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Can Vestibular Stimulation be Used to Treat Obesity?

Vestibular stimulation targeting the otoliths could rebalance energy homeostasis to trigger a leaner body habitus and thus treat metabolic syndrome

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It is hypothesized that repeated, non-invasive stimulation of the vestibular (balance) system, via a small electrical current to the skin behind the ears, will cause the brain centers that control energy homeostasis to shift the body toward a leaner physique. This is because these centers integrate multiple inputs to, in effect, fix a set-point for body fat, which though difficult to alter is not immutable. They will interpret repeated stimulation of the parts of the vestibular system that detect acceleration as a state of chronic activity. During such a physiologically challenging time it is preferable, from an energy homeostasis viewpoint, to both utilize fat reserves, and reduce the volume of these reserves and thus the energy cost of carrying them around. Hence, this type of vestibular stimulation could potentially be a therapeutic option for metabolic syndrome disorders such as obesity. This hypothesis is eminently testable via a clinical trial.

1. Introduction: Energy Homeostasis

The aim of this paper is to present and discuss the hypothesis that metabolic syndrome disorders, like obesity and type 2 diabetes mellitus, might be treatable by modulating the activity of the vestibular system. To develop this hypothesis, I first outline aspects of the relevant physiological areas, namely energy homeostasis, the neurology of obesity and the effects of vestibular stimulation on the body mass composition of animals. I then explore the hypothesis in more detail, before considering it in terms of the broader role of the vestibular system and discussing methods of how to test it.

Homeostasis, that is the maintenance of a stable and optimal internal physiological milieu, is a term that was coined by the American physiologist Walter Cannon. He wrote that the "coordinated physiological processes which maintain most of the steady states in the organism are so complex . . . involving as they may, the brain and nerves, the heart, lungs, kidneys, and spleen, all working cooperatively."[1] He went on to state that process of homeostasis should not be viewed as "something set and immobile" but rather "a condition which may vary, but which is relatively constant."[1] The objective of this process is to maintain the health and physiological integrity of the organism, and specifically to do so in a manner that optimizes energy efficiency. Indeed, the optimal use of energy, and the role that this plays in survival, is clearly a key driver underpinning the evolution of homeostatic mechanisms.[2]

The first suggestion of a role for the brain in the regulation of energy (specifically glucose metabolism) was made in the mid-nineteenth century by the French physiologist Claude Bernard,[3] who also coined the term *milieu intérieur*, and upon whose work Cannon built to develop the concept of homeostasis. As will be discussed subsequently, there are now known to be various, often reciprocally interconnected, centers in the brain, which act to maintain homeostasis via behavioral, endocrine, and neural routes.[2,3] The main neural route involved is the autonomic nervous system (ANS) with its two subdivisions – the sympathetic and parasympathetic nervous systems.[2] Moreover, as part of the homeostatic process it is the afferent inputs of the ANS that provide the brain with a constantly updated overview of the physiological state of the body.[2] As described below, homeostasis is also an underappreciated function of the vestibular system, which, like the ANS, is considered to be an evolutionarily ancient part of the central nervous system.

Although discussions regarding homeostasis have traditionally focused on apparent biological "thermostats," and the maintenance of "set-points," modern thinking is that, although perhaps conceptually useful, static, set-points are an oversimplification of the homeostatic process.[2] Indeed, as Craig puts it the "brain does not contain a collection of thermostats, each controlling a separate condition, and there is no single, overarching command center that controls all functions."[2] Instead "any constant level is actually a balance across numerous effectors" that are controlled in turn by various regulatory mechanisms.[2] Thus, any reference to the term set-point in the text below should be understood in this context – that is, as a acceptable range that arises when these mechanism are in a state of equilibrium.

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2. Can Obesity be Viewed as a Neurological Disease?

2.1. An Increasingly Obese World

In an optimally functioning system energy expenditure and food intake would be regulated by homeostatic mechanisms to maintain a state of equilibrium. This is the process of energy homeostasis.[3] Nonetheless, it is well known that over the last few decades there has been a burgeoning in the proportion of people, particularly in the developed world, who are overweight or obese.[4–7] In other words they are in a state skewed toward a positive energy balance; they have eaten more calories than they used, which are now stored as fat.

In adults the World Health Organization (WHO) defines being overweight as having a Body Mass Index (BMI) greater than or equal to 25, and being obese as a BMI greater than or equal to 30.[8] BMI is an index of weight to height and defined as an individual's weight in kilograms divided by the square of his height in meters. Indeed, according to the WHO's definition worldwide obesity has tripled since 1975 [http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight]; a phenomenon that appears to be driven by "Western" diets that are rich high calorie foods and replete with simple sugars and saturated fats, in combination with increasingly sedentary lifestyles [https://www.niddk.nih.gov/health-information/weight-management/prescription-medications-treat-overweight-obesity].[4] Consequently, as of 2016, 39% of adults worldwide were overweight and 13% obese. In certain countries the figures are even more dramatic: one estimate based on current trends, is that by 2030 just over 50% of adults in the USA will be obese.[9]

It is similarly well known that excess body fat is a major risk factor for a multitude of different chronic conditions, including: ischemic heart disease; stroke; type 2 diabetes mellitus; systemic hypertension; osteoarthritis; certain cancers (e.g., breast, prostate, and colon); and even cognitive decline and dementia.[4–7] As such, being obese or overweight in middle age is estimated to shorten life expectancy by 4 to 7 years.[4] It has been estimated that about $190 billion per year – that is, 20% of total annual US healthcare expenditure – is spent treating obesity and its associated conditions.[4] Current treatment approaches for obesity can be divided into lifestyle changes (i.e., diet and exercise), drug therapy and, for patients who are morbidly obese bariatric surgery (e.g., reducing the size of the stomach with a gastric band). Weight loss medications can be broadly divided into those that act on the brain (e.g., lorcaserin, phentermine, and topiramate) and the lipase inhibitor orlistat, which reduces fat absorption from the gut.[8] These medications have a range of associated side-effects that limit their use, such as gastrointestinal disturbance, dizziness, cough, dry mouth, paresthesia, and insomnia.[8]

2.2. Is there a Set-Point in the Brain for Body Fat?

It is not widely realized that the brain, through its role in maintaining homeostasis in general, and energy homeostasis in particular, plays a major part in determining level of body fat.[5,10] It has been known since the 1940s that the hypothalamus is involved in the control of appetite. Indeed, various hypothalamic subnuclei have been implicated, via lesion studies, in both overeating and anorexia.[10] However, it was only in the 1990s with the discovery of the so-called satiety hormone leptin (which leads to a reduction in appetite and feeding behavior) that attention focused on a particular area of the hypothalamus termed the arcuate nucleus (ARC).[10] This is because leptin binds strongly to the ARC, which is in a region with no blood brain barrier, meaning that it is fully exposed to circulating metabolic signals, such as hormones and dietary macronutrients like sugars, fats, and amino acids.[5,10]

It was then elucidated that the ARC lies at the heart of what is termed the central melanocortin system, which is a group of neurons that acts to regulate energy homeostasis. This melanocortin system contains two distinct populations of neurons that act antagonistically. These are the pro-opiomelanocortin (POMC) neurons, which suppress appetite (i.e., are anorexigenic), and neurons that co-express agouti-related peptide (AgRP) and neuropeptide Y (NPY), which stimulate appetite (i.e., are orexigenic).[11–15] Activation of POMC neurons, for instance by leptin, triggers the release of α-melanocyte-stimulating hormone (α-MSH), which then activates melanocortin 4 receptors (MCR4), causing reduced appetite and increased energy expenditure.[10] Conversely, AgRP/NPY neurons act to increase appetite and reduce energy expenditure, as well as directly antagonizing the action of α-MSH on MCR4.[11] In fact, AgRP/NPY neurons appear to provide a unidirectional, unreciprocated, tonic inhibition of POMC neurons,[10] meaning that there is an inherent neuroanatomical bias towards a positive energy balance, and thus the development of metabolic syndrome disorders.[10]

In order to optimally regulate energy homeostasis POMC and AgRP/NPY neurons are believed to maintain a "set-point" for total body fat.[10,16,17] As discussed above however the term set-point is an oversimplification, and the concept is more correctly viewed as an optimal range within which body fat is maintained by balancing the control systems of the various effectors to maintain a state of equilibrium. In the context of energy homeostasis such effectors would include metabolic rate, appetite, feeding behavior, brown adipose tissue activity, and fidgeting. Nonetheless, as a succinct, shorthand term set-point does have some conceptual utility, so long as it is understood in the manner described above. The aforementioned POMC and AgRP/NPY neurons act via a feedback control mechanism that responds to circulating macronutrients, hormones released by the digestive system and adipose tissue (e.g., insulin, leptin, and its counterpart ghrelin, the so-called hunger hormone) and neural inputs.[11] Of particular relevance is the parasympathetic nervous system; the "rest and digest" side of the ANS. Indeed, the major parasympathetic nucleus in the brainstem, the nucleus of the solitary tract (NTS), is in fact itself rich in POMC neurons, which form part of the central melanocortin system.[10,11]

In response to these various inputs the melanocortin system acts (primarily by modifying appetite and metabolic rate) to keep body fat within a specific range, deviations too far in either direction being vigorously resisted.[10,17,18] This explains why it is not only hard to lose weight via lifestyle changes, such as dieting, but also why subsequently maintaining the new lower weight is

often a Sisyphean task, and why weight soon returns to previous levels. It also explains the findings of overfeeding studies, such as a notorious one from the 1960s in which thin, adult male prisoners in Vermont were given very high calorie diets for several months while refraining from exercise.[18] The original intention of the study had been to create obese subjects to study, however, as the prisoners only gained relatively modest amounts of weight, it ended up as a demonstration of the resistance of the adult brain to deviating beyond the upper range of the set-point.

Obviously, the volume of body fat can vary enormously from person to person. In addition to influence by genetic and epigenetic factors,[19] there is also now evidence that the type of diet frequently consumed in the developed world contains excessive quantities of macronutrients that can, especially with repeated exposure, damage neuronal populations within the ARC and push up the set-point for body fat.[10,12,17] The particular macronutrients responsible are simple sugars (e.g., glucose and fructose) and saturated fats. The ARC seems most susceptible to such damage if the repeated exposure occurs in childhood or adolescence. The consequence of it is that the overweight body habitus becomes normal as far as the brain is concerned, and subsequently reverting to a leaner set-point once can be very difficult.[10]

Indeed, once adult life has been entered the set-point tends to be relatively fixed, and difficult to change, though it does often drift upwards over the years, as illustrated by the well known phenomenon of middle-aged spread. However, although the set-point for body fat is not readily amenable to adjustment, there is evidence that it is not entirely immalleable either and certain interventions can push it downwards. Possible ways to do so include eating a diet rich in polyunsaturated fatty acids, or reducing long-term dietary intake of sugar and saturated fats, both of which are thought to facilitate the recovery of hypothalamic neurons.[17] Remarkably, it is also now believed that bariatric surgery actually works, at least in part, by lowering the set-point, rather than by simply decreasing caloric intake.[20] This is because people who undergo such operations do not continue to get thinner and thinner but rather reduce to a new body weight about which they then settle.

2.3. Summary

Although it is well known that there is a major, and increasing, public health problem with obesity, and the diseases associated with excess body fat, the crucial role played by the brain in the pathogenesis of this problem is far less appreciated. **Figure 1** illustrates the coordinating role played by the central melanocortin system in maintaining energy homeostasis and the various streams of information that it synchronizes to do so. Neural pathways that evolved to optimize energy homeostasis and favor a positive energy balance are, in conjunction with the high sugar and fat diets of the developed world, trapping individuals into a cycle of metabolic syndrome diseases that can be extremely difficult to escape.

3. The Effect of Vestibular Stimulation on Body Fat

By use of a centrifuge, researchers can produce what is, in effect, a gravitational field greater than that on the surface of the Earth (1G), a phenomenon referred to as "hypergravity."[21] Intriguingly, there is evidence that chronic exposure to hypergravity (i.e., over a period of weeks) causes a significant reduction in the body fat of a variety of animal species.[22–24] The pattern of change observed in body mass composition is described as a shift in "the proportional distribution of body mass between fat and fat-free components."[22] Hypergravity has been reported to reduce the body fat of the following species: mice[22,23,25,26]; rats[25,27–30]; hamsters[31]; rabbits[32]; chickens[33–36]; and other domestic fowl.[37] The observed reduction in body fat has been found to be proportional to the field strength,[23] and can be quite significant, as evinced by the observation that chickens decrease from 30 to 3% body fat when centrifuged at the equivalent of 3G.[38] The change appears to be mediated by an increase in both metabolic rate and metabolism of fatty acids.[39]

Although a decrease in fat is the most striking change in body composition, several authors have also noted corresponding, less marked, changes in the muscles and bones of animals subjected to chronic centrifugation. Changes reported include: an increase in the types of myosin heavy chain proteins associated with both sprinting and endurance activities[39]; a corresponding increase in exercise capacity and increased maximum oxygen uptake[36,38]; improved resistance to fatigue in the gastrocnemius muscle, manifesting an increase in the strength of its tetanic contraction[40]; and an increase in skeletal mass and bone mineral density.[21,41]

A variety of mechanisms have been mooted as explanations for this response to hypergravity. These include that they are due to a non-specific effect of centrifugation, increased loading of skeletal muscles, changes in intracranial pressure, and fluid volume shifts.[22–24] However, evidence has now emerged that they are in fact mediated by the vestibular system.[22–24] The vestibular system, located within the labyrinth of the inner ear, is a major contributor to the sense of balance. It consists of three semicircular canals (that detect rotational movement) and two otolith organs, named the utricle and saccule. The utricle detects acceleration and head tilts in the horizontal plane, and the saccule does the same in the vertical plane.[42] They are both fluid filled sacs containing numerous free moving calcium carbonate crystals called otoliths, which move under the influence of gravity or acceleration to act upon receptor cells to modulate vestibular nerve activity.

Experiments on mutant mice suggest that it is the otolith organs that play a key role in mediating the physiological changes observed in response to centrifugation. In one experiment, mutant mice (lacking otoliths but with normal semicircular canals) and wildtype mice were subjected to 8 weeks of chronic centrifugation at 2G.[23] At the end of this period the body fat percentage was significantly reduced in the wildtype mice living at 2G compared to wildtype controls living at 1G, and the percentage lean muscle mass was increased. However, the mutant mice living at 2G showed no significant difference in their body composition compared to those living at 1G.[23]

A second study involved subjecting both wildtype and mutant mice (lacking otolith organs) to just two hours of centrifugation at the equivalent of 2G.[24] The animals were then sacrificed and their brains stained, using immunohistochemical techniques, for upregulation of c-fos; a protein used as a marker of neuronal activity. In the wildtype mice increased neuronal activity was

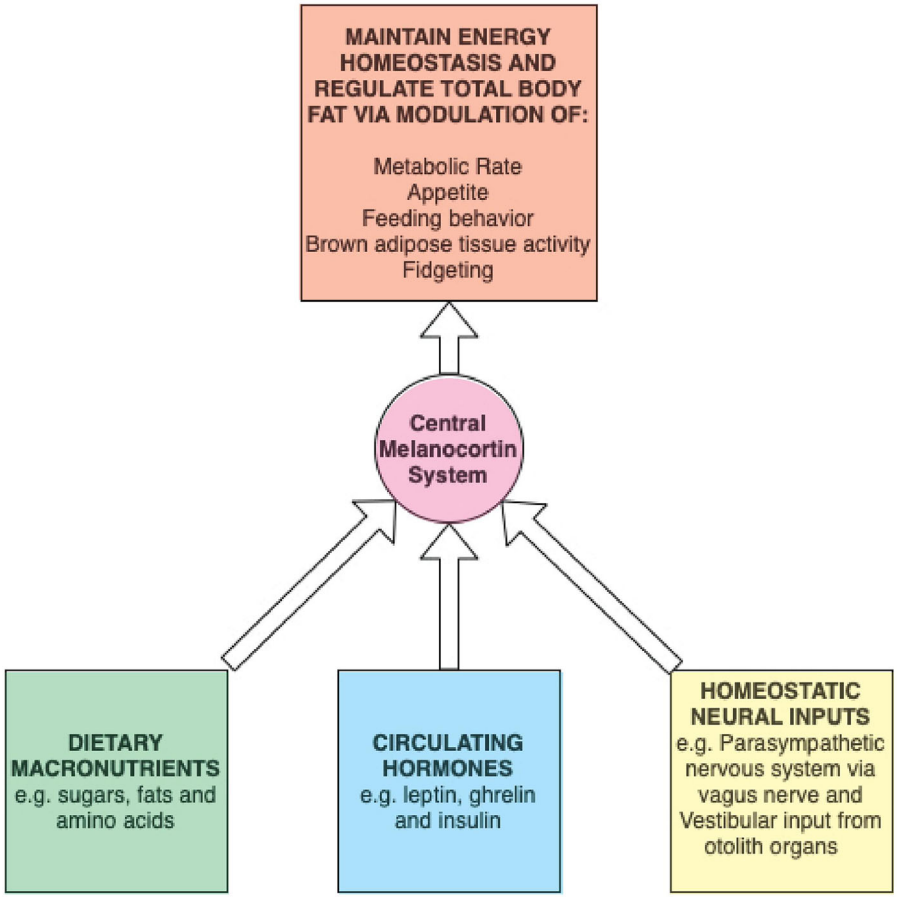

Figure 1. Coordinating role of the central melanocortin system in maintaining energy homeostasis and regulating total body fat.

seen in a variety of brain structures important in homeostasis including: the dorsomedial hypothalamus; the parabrachial nucleus; the amygdala; and, most notably, robustly in the ARC (the hypothalamic subnucleus involved in energy homeostasis and which sits at the heart of the central melanocortin system). Conversely, the mice without otolith organs did not show such activation. This led the authors to attribute the observed change in body fat from centrifugation to a vestibulo-hypothalamic pathway.[23,24]

In summary, there is extensive evidence across a variety of species that what is in effect hypergravity causes a marked reduction in body fat, and it now appears that this effect is mediated via afferent input from the otolith organs to the hypothalamus. This raises the tantalizing possibility that stimulation of the otolith organs in humans may offer a route to, in effect, re-equilibrate energy homeostasis, with the consequence of lowering the apparent set-point for body fat.

4. Can Activating the Otoliths Treat Obesity?

Given this possibility it would seem worth investigating whether stimulating the otolith organs in overweight humans could have a similar negative impact on body fat. Multiple techniques have been described as means of stimulating the otoliths, including: head-down rotation; linear acceleration in a sled; off-vertical axis rotation (OVAR); acoustic clicks; and galvanic vestibular stimulation (GVS).[43–45] This last technique, GVS, involves non-invasively stimulating the vestibular system by means of a small electrical current, and as such is both more practical than placing people in an apparatus to rotate or accelerate them, and more reliable than use of acoustic clicks.[44]

The technique of GVS has been known and used as a research tool for a long time. Indeed, Purkinje wrote about it in 1820,[43] and it is considered to have a good safety profile, with occasional mild headaches, dysequilibrium, or rarely, skin irritation being its reported side effects.[43,46] It is sometimes also called vestibular nerve stimulation, or VeNS. The stimulating electrodes can be placed on a variety of sites around the head, but typically a binaural application is used, which means that they are applied to the skin behind both ears and over the mastoid processes.

The current, typically in the range of 1 mA, can then be delivered as DC or AC, and in a variety of waveforms.[43–45] Although GVS is thought to activate, at least to some degree, all five components of the vestibular apparatus, lower currents (specifically under 3 mA) seem to particularly stimulate the otolith organs – that is, the part of the vestibular system that has been implicated in the hypergravity studies as mediating the reduction in body fat.[23,24,47] During a DC stimulation of

binaural GVS subjects report a sensation of sway towards the anodal side, and an AC delivery can produce, depending on the frequency, a sensation of back and forth sway that is analogous to being on a boat.[44,48]

Notably, it has been shown that levels of excess body fat are inversely proportional to sympathetic nervous system outflow, as measured by direct recordings of post-ganglionic muscle sympathetic nerve activity (MSNA).[49,50] This is relevant as AC binaural GVS has been found, when delivered with a low frequency (e.g., in a 0.5 or 0.2 Hz sinusoid) to entrain (synchronize) MSNA in line with the frequency.[51–55] The biggest effects have been observed at low frequencies distinct from the heart rate.[51–54] Moreover, when the user is sitting upright particularly strong bursts of MSNA become locked in phase with the frequency of the GVS, a phenomenon termed superentrainment.[55]

In summary, it is reasonable to hypothesize that repeated electrical stimulation of the otoliths via GVS would lead to a reduction in total body fat, and that this technique could thus be used as a potential treatment for individuals who are overweight or obese. Given the known inverse relationship between MSNA and body fat the best form of GVS to initially investigate is an AC binaural delivery with a waveform at a low frequency – for example a sinusoid or square wave at 0.5 Hz or less – and with a current under 3 mA, so as to preferentially stimulate the otoliths.[47,49–55] Also, repeated sessions of GVS might cause a corresponding increase in lean muscle mass and possibly in bone mineral density; an observation that, due to the bone and muscle loss that occurs during prolonged weightlessness, may be of relevance to astronauts.

5. Evaluating the Hypothesis

5.1. The Vestibular System's Role in Homeostasis

The observation that stimulation of the otolith organs causes a reduction in body fat seems to be rather odd and perplexing, at least when first encountered. Indeed, why should vestibular input have any role in determining body mass composition? In order to answer this question it is important to realize that the vestibular system, rather than just being a balance organ, also plays an important role in homeostasis, a fact likely rooted in its ancient evolutionary origin.[56]

This homeostatic function of the vestibular system is vividly illustrated when standing up from a sitting position. Doing so has the potential to cause blood to pool in the veins of the legs and thus postural hypotension, which can then lead to hypoperfusion of the brain and fainting. The traditional view is that baroreceptors in the vascular tree detect the change in pressure and act to correct it.[56] However, although baroreceptors do play a role, such a feedback system can act only in a reactive way to correct deviations after they have occurred. Conversely, any change in posture is also immediately registered by the vestibular system, which acts proactively in a feedforward manner, via the sympathetic nervous system, to cause vasoconstriction, and so maintain blood pressure within homeostatic norms.[56] In short, it is initially a vestibulo-sympathetic response that keeps us from passing out every time we stand up.

The role of the vestibular system in homeostasis extends well beyond maintaining cardiovascular stability. There is evidence that it can modulate the pattern of respiratory muscle activation to optimize blood oxygenation during movement, and vestibular stimulation has also been shown to have a range of effects on gut motility, and not merely those associated with motion sickness![56] It is interesting here to touch on the recent burgeoning interest in the role of the gut microbiome in obesity, and to register that there are clear interactions between the brain and the make-up of the microbiome. These include alterations in mucus production, immune function, intestinal permeability, and gut motility.[57] There is also a vestibular role in maintaining bone mineral density as damage to the vestibular system can cause a reduction in bone mineralization, an effect believed to be mediated by the sympathetic nervous system, and not attributable to decreased physical activity.[58,59]

5.2. Is there a Vestibular Role in Energy Homeostasis?

There is thus definite physiological evidence that the vestibular system plays an important wide-ranging role in homeostasis. The neuro-anatomical architecture that allows it to perform this role is established, and various brainstem homeostatic sites (including the parabrachial, dorsal raphe, and locus ceruleus) receive vestibular input.[56] However, four observations from mouse studies are of relevance to this paper, as they suggest a particular interplay with the melanocortin system, which as discussed regulates energy homeostasis. These are as follows: first, the observation that otolith stimulation appears to cause ARC activation[24]; second, the recent finding of melanortinergic neurons in the medial vestibular nucleus (MVe)[60]; third, an enzyme called prolyl carboxypeptidase that is important in the modulation of melanocortin signaling is expressed in both the MVe and the lateral vestibular nucleus[61]; and fourth, the MVe projects specifically to POMC neurons in the NTS, which as discussed are part of the melanocortin system.[15]

The role of the MVe here is noteworthy, as it is the main projection target of the utricle[62] (the otolith organ that detects acceleration on the horizontal), and centrifugation, as used in the animal experiments described above, delivers ongoing activation of the sensory cells in the utricle.[63] Also, retrograde tracer studies in hamsters have identified the MVe as one of the areas involved in the central control of the sympathetic nerves supplying both normal fat (properly termed white adipose tissue),[64] and brown adipose tissue (BAT),[65] which is a specialized type of fat that is rich in mitochondria, the intracellular organelles that generate energy. It is believed that activating BAT could act to reduce the total amount of white fat by metabolizing fatty acids, and thus have an anti-obesity potential, and moreover, improve insulin sensitivity, and thus ameliorate type 2 diabetes mellitus.[66] There are also definite but, as yet, anatomically less well delineated connections between the vestibular nuclei in the brainstem and the sympathetic nerves that innervate skeletal muscle and bone.[51,67]

This link between the MVe and the sympathetic innervation of BAT is particularly interesting as it suggests a possible route by

which the MVe could effect a change in metabolism. Such a mechanism would be in keeping with an indirect calorimetry (IC) experiment in which three adult volunteers underwent a one-hour session of binaural GVS (AC delivery at 0.6 mA with a 0.5 Hz square wave). IC is a technique that involves measuring oxygen consumption and carbon dioxide production, in order to provide data on various parameters, including metabolic substrate utilization.[68] In all three subjects the utilization of fat as a substrate increased during the GVS (by about 5 to 10%), and this effect was sustained with no decrement for at least 30 min after the 1-h stimulation period, which is when the IC was also discontinued (my unpublished data).

Given its described connections to the melanocortin system, and both sides of the ANS, the MVe does appear well placed to effect changes in body mass composition, but the question then arises as to why it should have any such effect? It seems reasonable to propose that the brain, in effect, interprets activation of the MVe (by horizontal movements stimulating the utricle) to indicate a state of increased activity. Homeostatically, if such a state were sustained, then it would be optimal, from an energy conservation point of view, to both liberate the energy reserves stored in fat, and to have a leaner, stronger physique in order to avoid wasting energy by carrying around excess fat during this physiologically challenging time. Moreover, stronger muscles and bones would be better able to cope during such a period. I suggest that the vestibular system is likely to effect these changes both via the modulation of behavior (i.e., altered dietary preferences and a reduction in appetite), and via an increase in metabolic rate, which is likely to be mediated via vestibulo-sympathetic activity, possibly involving BAT. As such, GVS could potentially act to improve compliance, and thus effectiveness, of a concurrent hypocaloric diet by reducing hunger.

5.3. Summary

It is well established that the vestibular system has a general role in the maintenance of homeostasis, and there are clear suggestions of various connections between MVe, the main projection target of the utricle, and the central melanocortin system. Repeatedly activating MVe is likely to be taken to indicate a state of ongoing movement, under which circumstance it makes sense from an energy homeostasis point of view to have a leaner, stronger body composition.

6. Testing the Hypothesis

6.1. Techniques for Measuring Body Fat

There are a number of ways of measuring total body fat that are reported to have a greater or lesser degree of accuracy. These include displacement techniques, such as underwater weighing and air plethysmography, caliper measurements, bioelectrical impedance, and dual energy X-ray absorptiometry (DXA).[69] A detailed consideration of the pros and cons of each of these is beyond the scope of this paper, however, the point is that body fat can be assessed, and the hypothesis can thus be tested. This is important as taking body weight alone as a measure could miss a reduction in fat if there has been a corresponding increase in muscle mass, as can be seen in resistance training.

Clearly the best way to test the hypothesis would be to carry out a double blind, randomized controlled clinical trial of overweight and obese individuals. They could have a baseline assessment of body fat, say using DXA since it also provides data on muscle mass and bone density.[69] The subjects would then undergo repeated sessions of GVS, or sham stimulation as a control, regularly for a period of time. The precise details of the treatment regime would need to be determined empirically as there is likely to be a dose response effect. However, I suggest that an hour a day for a period of 6 to 12 months would be good starting point, which would be in keeping with the duration of weight loss drug studies.[8] This falls within the definition of low intensity transcranial electrical stimulation (<4 mA, maximum of 1 h daily and electrodes between 1 and 100 cm^2), which animal studies and modeling suggest is not only safe but an order of magnitude below causing any damage.[70]

6.2. How to Optimally Test

It should be noted here that GVS is not a pure vestibular stimulus and, as such, there are certain confounders that would need to be controlled for as part of this trial, so as to demonstrate that any observed effect is truly a result of vestibular stimulation. These include the local effect of the electricity upon cutaneous nerves, which depending on current strength, might be perceived as a tingling, itching, or even painful sensation. As such, subjects should be encouraged to turn their device up to a level where they perceive a sensation, but not so high as to induce any pain.

In order to mitigate against the cutaneous side-effects of GVS it would be important to develop an appropriate type of sham device, which would cause the underlying skin to tingle without significantly stimulating the vestibular system. As GVS is in effect a specialized form of transcranial direct current stimulation (tDCS), in which electricity is delivered to various sites around the cranium so as to stimulate the underlying neural structures, the literature in this area provides insights on how to develop such a sham device.[71] It has been observed that the tingling or itching sensations perceived on the skin during tDCS typically last about 30 s or so before abating in perceptual salience.[72,73] Consequently, an appropriate type of sham device for use here is one that rapidly ramps up the stimulation for an equivalently short period of time before tapering off to stop over a comparable timeframe.

Moreover, as discussed MSNA has been directly linked to weight loss,[49,50] and given that the subjects will be naïve to GVS (i.e., they will not have experienced an active stimulation session), it would seem optimal for the sham to also transiently deliver vestibular stimulation, but with a frequency that has been shown not to significantly affect MSNA (e.g., 0.8 Hz).[52] This would have the benefit of controlling for the possible confounding factor that the subject may be expecting to experience some perception of movement, while simultaneously being unlikely to significantly alter MSNA. Such a sham device ought thus to provide an appropriate degree of verisimilitude as to keep the subjects blinded as to which device they have been

allocated. This could be confirmed by following the recommendation of the FDA that device trial subjects are asked to periodically, and privately, indicate whether they believe they have been allocated an active or sham device.

During the stimulation period diet and exercise would also have to be controlled between the two groups by giving both access to a standardized weight loss program, the mainstay of which would be a low-calorie diet. This is because such lifestyle changes are the standard of care for weight loss. Thus, any effect of GVS plus standard of care could then be assessed against sham device use and standard of care. As indicated above it is possible that GVS may act in synchrony with a low-calorie diet by reducing hunger and thus improving compliance. Body fat would then be assessed at the end of the study period using the same technique as at the beginning. Pertinent secondary endpoints would include questionnaires on quality of life and adverse events,[74,75] and serum markers of cardiovascular risk, such as lipid profile, high-sensitivity C-reactive protein, fasting glucose, and glycated hemoglobin.

An interesting question is whether any fat loss achieved through repeated sessions of GVS would be maintained after stopping the treatment, or if, as tends to happen on stopping weight loss drug therapy, it would at least return in part. In other words, would a newly established level of energy homeostasis be maintained or not after ceasing regular GVS? It does seem plausible that completely ending all GVS sessions would lead to a gradual rise in body fat, as the apparent period of physiological stress, as indicated by a state of recurrent movement, would be over. Ultimately, however, this is a question that can only be answered empirically.

Finally, it would be interesting to compare any observed reduction in body fat to GVS to response to a second form of otolith organ stimulation, such as OVAR or linear acceleration in a sled, as this would help improve the quality of the evidence for a vestibular cause. However, as these techniques involve the subject physically climbing into an apparatus their use is likely to be limited to the research laboratory. The effect of repeated sessions of GVS on the glycemic control of type 2 diabetics could be assessed in a similar manner by a trial with glycated hemoglobin as the primary endpoint.

7. Conclusions and Outlook

I propose that repeated sessions of GVS, over a period of weeks to months, will trigger the development of a leaner, lower fat, physique. And specifically that delivery of the current in an AC manner with a frequency lower than the heart rate is more likely to generate this effect. This eminently testable hypothesis would, if substantiated, constitute an entirely new, non-pharmacological, and non-invasive approach in the treatment of metabolic syndrome disorders.

There are currently two neuromodulation devices available for the treatment of obesity. Namely, the Maestro, which targets the vagus nerve (a major parasympathetic nerve),[76] and the Abiliti, which stimulates the nerves of the stomach wall.[77] However, unlike GVS, both these devices require surgical implantation and, because of the risks this entails, they are restricted, in the jurisdictions where approved, to only the most obese patients. There are also a variety of medications approved for the treatment of obesity, several of which, in a manner analogous to the proposed mechanism of action for GVS, target brain centers involved in energy homeostasis.[78] However, due to concern about side-effects they are also restricted in their use. Conversely, GVS, which has been safely used for a long time as a research tool, would have the potential to be used to treat a broader range of both overweight and obese patients.

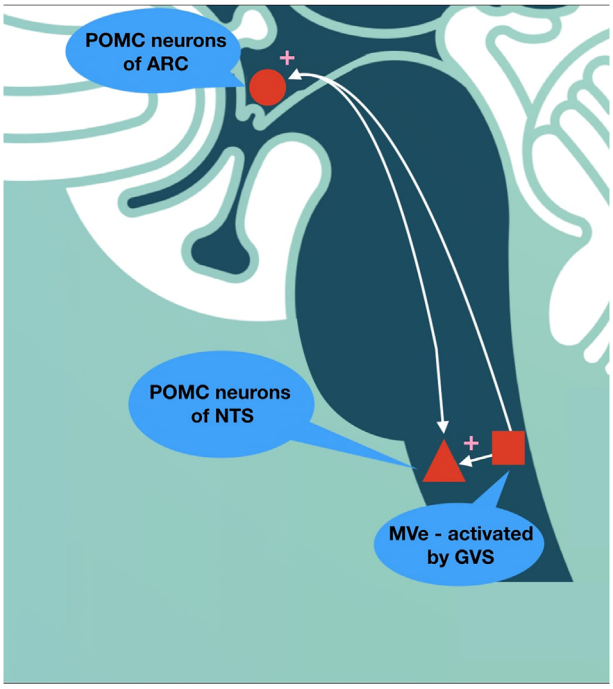

Figure 2. Sagittal schematic view of the brainstem and hypothalamus to illustrate the proposed interaction between the MVe and the POMC neurons of the ARC and NTS, which comprise the anorexigenic side of the central melanocortin system.

Traditionally discussions about how the human brain works have often been framed in terms of multiple, independently functioning modules, as illustrated by the idea, mentioned above, of biological thermostats in homeostasis. However, if the hypothesis presented here is confirmed, and repeated vestibular stimulation has a re-equilibrating effect on the regulation of energy homeostasis, then it would also support a more sophisticated view of brain organization, in which hierarchical systems (which likely evolved at different times), nonetheless interact dynamically to modulate one another's function.

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Conflict of Interest

Paul D. McGeoch is named as an inventor in a patent application filed by the University of California that relates to the ideas described above, and he is co-founder of a company called Neurovalens that aims to

commercially develop vestibular stimulation as a treatment modality for a range of conditions including obesity.

Keywords

central melanocortin system, energy homeostasis, metabolic syndrome, neuromodulation, obesity, vestibular, weight loss

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