Mitochondrial dysfunction as a common precursor of ageing in sensory receptors

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Abstract

The sensory system is a complex evolutionary and neurologically significant system, needed to maintain an environment suitable to survive most optimally. During the process of ageing, many mammalian species suffer from deteriorating senses, decreasing the quality of life and increasing the potential of obtaining harmful damage. The sensory system is divided in four primary receptor classes, which in this review have been widely explored to obtain and present the known age-related effects, deficiencies and health innovations. The reviewed literature suggests a widespread correlation between mitochondrial dysfunction and old age among the four primary classes of sensory system receptor cells, which may suggest health organizations to develop successful membrane potential-targeted innovations in the future, thereby improving the senses and thereby quality of life of elderly.

Introduction

To optimally be aware of environmental surroundings, many species have developed sensory mechanisms that are key to protect themselves from predatory hazards. All of these systems are responsible for processing the sensory information received, they are transducers from the physical world via sensory receptors and neurons that combine in the brain to ultimately perceive the information. With this information, organisms can correctly assess their environment and act upon it whenever necessary.

The ecological and evolutionary importance of the sensory system is significant. It is needed to maintain a suitable environment internally as well as externally, think about maintaining a feasible temperature, but primarily to locate and respond to potential threats and rewards (Grendon et al., 2015). The systems, divided into the auditory, olfactory, visual, gustatory, tactile/somatosensory and balance system, all feed towards the ultimate goal to transmit information to prevent being attacked and thus obtain harmful injury, find the best food and resources to thrive and secure yourself the best possible mate for offspring benefits and thereafter inform other members of the pertinent species of the same danger or food resources. Moreover, the systems can even be used with respect to the annual cycle, further improving chances of survival (Grendon et al., 2015).

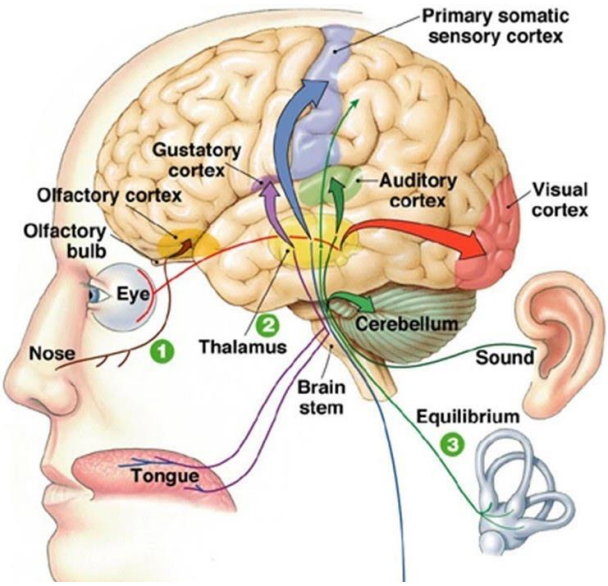

Figure 1: Sensory systems, Anatomical terminology

All the priorly mentioned sensory systems ultimately make use of four different classes of receptors. Each of these sensory system receptors (chemo-, photo-, mechano- and thermoreceptors) respond to

different stimuli, which is also commonly called the receptive field of a system (eg. light for the rods and cones on the retina). All receptors receive distinct physical stimuli, differentiated by intensity, type, location and duration, thereafter transforming the signal into an electrical impulse towards the brain where it is assessed (Marzvanyan and Alhawaj, 2020).

Chemoreceptors serve to detect a change in the normal environment they are located in, transducing a chemical substance into an action potential or other biological responses. In the gustatory system, the taste receptors located primarily in the oral cavity release certain neurotransmitters (primarily but not limited to 5HT) that activate a nerve fiber in the facial nerve, the glossopharyngeal nerve and the vagus nerve to the brain in response to chemical stimuli coming from ingested foods and nutrients (Pathway Medicine, 2021).

The extraordinarily sensitive photoreceptors are found solely in the retina of mammals. These cells are capable of visual perception by absorbing single photons and changing the membrane potential of the cell, thereby sending a signal in the form of an action potential to the brain. Photoreceptors can be divided up into three different cell types, namely the rod and cone, important for the visual system's sight and color capacity, and retinal ganglion cells that are photosensitive, important for the circadian rhythm and the pupillary reflex (Encyclopedia Britannica, 2010).

The sensory receptor class mechanoreceptor responds to mechanical stimuli classified as pressure or stretch. In the mammalian skin, four types of receptors responding to physical pressure can be recognized, that altogether are classified under the combined name of cutaneous receptors. These receptors respectfully are the Pacinian corpuscles that can recognize rapid vibrations (up to 300 Hz), the highly adaptive Meissner's corpuscles that respond to light touch (50 Hz vibrations), the Ruffini corpuscles that lay deeper in the skin and thus detect deep tension and the Merkel nerve endings, that are responsible for detecting sustained pressure. On top of that, receptors for cilia and other hair movements can also be found (eg. in the auditory system). The receptive fields vary greatly per receptor (Johansson and Flanagan, 2009; Iggo and Andres, 1982).

Finally, there are thermoreceptors, that are a free non-specialized part of nearly all sensory neurons that records direct change in temperature in the intracellular spaces. The system can be divided into two parts, namely unmyelinated C-fibers that are responsible for sensing increasing heat and the A-Delta fibers, that are responsible for sensing decreasing temperatures. These fibers are primarily located along the cardiovascular system and the peripheral nervous system's pathways (Zhang, 2015).

Ageing is a progressive degenerative process of biological and physiological functions important for survival, prevalent in nearly all existing organisms. These processes take place on a cellular level, in an organ or the whole organism, including the sensory systems. In most mammals, the term ageing embodies the accumulation of damaging molecular and cellular change, leading to a gradual decline of physical and mental capacity, for example the loss of reaction time or weakening of the immune system, a growing risk of diseases, and ultimately death (Developmental Biology, 6th edition). Humans are continuously trying to improve the quality of life, thereby increasing the total lifespan gradually. The lengthening of the human lifespan has revealed a lot of previously undetected age related problems, as well in the sensory receptors that keeps us functioning optimally, and in response we have sought to find solutions to these problems.

This review article serves to sum up and enlighten the current progress on understanding ageing in the four primary sensory receptor classes in specific, and expose interesting gaps and correlations that may open up a path to further research. I will review the start of the art of the receptors in four clear subtopics, one for each receptor class, and subsequently clear out any unclarities. In a final subtopic, I

will list possible implications for future studies. Lastly, interesting findings and/or abnormalities will be discussed in a conclusion and discussion.

Photoreceptors

Ageing photoreceptors

The ageing of the delicate photoreceptors found exclusively in the eye is a process which is best explained if differentiated between the various types. Whereas there's little knowledge on the ageing of the photosensitive retinal ganglion cells, there is on the rods and cones. Rod and cone photoreceptors have a high metabolic demand and thus are quite susceptible to age and pathology (Hoh Kam et al., 2019).

Rods

In both man and rodent, the scotopic sensitivity decreases over time. This phenomenon can be contributed to the fact that 30% of the rod photoreceptors gradually disappears over the course of a lifetime (age 34-90 years in man, age 6 months-2 years in rodents), primarily in the (peri)macular region (Cunea and Jeffery, 2007). The macula is a region in the center of the retina that processes clear and sharp eyesight for the central vision. In the macular rod photoreceptors, during the ageing process, mitochondria start showing abnormalities due to accumulation of mutations, primarily in the mtDNA4977 gene (Barron et al., 2001). This progressively leads to the decline of the mitochondrial membrane potential, which reduces the production of ATP and elevates pro-inflammatory reactive oxygen species, eventually leading to cell death (Barron et al., 2001). When this happens, vision declines making reading, focusing and (facial) recognition difficult. The presence of these effects are classified as several macular conditions, such as Age Related Maculopathy (ARM), affecting the whole retina and leading to loss of peripheral vision and then blindness eventually, and Age Related Macular Degeneration (AMD), primarily affecting your center vision (Curcio, 2001).

Interestingly, other factors contributing to photoreceptor ageing are significantly different between rodent and man. In ageing rodents, there is a buildup of extracellular deposition (drusen) in which amyloid beta is present that contributes to macular photoreceptor degeneration (Hoh Kam et al., 2010). The drusen and amyloid beta accumulates at the Bruch membrane, thickening it in the process. This process destroys the architecture of the outer retina and leads to further macular degeneration, contributing to central vision loss. Additionally, amyloid beta also accumulates along the blood vessels and on top of the outer rod photoreceptor segments, which will reduce the size of the segment (Cunea and Jeffery, 2007; Hoh Kam et al., 2010). Significant amyloid beta accumulation attracts extra macrophages to the eye that engulf the particles, leading to inflammation. Inflammation does not stop the accumulation of amyloid beta, but it does affect retinal perfusion and clearance of other waste.

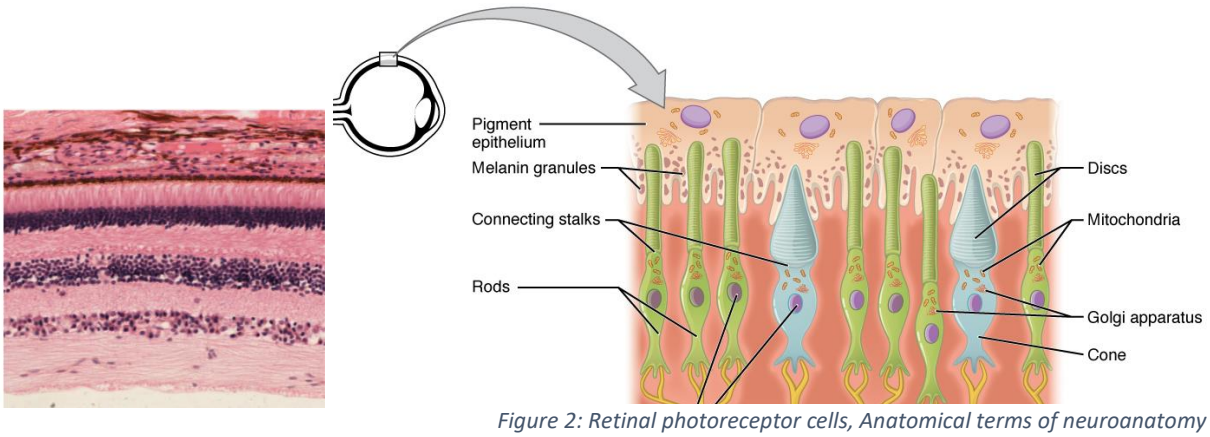

Figure 2: Retinal photoreceptor cells, Anatomical terms of neuroanatomy

Therefore retinal inflammation likely contributes to the massive rod loss of at least 30% that is observed (Hoh Kam et al., 2010). However in man, while there is drusen buildup causing the Bruch membrane to thicken similarly as in rodents, there is no amyloid beta present in the drusen. This means the detrimental effect of drusen applies differently for man. How this exactly affects humans differently is not well investigated, which may require further research. In addition to that, human outer segments and disk size swell/increase over time as often seen in human-dominant glaucomas, as opposed to rodents which may be an indirect result of the lack of amyloid beta (Cunea and Jeffery, 2007; Nork et al., 2000).

Cones

The photopic vision is affected differently compared to scotopic vision. While the photopic vision is affected similarly in both rodent and man, the consequences are quite diverging as rodents are nocturnal whereas man are not.

Similar to rods, also in cones the mitochondria start functioning less optimal over time. The membrane potential declines which leads to less ATP production and worsened function, which effect is further increased in cones as they gradually become more cytochrome-c oxidase deficient adding up to an almost 70% loss of metabolic function (Barron et al., 2001, Hoh Kam et al., 2019). Surprisingly, the survival of cones in this harsher metabolic environment is remarkably higher as compared to rods (Elsner et al., 2020). The cones are not entirely unaffected; they are shown to lose their sensor sensitivity over time (Elsner et al., 2020) which is likely due to the severe decline of ATP accessibility (Hoh Kam et al., 2021). The rate of sensitivity loss does however depend on the type of cone. There are three types of cones, that we classify under the RGB spectrum; red, green and blue wavelength sensitive cones. B-type cones are selectively more affected by age and pathology compared to their R and G counterparts due to less flexible adaptivity to harsher metabolic conditions, and therefore blue vision will be decreasing the most (Weinrich et al., 2017).

Also similar to rods, cones also deal with the accumulation of extracellular drusen particles clustering on the outer segments and blood vessels which cuts off cone blood supply creating a hypoxic situation. Again, only in rodents there is amyloid beta present in the drusen. Interestingly, in both rodent and man, while this also affects cone function, the actual survival of cones to this phenomenon is significantly better than seen in rods. Multiple studies suggest that cones possibly possess greater restoration capacity or flexibility through which they may survive, however no conclusive evidence has been found about why this happens (Weinrich et al., 2017; Hoh Kam et al., 2019). Because cones survive the ageing process significantly better, this means that the ageing of the photoreceptors does not affect man as much as it does rodents as we largely depend on cone function and are rarely fully dark adapted as a diurnal species, whereas rodents are nocturnal and primarily depend on their rods (Hoh Kam et al., 2019).

Innovations and implications

Literature has shown that the primary sources of photoreceptor insensitivity or loss can be attributed to severe metabolic loss and drusen accumulation. According to a study by Sivapathasuntharam, an exposure to 670 nm light for 10 minutes a day daily in rats significantly slowed the ageing process of photoreceptors by improving mitochondrial function, as long wavelengths of light were absorbed in the mitochondrial respiration cycle which maintained the mitochondrial membrane potential significantly longer (Sivapathasuntharam et al., 2019). A similar study done by Kokkinopoulos et al. showed similar results in mice, exploiting the possibility that this will work on multiple species possibly including humans (Kokkinopoulos et al., 2013). However, more future research is needed to reveal whether this could be extended to human retinal ageing as seen in ARM and AMD as well.

Chemoreceptors

Ageing chemoreceptors

While there is various chemoreceptors in mammalian species, all serving to detect a change in homeostasis levels and subsequently cause action to preserve homeostasis as can be seen in in pO2 and pCO2 levels in the body during exercise or as used in the nasal cavity to perceive smell, there is fairly little known about ageing on the wide chemical range of chemoreceptors. An exception can however be made for a specific group of receptors located at the upper end of the common carotid artery, accordingly named the carotid body. This small organ of just a couple millimeters in diameter consists of nerve fibers, connective tissues and islands of parenchyma containing two different chemoreceptor cell types, namely the chief cells (type I) and the sustentacular cells (type II). Together, they serve to control respiratory and cardiovascular function. Via complex neural pathways, its main function is to adjust respiration upon changes of gasses (pO2, pCO2) in the arterial blood (Sacramento et al., 2019).

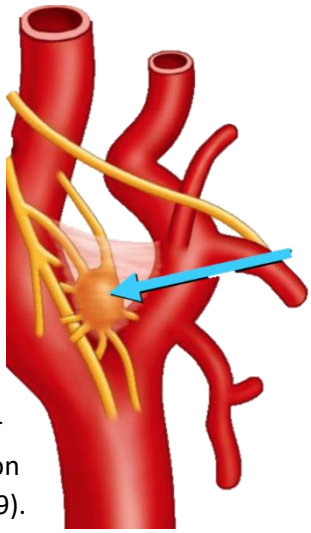

Figure 3: The carotid body, O2 chemoreceptor. Researchgate

During the ageing process, the carotid body undergoes a reduction in its capacity to maintain homeostasis for blood gas values, which is hypothetically an indirect result of decreased sensitivity of the receptors due to the loss of synaptic junctions that we see over time. Interestingly, when this happens an increase in diameter size of the carotid body can be observed (Di Giulio et al., 2018). Why this correlation is very prevalent is yet to be discovered, but the age-related reduction in synaptic junctions is speculated to be a protective mechanism against the accumulation of reactive oxygen species that gradually happens everywhere during the process of ageing (Di Giulio et al., 2009).

In all the different types of cells present in the carotid body, a variation in mitochondrial function can be observed over time. With age, also a reduction in mitochondria numbers and volume can be observed. This leads to the progressive loss of chief cells and progressive proliferation in sustentacular cells, in both cases leading to a reduced number of neurotransmitter/adenosine vesicles and ATP ready that are the key components for the carotid body to function (Sacramento et al., 2019; Pokorski et al., 2004), increase in fibrosis and loss of surface contact to glomus cells (also because the glomic tissue decreases over time) through which the carotid body becomes less sensitive and thus responsive to hypoxic blood gas changes (Di Gulio et al., 2018). This decreased function is however not observed in hypercapnic changes (Sacramento et al., 2019).

Figure 4: Young and aged carotid body cell morphology. Pokorski et al, 2004

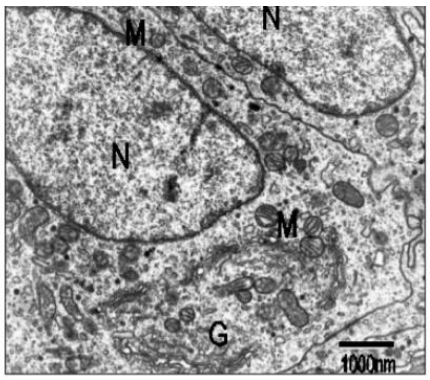

Fig. 1. Electron micrograph of young carotid body chemoreceptor cells. N, nuclei; M, mitochondria; G, Golgi apparatus. Primary magnification, 6k.

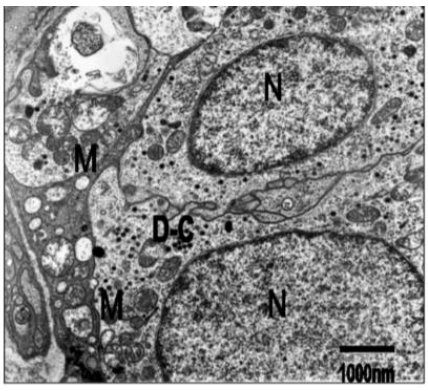

Fig. 2. Electron micrograph of old carotid body chemoreceptor cells. N, nuclei; M, mitochondria; D-C, dense-cored secretory vesicles. In the upper left part of the picture a dark, necrotic cell with vacuolisation is seen. Primary magnification, 6k.

Conclusively this means that loss in mitochondrial function or complete degeneration of mitochondria in the carotid body causes a decrease in adenosine and ATP, which are important to maintain cellular function, and indirectly increases the amount of reactive oxygen species after which the amount of synaptic junctions to the neural pathways involved decreases, thereby further negatively impacting its function to respond to primarily hypoxic changes in the blood (Di Gulio et al., 2018; Sacramento et al., 2019).

Additionally, studies have shown that the environmental conditions of the body contribute to the morphology and thus the function of the carotid body. Dos Santos et al. showed that a sugar rich diet, eventually leading to insulin insensitivity, caused changes in the ratio of chief- and sustentacular cells in the body respectively (Dos Santos et al., 2018). This could lead to possible consequences on the ageing carotid body, as these two cell types proceed differently over the course of time. The study showed a significant increase in the ratio of type I chief cells whereas the type II sustentacular cells decreased under diabetic conditions. Type I cells have shown to degenerate much more drastically than the type II cells, therefore morphological changes due to environmental changes in the body could contribute to the onset of further problems caused by the increased detrimental effects of ageing on the carotid body. More studies should be done to either confirm or reject this hypothesis.

Innovations and implications

Hypoxia responses and the morphological, physiological and biochemical changes of the carotid body seem to share several common pathways, which would allow for the use of hypoxic models to be used for the study of the ageing processes in the type I and II chemoreceptor cells. Suggested appropriate models for ageing and development regard changes in oxygen supply to the carotid body such as those seen in (chronic) hypoxia. These models would also cover the mitochondrial degeneration, as this results in a decreased cellular capacity for work similar to hypoxic situations (Di Gulio et al., 2018). Possibly also other models could be important tools for ageing study, such as in diabetes where oxygen-sensitive mechanisms could be less or more sensitive to hypoxia (Dos Santos et al., 2018; Di Gulio et al., 2018)

Simultaneously a question could be posed about whether the decrease in adaptive functionality of the carotid body has an effect on other parts/organs of the body, as it is responsible for maintaining appropriate oxygen levels in the blood. Further study is needed to discover whether (chronic) hypoxia could accelerate the ageing process and if this effect can be contributed to the degeneration of chemoreceptors in the carotid body.

Thermoreceptors

Ageing thermoreceptors

Measuring the in- and external temperature, and subsequently the capacity to generate a bodily response to it is an important component for optimal function and survival in many mammals (Grendon et al., 2015). Thermoregulation via thermoreceptors thus has a vital role in a homeostasis where the body responds autonomically by increasing sweat production and blood flow in hot conditions and shivering and decreased blood flow in cold conditions. However, the ability to adapt to suboptimal temperatures via behavior as can be seen in humans (eg. taking off clothes), widely reduces the need for autonomous responses (Coull, 2019).

Over time though, the capacity to regulate and measure in- and external temperatures in mammalian species decreases, which is associated with a progressive deterioration of the structure (and thus function) of the CNS and the cardiovascular system, which the thermoreceptors are generally placed alongside of. Because of this desensitization, younger individuals are more protected against

temperature related illness and injuries compared to the elderly. Moreover, the deterioration of the cardiovascular system and the loss of thermoreceptor sensitivity primarily result in a reduction in blood flow and subsequently a reduced output of the executive mechanisms of the thermal receptors, such as the sweating glands, that leave elderly more susceptible to heat strokes (Millyard et al., 2020).

Body temperature in both rodents and men is maintained by metabolic activity (endotherm). The basal metabolic activity required that is delivered via the mitochondrial output to maintain this temperature is primarily obtained via the oxygen supply, delivered by the blood flow. Due to the decay of the CNS and cardiovascular system (Coull, 2019) resulting in less blood flow, the mitochondrial output is also negatively affected. This results in a lower basal metabolic activity and decreased ATP production which among other things eventually reduces body temperature in elderly, leaving them more susceptible for colds as suggested in the study by Duquet. Additionally, reactive oxygen species will increase, which could possibly negatively affect afferent executive processes (Florez-Duquet and McDonald, 1998).

Innovations and implications

The studies of Duquet and Millyard demonstrate that the positioning of thermoreceptors is rather unfortunate for two separate reasons unrelated to the receptors themselves, as the cause of heat and cold susceptibility in elderly is propelled onto otherwise age-related deteriorating mechanisms such as the CNS and the cardiovascular system which the majority of the thermoreceptors is placed alongside of (Florez-Duquet and McDonald, 1998; Millyard et al., 2020). This suggests that for future developments aimed to increase the quality of life in elderly regarding temperature susceptibility, studies should focus on different mechanisms than the one coming to mind first, namely age-related CNS and cardiovascular degradation. Possibly, studies about the CNS or cardiovascular system could be combined with those known from the thermoregulations, which may open up a different pathway to health innovations.

However, it should be noted that thermoreceptor nerve-fibers have not been studied appropriately. It is known that thermoreceptor fibers consist of unmyelinated C-fibers that are responsible for sensing warmth and the A-Delta fibers, that are responsible for sensing cold (Zhang, 2015). No study has focused on the plausible degeneration of this set of nerves that run along the PNS, and that eventually connect to the CNS. Implications could and should certainly be made about this knowledge gap.

Possibly, the executive mechanisms that respond to thermoreceptor signals such as the sweating glands may separately age as well. Studies already suggest they shrink and become less sensitive to activating signals, especially in females, but more studies are required to come to conclusive evidence as to whether this is an effect of ageing skin or ageing thermoregulation (Fenske and Lober, 1986).

Mechanoreceptors

Ageing cutaneous receptors

As mammalian bodies age, the skin undergoes a lot of modification and neurological change affecting, among other things, tactile sensation. The muscle mass decreases significantly (Florez-Duquet and McDonald, 1998), the elasticity deteriorates and stiffness increases, as well as the flattening of dermal-epidermal junctions and the thinning of the skin layers (Jobanputra et al., 2020); all of these changes subsequently have varying effects on several mechanic receptors located in the different skin layers, thereby deteriorating our fine touch (Jobanputra et al., 2020).

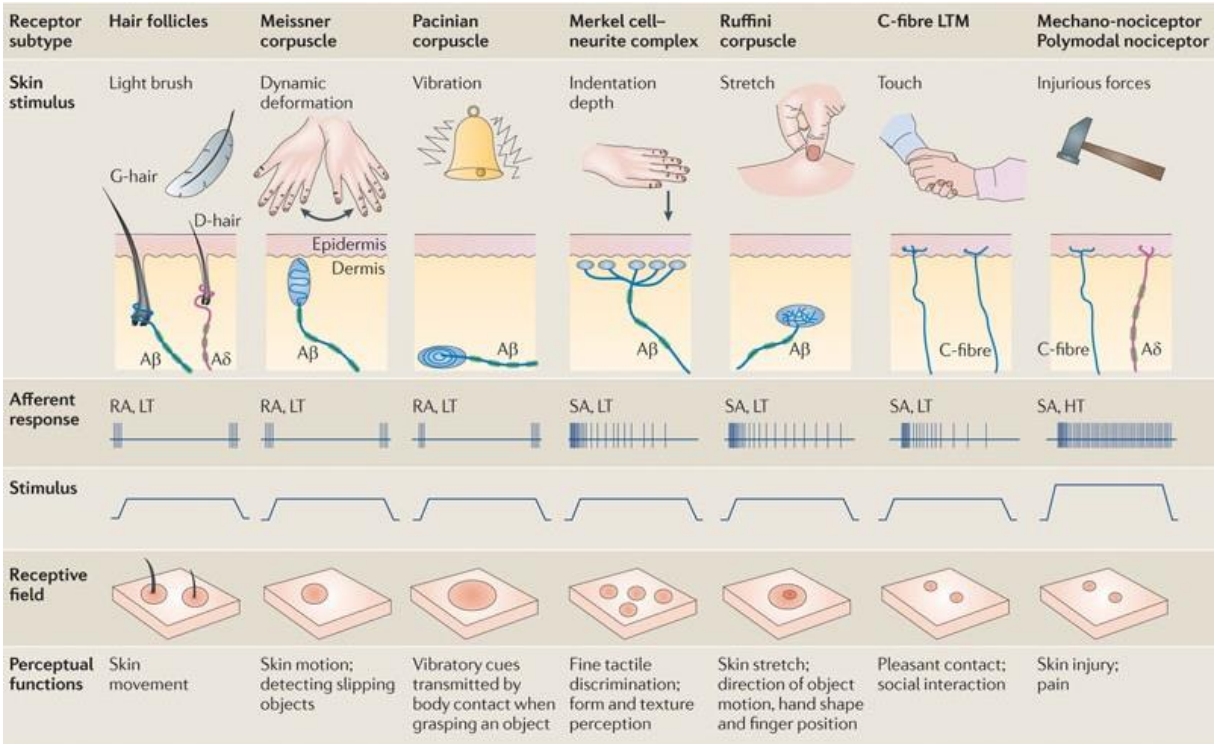

Figure 5: Cutaneous mechanoreceptors, Nature Reviews - Neuroscience

These mechanical skin receptors, combinedly called cutaneous receptors, respond to physical changes on and in the skin, such as pressure, touch, vibration and stretch (Johansson and Flanagan, 2009).

There are four main classes detecting these stimuli that this review will discuss, thereby excluding the hair follicles. These are the encapsulated Meissner corpuscles located in the dermal papillae that can detect denting of the skin and the movement of objects over the skin; the Merkel discs in the basal epidermis that perceive structure and texture of objects; the encapsulated Pacinian corpuscles located in the deep dermis that are responsible for detecting vibration and the Ruffini receptors that can detect stretch via sodium influxes (Marzvanyan and Alhawaj, 2020). These, and also the skin thermoreceptors, are all low threshold because they are not responsible for pain signaling. In the skin, nociceptors are responsible for signaling temperature and pressure related pain, which will not be discussed in this review.

Via the use of models, immunohistochemistry and even in vivo vibration and texture measurements, several studies managed to record various changes that the cutaneous undergo during ageing that will be separated in receptor classes below.

Meissner's corpuscles

Over time, the environment of the receptors which is the skin undergoes physiological change such as stiffening of the skin. Subsequent to this change, the Meissner corpuscles derogate the magnitude of the senses perceived of movement in the dermis, and the denting of the skin generates less action potentials up to 36%, especially in receptor-rich areas like the paws/fingers, which indicates that the Meissner's corpuscles are significantly affected by ageing (Jobanputra et al., 2020; Mildren et al., 2017). Additionally, the flattening of the epidermal junctions seem to flatten the proportion of stimuli generating an afferent response which possibly causes further insensitivity (Mildren et al., 2017).

Not only the environment of the corpuscles causes functional change; ageing on its own also affects the cells itself. Primarily, the size reduces, and with that the shape of the cell decays to a more circular shape. Additionally, the receptors seem to slowly retreat to deeper areas of the skin (García-Piqueras et al., 2019). This on its own may cause a decrease of afferent impulses generated, but it has not yet been suggested or properly investigated. The reduction of the cell size may have to do with a reduced metabolic capacity of the cells, like seen in other receptor type cells, suggests the study by Piqueras; possibly, simply a reduction of the availability of ATP by the loss of mitochondrial membrane potential could cause the observed desensitization (García-Piqueras et al., 2019). Substantiated reasons for these morphological changes have not yet been discovered or studied properly.

Additionally, in late stages of ageing, the corpuscles start to completely denerve and subsequently the total number of cells decreases (García-Piqueras et al., 2019), further decreasing the sense of touch and movement. The changes in this receptor cell-type seem to be non-reversible.

Merkel discs:

The physiological altering of the skin also has an effect on the Merkel discs, especially on their tactile discrimination ability which is a result of the skin thinning gradually; there is a clear, statistically significant reduction in the fine texture recognition correlated to thinner skin presented in a study by Skedung et al., in which participants of several age classes compare a presented texture with a reference texture and conclude whether it was the same or not with a finger, which is accordingly a skin area rich for touch and tactile recognition. The results showed that per age class, the recognition worsened, especially on very textured surfaces, parallel to the skin thinning (Skedung et al., 2018). The same is shown for the conscious feeling of vibration in a study by Mildren et al., also primarily focused in the paw/hand area. Light touch and the vibrotactile sensitivity threshold was greatly reduced as was measured by subsequently generated action potentials (Mildren et al., 2017).

Remarkably, active training in the form of repeating these experiments improved the results in all age groups, suggesting that elderly can retain their active fine texture discrimination by Merkel discs to a certain extent (Skedung et al., 2018). Since the mechanical skin properties within Meissner's corpuscles and Merkel discs are comparable, the difference in response between the receptor in this experiment shows a difference in plasticity that possibly means there might be a difference in receptor sensitivity, density or signal transmission between the two (Skedung et al., 2018). Whereas a certain number of cutaneous receptor cells is lost over time, the remaining receptors show a surprising level of plasticity that may be interesting to look into in the future as it may lead to health implications regarding the quality of life in elderly.

Pacinian corpuscles

The Pacinian corpuscle is developed for registering vibrational change, with emphasis on change. Pacinian corpuscles respond to mechanical stimulation during movement, but not when held in a constant position (Jobanputra et al., 2020). Therefore they are highly adaptable and this has provided them a head start when it comes to ageing; the Pacinian receptor features almost no age related physiological alterations as presented in current studies, however the number of cells do slightly decrease over time (Jobanputra et al., 2020). Since the cell is located deeply in the skin, it cannot be excluded that the morphological skin changes over time may have less effect on this receptor and it therefore simply does not deteriorate as much, instead of persisting due to the suggested high plasticity.

Ruffini endings

These stretch specialized receptors are, unlike and opposed to Pacinian receptors, remarkably slow-adapting. Similar to Meissner's corpuscles, the morphology and size of the receptors differed slightly

in older individuals; the cells appeared to have flattened configurations (Aydog et al., 2006). Additionally, whereas all cutaneous mechanoreceptors decrease somewhat in number over age, the number of Ruffini receptors in aged rodents decreased significantly compared to other skin mechanoreceptors, primarily in the anterior cruciate ligament complex (regions within joints susceptible to stretching). Within these joint regions this type of receptor is most abundant (Aydog et al., 2006; Jobanputra et al., 2020). The reason as to which this cell type reduces in such numbers is not yet known, but it could be related to the great amount of metabolic or physical strain put on these cells during a lifetime. Whether this is translatable to human joints is not yet investigated.

Additionally, joint regions are more prone for inflammations to occur, especially in pathologic conditions such as arthritis that usually occurs more often in older individuals. Inflammation in the anterior cruciate ligament can, as suggested by Aydog et al., cause swelling that is detrimental for several cell types under which possibly the Ruffini's endings (Aydog et al., 2006).

Innovations and implications

Some skin mechanoreceptors seem to be prone to irreversible damages like the Meissner corpuscles sensitivity. What is more interesting, as shown by Skedung et al., is that other cell types possess a rather unique capacity to regenerate their lost sensitivity after repeated use (Skedung et al., 2018). This effect has been prominently measured in the Merkel discs, but perhaps similar experiments could reveal the same outcome for other skin (mechano)receptors. Additionally, highly adaptive receptors such as the Pacinian corpuscles, show minimal signs of age-related degeneration. Both of these findings suggest that increased adaptivity may have beneficial effects for ageing, which coincides with the general consensus that actively using the body and mind often decreases ageing effects. To test this hypothesis, a study that measures the difference in skin receptor ageing between blind aged individuals predominantly using braille and control aged individuals could be suggested.

Possibly, existing innovations against ageing like Whole Body Vibration could thus have a wider range of beneficial effects than previously imagined. An idea for skin benefits could be to localize this type of treatment on the hands, where touch recognition and identification is most often needed.

Discussion and conclusion

In several classes of sensory receptors, it has been observed mitochondrial function can be abided as a contributing cause to age-related deterioration. In the retina's photoreceptor cells, mitochondrial abnormalities occurred after a progressive buildup of common gene mutations, leading to a decrease of the membrane potential (Barron et al., 2001). This decrease or sometimes total loss reduces ATP production, but also leaves the receptor cell more vulnerable to the buildup of destructive reactive oxygen species. The accumulation thereof creates further damage that facilitates further age-related symptoms like AMD (Curcio, 2001).

Similar to retinal photoreceptors, type I and II chemoreceptor cells found in the carotid body alongside the aortic arch of the cardiovascular system are insinuated to be suffering detrimental effects because of, among other things, loss of mitochondria altogether and mitochondrial dysfunction resulting in less available ATP (Sacramento et al., 2019; Pokorski et al., 2004). The studies implied this protrudes the cause of age-related chemoreceptor insensitivity. Moreover, coupled to the cardiovascular system are the thermoreceptor cells. The aged cardiovascular system together with the age-related deterioration of the CNS proposed a risk for mitochondrial function inside thermoreceptors as well, increasing radical oxygen species (FLorez-Duquet and McDonald, 1998). In the skin, Meissner corpuscles were observed to shrink, which was hypothesized to be partially caused

by ATP deficiencies that can be attributed to metabolic/mitochondrial dysfunction as well (García-Piqueras et al., 2019).

Interpretation of review findings

That mitochondrial function is frequently recognized as an age-inducing agent is not surprising. The cause of cellular deterioration observed in ageing has been investigated for several decades, and repeatedly studies appointed reactive oxygen species to be a main cause for cellular and genetic damage (Bergamini et al., 2004; Banyopadhyay et al., 1999). Following upon those conclusive investigations, the origin of reactive oxygen species was not appointed to originate from mitochondria itself, but mitochondria were found play a major role in maintaining accumulation thereof below a certain damaging threshold via Cytochrome-C oxidase production (Barron et al., 2001;. Srinivasan and Avadhani, 2012). Subsequently, if mitochondrial function is then significantly decreasing due to either mutation over time (ageing) or physiological stress, the mitochondrial membrane potential decreases which thereafter generates an imbalance between available Cytochrome-C oxidase and reactive oxygen species which has a direct correlation with the observed detrimental effects for (receptor) cells (Srinivasan and Avadhani, 2012; Müller-Höcker et al., 1992; Koll et al., 2001). These correlations were confirmed with studies wherein with drugs or therapies, mitochondrial membrane potentials were manipulatively increased or decreased. These studies then showed that by increasing the membrane potential, the detrimental effects of ageing or physiological stress could be opposed (Schloesser, 2015). The other way around, studies also showed that drugs or therapies decreasing the membrane potential increased age-related effects (Cavazzoni et al., 1999), thereby finally linking mitochondrial function to age-related cell deterioration.

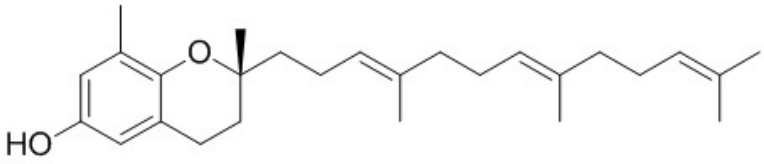

Figure 6: δ-tocotrienol, a membrane potential-improving drug. Schloesser, 2015

However, not every cell type experiences deteriorating effects through mitochondrial dysfunction, therefore making it difficult to link ageing to this singular cause. This review demonstrates that in the case of sensory receptor cells, mitochondrial dysfunction however can be appointed to a main cause of age-related deficiencies which could possibly be a new lead for future health innovation proposals.

Outlying findings

Apart from the Meissner's corpuscles in the skin, all other skin mechano-/cutaneous receptor studies did not show or suggest any form of mitochondrial disfunction as a source of the observed ageing effects. This result could possibly be designated to the location of these receptors, which is in the skin dermis layers. The skin is prone to receive significant amounts of UV-radiation. UV-radiation (especially UV-A1) also generates additional reactive oxygen species, creating a mitochondria-independent Cytochrome-C oxidase imbalance. Additionally, UV-A1 radiation potentially acts on mitochondria detrimentally, by inducing the Jurkat type apoptosis that among things decreases the membrane potential (Matz, 2007). Since the effects of UV-radiation are large and often visible before the onset of old age, skin cutaneous receptors may therefore show similar but unrelated deteriorative signs observed in the mitochondria of elderly (Matz, 2007).

Synopsis

In conclusion, the in this review collected studies independently suggest there to be a widespread correlation between mitochondrial dysfunction in the four primary classes of sensory system receptor cells and old age, which may direct health organizations to focus on developing successful membrane potential-targeted innovations in the future, thereby improving sensory senses and thereby quality of life of elderly.

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