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REVIEW ARTICLE

Epidermis as the "Third Brain"?

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ABSTRACT

The role of the brain includes reception, processing, and transmission of environmental information from sensory organs to the systems of the whole body. Interestingly, the digestive organs have an independent nervous system, which has been called the "second brain". We propose that the epidermis, which forms the interface between the body and the environment, could be considered a "third brain", as it contains multiple environmental sensors and a sensory information-processing system, and it generates a variety of hormones and neurotransmitters with the potential to influence whole-body states and emotions. Specifically, epidermal keratinocytes contain sensors of mechanical stress, temperature and chemical stimuli. Furthermore, we have shown that a series of neurotransmitter receptors, which play key roles in the central nervous system and brain, are functionally expressed in keratinocytes. Cultured human keratinocytes can generate structures similar to those seen in the brain. Moreover, all the components of the hypothalamo–pituitary–adrenal (HPA) axis appear to be present in epidermal keratinocytes. Overall, these results are consistent with the hypothesis that the epidermis plays a significant role in adapting whole-body physiology, and also emotional response, to changing environments.

Introduction

The brain serves as a receptor of environmental information from multiple sensory organs, and its massively interconnected neuronal network processes this information and transmits it to the systems of the whole body by secreting hormones and other messenger molecules to maintain homeostasis or generate appropriate responses. However, the digestive organs have an independent nervous system, which has been called the "second brain".[1] Here, I propose that the epidermis, which forms the interface between the body and the environment, can be considered a "third brain". The basis for this idea is that epidermal keratinocytes express a variety of functional environmental sensors of temperature, mechanical stress, and chemical stimuli,[2] as well as a series of neurotransmitters and their receptors that are known to play crucial roles in the brain.[3] They can also secrete a range of hormones and neurotransmitters that influence whole-body state and emotions.[4] Furthermore, cultured human keratinocytes can generate spatio-temporal electrochemical patterns similar to those seen in the brain. All the components of the hypothalamo–pituitary–adrenal (HPA) axis appear to be present in epidermal keratinocytes.[5] Taking these results collectively, it is clear that the epidermis has many of the functional activities of the brain, in addition to sensory systems for multiple physical and chemical environmental factors. Here, I explore the hypothesis that the epidermis can be considered a "third brain", by briefly reviewing the functions of epidermal keratinocytes and comparing them with those of the brain.

Sensory systems and signaling pathways of epidermal keratinocytes

In the last decade, members of the transient receptor potential (TRP) family of receptors, which are activated at defined temperatures, have been cloned. These polymodal receptors were discovered mainly in the nervous system, where many of them act as sensors of temperature or other physical and chemical factors.[6] Some of these TRP receptors are also expressed in epidermal keratinocytes (Table 1).[7]

TRPV1 in epidermal keratinocytes is activated by temperature (>43°C), protons (pH < 6.6) and capsaicin.[8,9] TRPV3 in epidermal keratinocytes is activated by oregano, thyme, and clove-derived flavor components, such as carvacrol, eugenol, and thymol.[10]

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Table 1 Thermo-sensitive TRPs expressed in keratinocytes.

Temperature	Agonists	Other factors
TRPV1 >43°C	Capsaicin and protons	
TRPV2 >52°C		
TRPV3 ~30°C	Camphor, 2-aminoethoxydiphenyl borate	
TRPV4 ~30°C	4α-Phorbol 12,13-didecanone	Osmotic pressure
TRPM8 <22°C	Menthol	
TRPA1 <17°C	Allyl isothiocyanate, cinnamaldehyde	Mechanical stimuli?

Note. From "Roles of transient receptor potential proteins (TRPs) in epidermal keratinocytes," by M. Denda and M. Tsutsumi, 2011, *Advances in Experimental Medicine and Biology, 704*, p. 847. Reprinted with permission.
TRP = transient receptor potential family of receptors.

Interestingly, TRPV3 in epidermal keratinocytes is activated by camphor, whereas TRPV3 in sensory neurons is not.[11] Thus, TRPV3 in epidermal keratinocytes might be a sensor of these herbal extracts. TRPV4 is activated by osmotic stimuli.[12,13] We previously demonstrated that environmental humidity influences many aspects of epidermal homeostasis,[14–16] and activation of TRPV4 accelerated epidermal permeability barrier recovery after barrier disruption.[17] Thus, TRPV4 in epidermal keratinocytes might be a sensor of environmental humidity. We also recently demonstrated that mechanical stress induced elevation of intracellular calcium in cultured keratinocytes,[18] and this elevation was blocked by a nonspecific TRP antagonist, ruthenium red. Thus, TRPs in keratinocytes might also serve as components of a cutaneous sensory system for external mechanical stimuli. Furthermore, TRPM8 in epidermal keratinocytes is activated at low temperature (<22°C) and by menthol,[19,20] and similarly, TRPA1 in epidermal keratinocytes is activated at low temperature and by several chemical stimuli.[19,21] Activation of TRPM8 and TRPA1 in epidermal keratinocytes accelerated barrier recovery after disruption.

In addition, we have shown that a variety of environmental factors, including visible light, sound, and external electrical potential, influence epidermal permeability barrier homeostasis.[22–24] These results led us to hypothesize that epidermal keratinocytes might also sense these environmental factors. Indeed, we found that photoreceptor-like proteins present in the retina are also expressed in epidermal keratinocytes.[25] Voltage-gated calcium channels, which play a key role in the nervous system, are also expressed in keratinocytes.[26] These, and perhaps other unidentified proteins, might be involved in other so far undiscovered sensory systems of epidermal keratinocytes.

Thus, epidermal keratinocytes have sensory functions for a wide range of environmental factors, even though the full extent of these functions remains to be established. The next question is, are these signals from the environment passed to the nervous system? Indeed, various interactions between keratinocytes and the peripheral nervous system have been suggested. We demonstrated that excitation of keratinocytes was transferred to nerve fibers in a keratinocyte-neuron co-culture system.[27] The effect was partially blocked by application of an adenosine triphosphate (ATP)-degrading enzyme, suggesting that ATP plays an important role in signal transmission from keratinocytes to the nervous system. Another study indicated that prostaglandin E(2) may also act as a messenger from keratinocytes to the nervous system.[28]

Information processing

Information derived from the environment is transferred by afferent nerve fibers to the central nervous system, and processed in the brain, with the aid of multiple neurotransmitters and specific receptors. We have shown that many of the neurotransmitter receptors originally found in the central nervous system are also expressed in epidermal keratinocytes.[3] We also showed that glutamate, dopamine, and nitric oxide are released from keratinocytes immediately after insult of the stratum corneum[29–31]; and these molecules are candidate messengers from keratinocytes to the nervous system. Interestingly, they also influence epidermal permeability barrier homeostasis. These findings are consistent with the idea that various communication modes between epidermal keratinocytes and the nervous system operate in the epidermis as a part of the cutaneous sensation system. Epidermal keratinocytes also generate many other messenger molecules, including neurotransmitters, neuropeptides, and hormones, which would be required for processing sensory information, and transmitting messages to the central nervous system.

Even in monolayer-cultured human keratinocytes and rat skin organ culture, distinct spatio-temporal patterns were observed after physical or chemical stimulation.[32–35] The brain shows similar spatio-temporal dynamics after stimulation, and this phenomenon is strongly associated with information processing.[36] It was recently suggested that information processing in response to mechanical stimuli might be carried out in the skin.[37] Although the role of the electrochemical patterns observed in keratinocytes has not yet been clarified, it is plausible that they are associated with information processing in the skin.

Signaling from keratinocytes to modulate whole body physiology and emotion

Immediately after barrier disruption, epidermal keratinocytes generate multiple cytokines, including interleukin-1 alpha and beta (IL-1α,β), IL-6, tumor necrosis factor alpha (TNFα), and interferon gamma (INFγ).[38] For example, skin surface dryness induces IL-1α generation.[39] UV-B-exposed keratinocytes secrete ATP, which induces IL-6 release.[40] Thus, barrier abnormality or insult and UV-B irradiation may lead to release of multiple cytokines from epidermal keratinocytes. This is significant, because elevated serum cytokine levels are associated with impaired mental state, such as depression, in cancer patients[41,42] Also, in patients with severe dermatitis, a large area of skin may be involved, and secretion of cytokines might be sufficient to influence mental state. This idea is consistent with a report that application of etanercept, a TNFα inhibitor, improved symptoms of depression and fatigue in psoriasis patients.[43]

Epidermal keratinocytes produce not only cytokines, but also neurotransmitters and neuropeptides[3] that could influence the peripheral nervous system or circulatory system. Moreover, all the components of the HPA axis appear to be present in epidermal keratinocytes.[5] We previously demonstrated that keratinocytes generate and secrete oxytocin in response to stimulation with a stable ATP analog.[44] Oxytocin is involved in behavior, memory and social bonding.[45] Systemic oxytocin infusion reduced repetitive behavior in patients with autism and Asperger's syndrome.[46] Therefore, oxytocin produced in epidermal keratinocytes could potentially influence mental state. Keratinocytes also generated neurotrophins like those originally found in the central nervous system.[47]

Glucocorticoid also plays an important role in depression and post-traumatic stress disorder (PTSD),[48,49] and might directly affect the hippocampus. We recently demonstrated that low environmental humidity induced generation and release of cortisol from epidermal keratinocytes of a skin equivalent model.[50] We incubated the skin equivalent model under dry (relative humidity: <10%) and humid (relative humidity: approximately 100%) conditions for 48 hours and evaluated cortisol secretion and mRNA levels

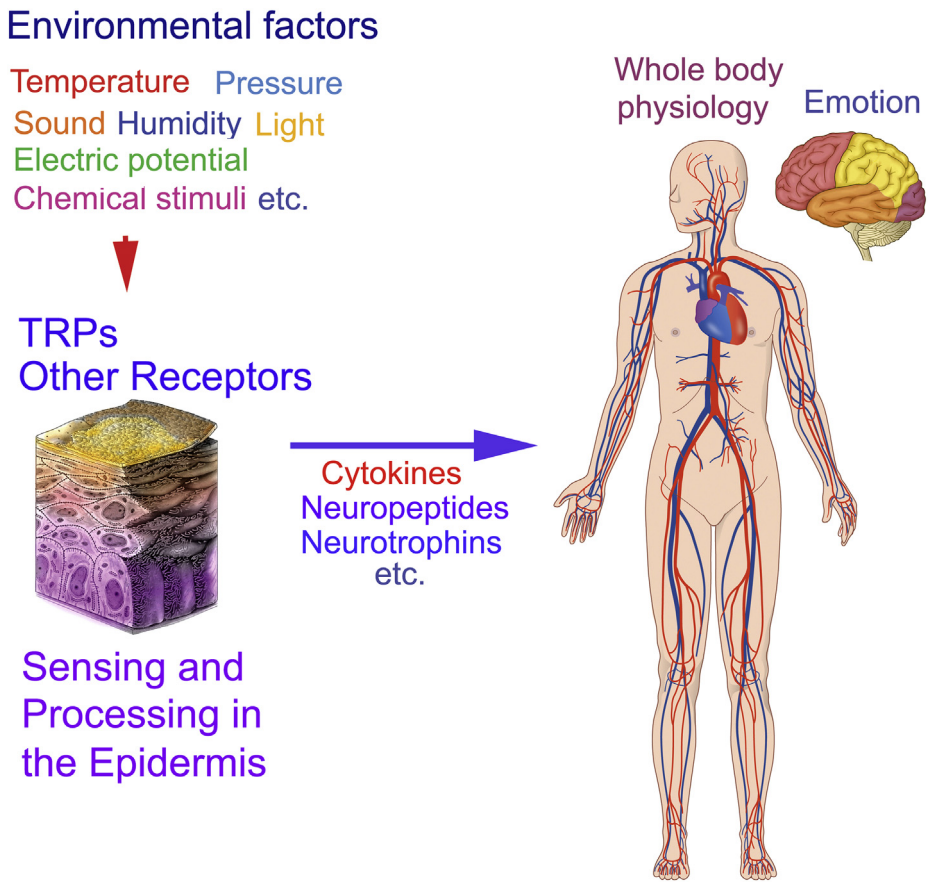

Figure 1 Schematic illustration of the putative roles of epidermal keratinocytes. Epidermal keratinocytes can sense a variety of environmental factors and stimuli. This information could be processed in the epidermis and passed via the nervous system to the whole body and brain. TRP = transient receptor potential family of receptors.

of cortisol-synthesizing enzyme (steroid 11β-hydroxylase; CYP11B1) and IL-1β. Cortisol secretion increased three-fold, and CYP11B1 and IL-1β mRNAs increased 38-fold and six-fold, respectively, in the dry condition versus the humid condition. Occlusion with a water-impermeable plastic membrane partially blocked the increases of cortisol secretion and CYP11B1 and IL-1β mRNA expression in the dry condition. Thus, environmental dryness might induce increased cortisol secretion in epidermis of diseased skin characterized by epidermal barrier dysfunction, potentially influencing mental state and systemic physiology.

Consequence of the hypothesis and discussion

There is extensive evidence that multiple sensory systems are functionally expressed in epidermal keratinocytes, together with a range of neurotransmitters and their receptors. Epidermal keratinocytes also secrete multiple bioactive molecules with the potential to influence whole-body physiology and emotional state. Thus, the epidermis appears to have the functional systems required for reception of environmental information from sensory organs, processing of that information, and transmission of it to the systems of the whole body. In other words, the epidermis, like the brain, has the capability to act as an interface between the body and the environment (Figure 1). Although much further research is needed to validate the idea that the epidermis serves as a "third brain", this concept is an exciting one, opening up new vistas for the treatment of skin diseases and for our understanding of whole-body homeostasis.

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