A potential role for endogenous oxytocin in adaptation to cold; implications for health?

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ABSTRACT

Cold water swimming is thought to provide mental and physical health benefits, although the details of the potential signalling pathways involved in the body have not yet been fully established. We know that brown fat/brown adipose tissue is important in thermogenesis, thereby possibly helping in training the body to adapt to cold stimuli. As a result of brown adipose tissue thermogenesis during cold exposure, the body uses up the stored fat energy to produce heat energy. Such metabolism of fat can therefore help combat diseases associated with gain of fat, such as obesity and type 2 diabetes mellitus. Here, we present a potential role for oxytocin in stimulating brown adipose tissue thermogenesis during cold exposure and adaptation. We discuss cold adaptation and brown adipose tissue thermogenesis, and present our hypothesis for the role of oxytocin in cold adaptation and its perceived benefits for health.

INTRODUCTION

Cold adaptation in the form of cold water immersion has historically been considered a potential natural method of improving health. More recently, the popularity of cold water swimming has increased, both in competitive and recreational forms. However, much of the evidence for the benefits of cold water immersion is anecdotal. If the perceived benefits are accurate, little is known about the pathways through which cold adaptation works to provide health benefits. Here, we propose a key role for endogenous oxytocin as a key mediator of cold adaptation through stimulation of brown adipose tissue thermogenesis.

THE CONCEPT OF COLD ADAPTATION

Cold adaptation is the process through which the body is trained to survive in cold environments through training of homeostatic responses to repetitive exposure to cold stimuli.[1] It is thought by some that such adaptation to cold can not only result in benefits of increased chance of survival in extremely cold environments, but also that it may have other health benefits for individuals. For example, there is anecdotal evidence that cold water swimmers report less severe and less frequent upper respiratory tract infections.[2] Cold water immersion is thought to result in health benefits through an increase in anti-oxidant formation and induction of anti-inflammatory responses.[2] Research has shown that anti-oxidants are higher in winter swimmers and in addition, there is evidence that adapted cold water swimmers have improved mental health when compared with unadapted volunteers.[2] The proposed mechanism that is thought to account for this is that cold adaptation may reduce pro-inflammatory responses, thereby removing inhibition of serotonin secretion. The resultant increase in serotonin release can act as a mood enhancer to help combat depressive symptoms.[2]

It is postulated that the stress response activated during cold exposure potentially shares similar effector systems to stress responses by other stimuli.[2] If correct, this means that by developing adaptation to cold and thus controlling the effector systems for the response to cold, it would allow one to control the response to other stressors too. This could potentially mean less negative stress responses to other physiologically stressful stimuli, such as infections.

Human and animal models have shown that repeated exposure to cold water immersion can lower the intensity of the cold shock response, allowing for adaptation to cold.[3] Such intermittent exposure to cold is also favoured, since continued stress could lead to altered cortisol levels and so may induce immunosuppression.[2, 4]

So, what controls cold adaptation? To our knowledge, the answer has not yet been fully identified. However, the initial response to cold adaptation studied through cold water immersion is thought to be a central process,[3] controlled by the brain. Therefore, if it is a central process, this implies that it is possible to adapt the body to the cold by only exposing a limited amount of skin surface to the cold stimulus,[3] as this would still trigger a response in the brain. This would suggest that one could benefit from the effects of cold adaptation through short intermittent exposure to cold, for example by soaking the hands and arms in cold water before or after hand washing. If this is the case, this would be a practical and simple lifestyle change that we could incorporate into our daily routines to gain the health benefits of cold adaptation.

Brown adipose tissue thermogenesis

Although the complete downstream effects from repeated exposure to cold stimuli are not fully clear, it is likely that brown fat, also known as brown adipose tissue (BAT), is involved in this adaptation process. BAT, in contrast to the better known white fat or white adipose tissue (WAT), is responsible for energy expenditure through thermogenesis.[5, 6] In other words, the induction of fat metabolism of BAT results in the generation of heat energy, making BAT an important organ for cold adaptation.

Much like cold adaptation, BAT metabolism is also thought to be a centrally controlled process,[7, 8] with involvement of various signalling proteins and transcription factors such as melanocortins, endocannabinoids and steroidogenic factor 1 (SF1),[9] to name a few.

Oxytocin, a neuropeptide hormone is also thought to be involved in upregulating thermogenesis, potentially through the stimulation of BAT activity. We know that oxytocin is produced centrally by the hypothalamus, and studies have shown that BAT activation through sympathetic nervous system activity may also be at least partly controlled by this same area of the brain.[9-11]

Evidence for the role of oxytocin

Oxytocin, known for its antistress effects,[10] is thought to be important in the response to cold exposure. A recent study identified that in response to cold stress, administration of oxytocin reduced the stress response through anxiolytic and anti-oxidant effects.[12] When exposed to low temperatures, the expression of oxytocin was shown to be upregulated in the hypothalamus of mice.[13] In further support, oxytocin knockout mice were shown to have lower body temperatures compared with wild type mice in response to cold exposure.[14]

One study showed that in response to both short and long-term cold exposure, there was an upregulation of the oxytocin receptor in the brain of mice, whereas peripheral oxytocin and oxytocin receptor expression in BAT were downregulated in both cases.[15] This supports the idea that oxytocin acts through centrally situated pathways to control the response to cold exposure. Furthermore, a loss of correlation in the expression of genes thought to be involved in thermoregulation was observed when oxytocin receptor expression gene data were removed in regression studies,[15] providing supportive evidence for the key role of oxytocin as a «master gene» in cold induced thermogenesis.

To add to this, experiments on mice showed that ablating the oxytocin pathway through ablation of oxytocin neurones led to a deficit in cold stress response, resulting in less BAT being formed when exposed to extreme cold[16]. This was overcome when oxytocin was administered to the mice. This suggests that oxytocin is important in regulating BAT related thermogenesis during the stress response. Experiments using oxytocin knockout mice have shown that in addition to the loss of cold induced thermogenesis, there is an accumulation of fat in the form of large lipid droplets within BAT.[17, 18] This shows that without oxytocin activity, BAT fat metabolism and cold induced thermogenesis are hindered, thus, supporting the idea that oxytocin has a key role in controlling these processes. In addition, studies have shown that oxytocin induces inguinal WAT browning in mice and so, as a result of burning the stored energy in fatty/adipose tissue, it also helps combat obesity and metabolic dysfunction.[13]

Possible mechanisms of action of oxytocin in the induction of BAT thermogenesis and cold adaptation

Whilst, to our knowledge, the definitive answer to how oxytocin is involved in these mechanisms is not yet fully established, we hypothesise that both central and peripheral pathways are likely to be involved, since oxytocin can act through a multitude of signalling pathways in the body. A detailed discussion of the mechanisms and pathways involving oxytocin are beyond the scope of this paper. A concise overview of oxytocin's interactions with other signalling molecules is provided in a review article.[19]

Of note, oxytocin has been shown to influence some pathways similar to those described above involving BAT activity, namely alpha-melanocyte stimulating hormone (a-msh),[20, 21] endocannabinoids[22, 23] and SF1.[24] Moreover, a potential role for oxytocin-induced downregulation of corticotropin releasing factor (CRF) expression during adaptation to chronic stress has also been described.[10]

The exact site(s) of action of oxytocin within the brain that are important for cold adaptation are starting to come to light. For example, as already discussed, it is thought that adaptation to chronic stress may involve hypothalamic oxytocin receptors,[10] since oxytocin knockout mice regain thermoregulatory abilities after selective restoration of hypothalamic oxytocin receptors.[11] Furthermore, the rostral medullary raphe which is a site known to control thermogenesis in BAT, is also thought to be a key central site for oxytocin activity. One study has shown that mice express oxytocin receptors in the rostral medullary raphe in response to cold exposure.[18] In addition, oxytocin knockout mice showed significantly lower body temperatures compared with knockout mice that had oxytocin receptor expression restored specifically in the rostral medullary raphe.[18] Therefore, these studies illustrate the importance of oxytocin activity at these central sites in the modulation of cold induced thermogenesis.

However, other central and peripheral systems may also be involved in this adaptation process that are not yet fully understood. The differential expression of adrenergic receptors secondary to oxytocin activity in response to cold induced stress[11, 25] support the involvement of the sympathetic nervous system. Moreover, some studies have shown upregulation of oxytocin in bone after long-term cold exposure, suggesting a role for oxytocin in bone homeostasis but also a possible role for bone in cold adaptation.[15] In addition, one paper has recently hypothesised a role for skeletal muscle slow twitch fibre contraction in mediating the response to cold via oxytocin feedback systems.[26]

Given the complexity and the large number of pathways that oxytocin can be involved in, it is highly likely that the mechanisms of action of oxytocin in adaptation to cold exposure are more complex than we might expect.

Emerging roles of oxytocin in health and disease

According to preliminary studies, oxytocin may be beneficial in managing glycaemic control in diabetes mellitus. Gliptins, widely recommended as a second line choice for the treatment of type 2 diabetes mellitus, inhibit a serine protease dipeptidyl peptidase-4 (DPP4) to reduce blood glucose levels. Recent papers have shed light on how oxytocin is also a potent DPP4 inhibitor in a concentration dependent manner.[27, 28] In addition, there are reports of cardioprotective effects of oxytocin. For example, oxytocin, through the release of atrial natriuretic peptide and nitric oxide, exerts cytoprotective properties to reduce the inflammatory response and aids in functional recovery of ischaemic reperfused heart.[29]

Oxytocin has also been shown to be involved in a multitude of psychiatric disorders,[30, 31] which are comprehensively covered by Marazziti et al in a separate article in this journal issue.

Further perceived roles of oxytocin in health are its effects on the immune system, since oxytocin is considered to have anti-inflammatory and pro-immune functions.[32] Consequently oxytocin may also have a role in protecting against infections, including COVID-19.[33, 34] Further research is necessary to consolidate on the work of these studies to establish further evidence of the role of oxytocin in health and disease.

DISCUSSION

In this article, we have discussed cold adaptation and its potential health benefits and how oxytocin and BAT may be involved. We have linked evidence from different studies that together demonstrate how oxytocin may be upregulated in cold adaptation, which results in BAT activation and stimulation of thermogenesis. This can mean potentially making use of the benefits of cold adaptation, such as improved mood, increased anti-oxidants and immune regulation, to help us build resilience against diseases such as the current COVID-19 pandemic. A further benefit is the possibility of converting WAT into BAT which can be preferentially used in thermogenesis to burn fat reserves and so help to combat obesity and metabolic syndrome.[7]

However, it is prudent to highlight that there are documented risks of cold exposure, such as arrhythmias, fatigue and of course hypothermia[2]. Therefore, if cold adaptation is practiced it should be performed in a controlled manner to the tolerance threshold of an individual, so that it stimulates the body but does not result in undesirable effects. As discussed above, since cold adaptation is considered to be a centrally controlled process, exposure of a small amount of skin surface may be enough to reap the benefits of cold adaptation without putting oneself at risk of the potential negative effects of full body cold water immersion.

Furthermore, in the current literature there is lack of evidence regarding the optimum temperature at which one can benefit from cold adaptation without exposing oneself to undue risks. Therefore, further research is warranted to identify the optimum temperature for cold adaptation. This could mean that exposure of a limited amount of skin surface to short and intermittent doses of cold at an optimum level could act to 'prime' the immune system, in a way to assist in improving our immune system's ability to fight infections.

As discussed, oxytocin's mechanisms of action and pathways are quite complex, and it is possible that more than one pathway may be involved in cold adaptation. Moreover, it is also within the realms of possibility that additional molecules and hormones are involved in this process, working alongside oxytocin to control responses to cold exposure and adaptation. It should also be noted that most of the evidence for BAT thermogenesis and the role of oxytocin come from studies on rodents. Research is yet to be conducted to show whether these findings are also relevant for humans and to what extent if so.

We hope further research can be performed in this field to help build a better picture of the pathways and systems involved in cold adaptation in humans and to aid in identifying the safe and beneficial methods of cold adaptation. The overall aim would be to help us to potentially make another simple and practical change to our lifestyle, along with factors such as exercise and eating well, to become healthier individuals and more able to combat infections and diseases.

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FEEDBACK ON THE JOURNAL

Dear Shadaba,😌😌

I hope you and your family are well.

Please may I say what a stimulating and fascinating read the MBMJ is.

I found this month's edition to be enlightening and moving in terms of the articles and book reviews that were featured. It was a real joy and an eye-opener to read the in-depth articles on the subjects of melanocytic lesions, ophthalmology, eye health, the work of therapy teams, sinusitis and vaccines.

Even with a 'non-medical' background, I found the different perspectives engaging, especially as most of the articles and reviews also referenced the COVID-19 pandemic.

It was also moving to read of colleagues we have lost and to read more about their outstanding lives.

Thank you to you and the entire editorial team for brightening my day and giving me a deeper insight into the medical world.

I really appreciate your work and look forward to the next edition.