Oxytocin and NRF2: free and frugal pathways to healthy ageing

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INTRODUCTION

This "Perspective Piece" will provide a brief overview of the hormone oxytocin and the transcription factor nuclear factor (erythroid-derived 2)-like 2 (NRF2) and their roles in ageing. Possible pathways by which oxytocin and NRF2 could interact will briefly be touched on as well as lifestyle choices that could affect both oxytocin and NRF2. This will provide some simple actions we can all continue with or introduce into our daily lives in order to try to age healthily.

OXYTOCIN AND NRF2

Ageing is a complex process. Although not exhaustive, there are nine "hallmarks of ageing": "genomic instability and telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, stem cell exhaustion and altered intercellular communication".[1]

Oxidative stress and inflammation are very important factors leading to ageing because they affect these "hallmarks". Reducing oxidative stress and inflammation can therefore slow ageing. A drug which is both antioxidant and anti-inflammatory might therefore be of help in slowing ageing.

One such exogenous drug, which is also an endogenous hormone, is oxytocin. Oxytocin has been researched for over half a century. It is well known as a drug for inducing labour. It is a cyclic peptide hormone which is produced in the hypothalamus, transported and stored in the posterior pituitary gland, and from there, released into the systemic circulation. Oxytocin is composed of nine amino acids, including two cysteines which form a disulphide bond and leads to the designation of "cyclic" as it forms the circular part to the peptide. One of the other important amino acids it contains is tyrosine.

Oxytocin has been looked at for its anti-ageing effects.[2] It is an antioxidant, partly by virtue of its tyrosine[3] and possibly via its disulphide bond which could take part in thiol-disulphide exchange reactions.[4] Oxytocin is also an anti-inflammatory; it can reduce the increase in pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNFα) and interleukin 6 (IL-6), in healthy men who are given a bacterial endotoxin.[5]

Positive social relationships increase oxytocin, which in its turn can slow the rate of telomere shortening, essentially, slowing ageing.[6, 7] Oxytocin can have epigenetic effects; therefore, it might be able to influence ageing through epigenetic as well as telomere effects. For example, perinatal exogenous oxytocin seems to have ongoing epigenetic effects.[8] Oxytocin has also been shown to provide epigenetic protection against drug addiction.[9] Further, oxytocin has positive effects on mitochondrial function,[10] cellular ageing[11] and even stem cells.[12,13]

As we age muscle mass decreases and bone quality reduces leading to osteoporosis in some elderly people, especially women. Oxytocin is able to maintain and regenerate muscle.[14] It strengthens bone and it can protect it against osteoporosis.[12, 15] It can even slow the ageing of our skin.[11]

NRF2 is a transcription factor, i.e., it is a protein which controls the activity of other genes, over 200.[16] Indeed, it is regarded as the master regulator of oxidative protection and therefore of vital importance in ageing.[17]

NRF2 also influences oxytocin function in terms of both the peptide and possibly the receptor. Matsui et al. showed that an NRF2 activator upregulated oxytocin mRNA expression.[18] In addition NRF2 might be able to upregulate oxytocin receptor gene expression by interacting with MAFF (basic leucine zipper transcription factor, musculoaponeurotic fibrosarcoma F).[19, 20] Coming full circle, Cho et al. showed that oxytocin, via the oxytocin receptor, can lead to activation of NRF2.[11] Therefore, it can be postulated that a mutual NRF2-oxytocin activation loop may exist.

Slowing ageing, or at least growing old healthily, is a significant focus of science and medicine. Slowing ageing can be attempted in numerous ways. Some are highly technical and expensive whilst some are very mundane and frugal. The more mundane and frugal will be examined here; ways in which we can all make a difference in our ageing process. These relatively simple actions and changes in lifestyle can affect both oxytocin and NRF2 and thus, probably, slow ageing. The areas looked at here will be sleep and sunlight; exercise and cold; fasting and food.

METHODS OF SLOWING AGEING

Sleep and sunlight

Sleep heals and keeps us youthful. Sleep releases the "sleep hormone" melatonin. Melatonin in turn stimulates the release of oxytocin.[21] In addition melatonin is believed to activate many of its healing properties via NRF2.[22, 23] Whilst the darkness of sleep heals, the light of the sun also heals. Sunlight produces vitamin D in the skin and vitamin D can increase oxytocin function.[24] Vitamin D also activates the NRF2 pathway and helps keep us young and healthy.[25]

Exercise and cold

Exercise, such as running[26] and martial arts,[27] stimulates oxytocin release. In a mouse study exercise has been shown to reduce the size of breast cancers; this was via oxytocin secretion.[28] In a review it was shown that regular exercise leads to oxidative stress which activates Nrf2.[16]

Cold exposure might be able to increase oxytocin indirectly via peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), because cold increases PGC-1α which in turn regulates oxytocin.[29] There are probably other indirect pathways linking cold adaptation with oxytocin.[30] Cold exposure has been shown to activate NRF2 also.[31]

Fasting and food

Oxytocin helps reduce calorie intake[32] but has not been shown to be increased in short-term fasting, at least in one limited study.[33] However, fasting does increase PGC-1α[34] which is a master regulator of mitochondrial function. PGC-1α has been shown to increase oxytocin,[29] therefore it may be possible

that fasting increases oxytocin via PGC-1α under certain conditions. Fasting has many health benefits and this is partly through activation of NRF2.[35, 36]

Food provides many micronutrients, such as vitamins and minerals, which are important in oxytocin function. Vitamin D may increase both oxytocin and oxytocin receptor.[24] Vitamin A can increase oxytocin via CD38.[37] Vitamin C is required for oxytocin synthesis.[38] The mineral magnesium is required for optimal oxytocin receptor function.[39] Many foods, herbs and spices also activate NRF2: sulforaphane which is found in cruciferous vegetables such as broccoli,[40] beta-carotene from carrots,[41] vitamins A,[42] herbs such as rosemary,[43] and spices such as turmeric.[44]

CONCLUSION

There is growing research into oxytocin and NRF2 in ageing. Much more research is needed to confirm these findings but it is very promising. As can be seen here so much of what we do in our daily lives can affect both of these. Part of long-term, healthy change is to know the simple actions we can take.

It is well known that sufficient amounts and quality of sleep is vital for healthy ageing. The mechanisms whereby this is achieved are not fully elucidated. However, here two probable mechanisms are shown. Sufficient sunlight is also of vital importance partly because of its link with vitamin D which has numerous health benefits.

Exercise is a cornerstone of healthy ageing. Also cold has many health benefits which are still under active investigation. It is interesting to note that in the last few years when lock-downs and social distancing have been in place, outdoor swimming in relatively cold waters has increased. This may have synergistic effects as oxytocin and NRF2 are triggered by both exercise and cold. An even more simple method of cold exposure is taking cold showers.

Fasting has been a part of many cultures and religions for millennia. It has recently had a resurgence in the English speaking world because of research that confirms this ancient knowledge; periods of fasting are vitally important for health. Fasting can be instituted in many ways, some of which are easy to implement, such as "time-restricted eating" which involves decreasing the time between the first and last meals of the day.[45] At the same time, many foods have been identified as super-foods; foods having special health benefits. However, it may be that all non-processed foods have, to a lesser or greater extent, significant health benefits. It would seem prudent to concentrate on the quality of our food and not just the quantity. We should make healthy food choices and eat a variety of foods (even everyday foods such as broccoli and the humble carrot), the majority of which should be fresh and preferably organic in order to provide optimum benefits for healthy ageing.

In summary, it would seem that healthy ageing is attainable through very mundane and everyday actions such as getting sufficient sleep, sunlight, regular exercise, taking cold showers, fasting and eating high quality foods. These are simple things each of us can take home and implement today.

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Memories of HM The Queen

This was Her Majesty's visit to Stockton-on-Tees as part of her Silver Jubilee celebrations in 1977. I am on the left (blond hair and glasses) with my parents and little brother. My dad is the younger man in the wheelchair. Prince Philip is just behind the Queen in the photo. As he passed my dad, he took the time to go over to him and had a chat, remarking how dad was the youngest wheelchair user. It meant the world to mum and dad that Prince Philip took the time as my dad was very ill at the time.

A very happy memory for us as a family, particularly as both my parents have passed away now. And I recall being very happy that schools were given the afternoon off to welcome the royal party!

kindly shared by **Ms Johanne Herman**