2012). While this mechanism remains an open question from a current biological standpoint, simulation in the brain could be a mechanism to predict the existence of unknown phenomena outside of our bodily systems.

5. Predictability of Biological Phenomena

There is evidence that biological phenomena are susceptible to simulation and prediction. For example, we recently showed that computer simulation based on a mathematical model of epidermal homeostasis (an "in silico" epidermis) could be used to guide the development of a functionally capable epidermal equivalent system with a highly competent permeability barrier (Denda et al., 2014; Kobayashi et al., 2014, 2016; Kumamoto et al., 2018). Specifically, the simulations predicted that when the basal layer of the epidermal model felt undulations, the epidermis would become thicker and the stratum corneum would become flatter (Kobayashi & Nagayama, 2016), and these predictions were verified *in vitro* (Kumamoto et al., 2018). Thus, it seems reasonable that our far more complex brain could utilize its enormous information input from the epidermis to predict the existence of such things as new elementary particles or quantum-mechanical effects. In other words, the information gathered by the epidermis might be used not only for responding rapidly to emergencies, but also for running long-term simulations in the "virtual space" of the cerebral cortex. Furthermore, this ability might have dramatically increased after humans invented writing for information storage and might still be increasing with the help of artificial intelligence (AI).

6. Discussion

6.1. Speculation from the Standpoint of Comparative Anatomy

We recently hypothesized a relationship between the shedding of hair from the skin of *H. erectus* and the evolution of larger brain size (Denda et al., 2018). We suggested that hairless skin offered an evolutionary advantage, because it was more efficient at sensing danger signals from the environment, because its sensory systems are more accessible. Then, because of the dramatically increased amount of environmental information generated from hairless skin, the brain size of hominins needed to expand in order to process all this sensory input efficiently. This hypothesis is supported by the finding that the plethora of peripheral sensations in the octopusis associated with a larger and more sentient brain. The octopus must integrate sensory inputs not only from its eight tentacles and its separate peripheral "brains", but also from its highly "sentient" skin. As a result, the octopus has a brain with 6-fold more neurons as compared to rodents (Hochner, 2012, 2013). Some species of squid have an even bigger brain; i.e. a higher ratio of brain/whole-body weight than the octopus (Packard, 1972). They also have the ability to change their body color pattern quickly for crypsis or communication (Hanlon et al., 1999). Furthermore, electric fish of the genus *Gnathonemus* possess a huge number of epidermal electroreceptors covering its whole body that allow these organisms to accurately assess the distance, size and shape of surrounding objects by transmitting an "electric image" to the brain (von der Emde et al., 1998). Indeed, the brain: body mass ratio of these fish is higher than that of any other vertebrate, including humans, and the brain accounts for 60% of bodily oxygen (O_2) consumption, compared to the 2% - 8% in resting humans (Nilsson, 1996). These three examples suggest that the combination of an exposed, environmentally sensitive skin and a large brain might have played a key role during animal evolution.

Several terrestrial mammals are largely hairless, including the hippopotamus, elephant, rhinoceros and naked mole rat, and the hippopotamus and rhinoceros do not have large brains (Lyras, 2018; Bhagwandin et al., 2017). We propose that because these two animals have thick skin, it might have been difficult to construct tightly-organized, arborizing peripheral nerve networks in their skin. Elephants have relatively large brains (Lyras, 2018), but their skin could also be too thick to construct peripheral nerve networks. We speculate instead that the elephant has a flexible arm, its long nose. To control this "arm", an elephant might need a bigger brain in comparison to a hippopotamus or rhinoceros. Consider the octopus which has eight flexible arms and substantial cognitive ability. Likewise, humans have two arms, each of which has ten flexible fingers. Flexible arms and fingers might require a larger brain. While naked mole rats admittedly do not have large brains (Kverková et al., 2018), they live at high population densities, making a complex sensory system unnecessary for their survival.

We can also look at this question in yet another way. A large group of arthropods—insects—have their entire bodies covered with a chitinous shell, with their tactile senses limited to their antennae. That is, they do not have skin sensations. Notably, their brain size is small, and the number of neurons in their brain is only around a million. Nevertheless, some of them, such as ants or bees, have complex social structures. Leaf-cutter ants carry out a kind of agriculture (Blanton & Ewel, 1985) and honeybees can pass on very complex information (Menzel, 2012). Dragonflies can construct spatial and temporal images in their nervous systems to help catch their prey (Mischiati et al., 2015). Thus, even with a small brain, quite sophisticated actions are possible by discarding skin sensation, these insects can survive in a variety of environments without the high energy cost of a larger brain. The number of insect species is thought to be around one million, and they have persisted for over 400 million years, so this "protective shell—small brain—low energy" tactic has been successful and represents a valid alternative to the "exposed skin—big brain—high energy" strategy.

6.2. Why Has *Homo sapiens* Outlasted Other Human Subspecies?

Traces of early hominin subspecies, including *Homo neanderthalensis* and *Denisova hominin*, have been found only in limited areas of Eurasia. On the other hand, *Homo sapiens* reached Australia around 65,000 years ago and South America about 13,000 years ago at the latest. It has been suggested that because *Homo sapiens* have both "generalist" and "specialist" abilities (Roberts & Stewart, 2018), they could successfully enter new ecological niches, and adapt to a variety of environments, allowing them to eventually colonize the entire world. Pertinently, the trait of autism (without intellectual impairment) is known to be associated with valuable technical and social skills (Spikins et al., 2016). Hence, autism might not be due to a lack of sociability, but rather to a lack of a rules-based theory of mind, and thus autism might be favorable for innovation and communication within certain cultural groups. Indeed, some genes implicated in autism are found in modern humans, but not in *Homo neanderthalensis*. Thus, autism might be required for an ability to be both a "generalist" and "specialist". Furthermore, because autism may render people less willing to be followers, Spikins et al. (2016) points out that people with autism often attain notable positions in society, particularly in the fields of medicine, engineering, mathematics, physics and information technology. Thus, a key point in human intellectual evolution might be tolerance of a variety of individual characteristics, including autism.

Green et al. (2010) sequenced the *Homo neanderthalensis* genome and identified ancestral genes that are "fixed" in present-day humans, together with others that changed over time in *Homo sapiens*, presumably due to positive selection (Green et al., 2010). Among the list of un-fixed genes of *Homo neanderthalensis*, several are related to epidermal keratinocytes. These include: 1) the RPTN gene encoding repetin, an epidermal structural protein and cornified cell envelope precursor that plays a crucial role in constructing the stratum corneum barrier (Huber et al., 2005); 2) the K1C16 gene encoding a keratin; 3) type I cytoskeletal keratin 16, which plays an important role in wound healing (Paladini et al., 1996); as well as 4) the OR2AT4 gene encoding olfactory receptor, family 2, subfamily AT, member 4, which accelerates wound healing (Busse et al., 2014). These results suggest that the epidermis and keratinocytes of *Homo sapiens* might be better protected from environmental insults than *Homo neanderthalensis*, and this capacity in turn may indicate their important role in a species' survival.

7. Conclusion

Homo sapiens is mostly unique among mammals in having a hairless epidermis, expressing a wide range of molecules that function in sensory and information-processing systems, as well as possessing the largest brain in terms of the ratio of brain to whole-body weight. Here, we present the hypothesis that the evolutionary success of *Homo sapiens* is at least in part due to the existence and cooperative action of these two systems. We suggest that keratinocytes that comprise the hairless epidermis are equipped with multiple sensory and information-processing systems that detect environmental information, both for immediate response to environmental danger signals, and for passage onward to the brain, where this information can be used for simulation and prediction to guide future actions, which in turn can be modified by further sensory feedback (**Figure 2**).

The "protective shell—small brain—low energy" strategy is robust, because huge numbers of species that employ it, such as insects, have survived over the past half billion years. On the other hand, among terrestrial mammals, only *Homo sapiens* has survived by employing the "exposed skin—big brain—high energy" strategy, while all other human subspecies have disappeared within the

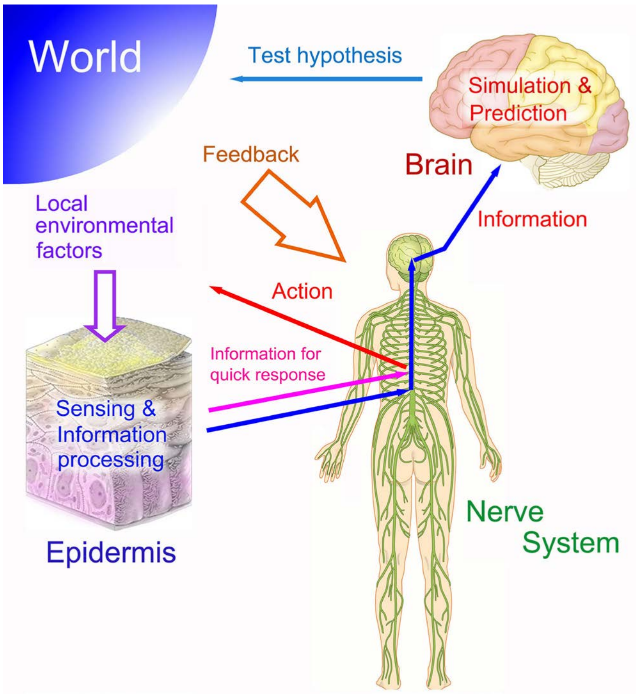

Figure 2. Schematic illustration of the putative roles of epidermal keratinocytes and brain. Epidermal keratinocytes sense a variety of environmental factors and stimuli. This information is processed in the epidermis and passed via the nervous system to the whole body and brain. In the brain, this information is used for simulations and predictions to guide future actions, which in turn may be modified by further sensory feedback.

past 30,000 years. These considerations suggest that the anatomical structure of *Homo sapiens* is very specific and potentially fragile in the face of mutations and evolutionary pressures.

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Conflicts of Interest

None declared.

Author's Contributions

MD wrote initial draft and provided initial concept. SN provided critical information about molecular biology aspects.

Data Accessibility Statement

Note: if data, scripts, or other arte facts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

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