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An Overview of the Effect of Exercise and Probiotics on Mood and Associated Health Conditions.

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Abstract

The current paper provides a review of the current knowledge on the health benefits of probiotics and the effect they may have on mood disorders. It also highlights the role of exercise as an alternative therapy for combating mood disorders. Depression is a substantial contributor to the global disease burden and therefore any alternative therapy must be considered. Probiotics influence the gut microbiota through a complex network of events which can influence mechanisms leading to development of mood disorders such as depression and anxiety. Similarly, through a complex interaction between psychological and neurobiological mechanisms, exercise has been found to play a key role in mood enhancement.

Keywords Probiotics, gut microbiota, chronic disease, exercise, obesity

Background

At birth, the sterile human gut is immediately colonised with several types of microorganisms from both the mother and the environment. This results in each individual developing a unique bacterial profile by the time they reach 12 months in age, forming the basis of their

adult gastrointestinal (GI) tract (Forsythe et al., 2010). The distinct microbiome of each individual is determined through interactions between sex, diet, immune status, infection, GI disorders, antibiotics and drugs with the adult human GI tract comprised of at least 160 different bacterial species from a pool 1000-1150 (Marik, 2012). Within the pool there are neutral and pathogenic bacteria species alongside probiotic bacteria which prevail in a healthy gut (Desbonnet et al., 2004; Messaoudi et al., 2011).

Probiotic – 'supporting or favouring life' (Lilly and Stillwell, 1965)

Probiotic bacteria are live microorganisms known as 'friendly' gut bacteria which when present and/or administered in adequate amounts can have potential health benefits to the host organism (WHO, 2001; van Baarlen et al., 2011; Bravo et al., 2012; Pyne et al., 2015).

The health benefits of 'probiotic bacteria' have been recognised for several hundred years (Jankovic et al., 2010), with the earliest record from 76 BC where Roman historian Plinio described how fermented milk could be used as a therapy for GI disturbances (Bottazzi, 1983). However it wasn't until the invention of the microscope that micro-organisms and bacteria were discovered. At the turn of the 20th century, Elie Metchnikoff suggested that fermented milk could suppress the growth of proteolytic bacteria and in turn reduce putrefaction in the gut and so prolong the lifespan of the host (Metchnikoff, 1907). Following this discovery, lactic acid bacteria and other bacteria began to be added to drugs used to treat diarrhoea and to food products to promote intestinal health and disease prevention (Jankovic et al., 2010).

Within contemporary society, probiotic bacteria are widely used for health promotion and health improvement (Ohashi and Ushida, 2009). Probiotic bacteria occur naturally within fermented food products such as yoghurt, sauerkraut, cabbage kimchee and soy bean based miso and natto (Nichols, 2007). However, food supplements generally in the form of

cultured dairy products are now widely available to consumers which have added probiotic bacteria. More recently 'probiotic shots' have been developed where probiotics can be consumed as a capsule. Contained within these food supplements there can be many strains of bacteria; however, the most common strains belong to the species *Lactobacilli and Bifidobacteria* (Benton et al., 2007), both of which are recognised for their health benefits on the human body. For example, both these strains of bacteria are known to be involved in essential physiological functions such as the stimulation of immune response, the prevention of pathogenic bacteria formation, the production of short chain fatty acids, metabolism of cancerogenic substances and the synthesis of vitamins such as B and K (Logan et al., 2003).

For bacteria to be classed as a probiotic, there are five essential criteria which have to be fulfilled. The current essential criteria are outlined by West et al., (2009) as:

1. Viability during processing, transport and storage.
2. Ability to survive gastric transport.
3. Ability to adhere to and colonise the GI tract.
4. Ability to antagonise pathogenic bacteria.
5. Demonstration of clinical health outcomes

It is, however, important to realise that these criteria are continually evolving, largely due to the increasing research within the field.

Health Benefits Of Probiotics

Overview

The proposed health benefits of probiotics are widespread. For example, West et al., (2014) found that probiotics could be used to reduce the risk of developing upper respiratory tract infections (URTI) in healthy young adults. However, the focus of the present paper will be

on the influence of probiotics on chronic inflammatory disease, chronic medical conditions and mood disorders. This is pertinent as there is substantial evidence supporting the co-morbidity of mood disorders and chronic medical conditions (Forsythe et al., 2010). This is evident in individuals with depression who also have high rates of obesity, hypertension, dyslipidaemia, metabolic syndrome and diabetes (Basu et al., 2004; Heiskanen et al., 2006). All the afore mentioned conditions are also linked to a lack of physical activity, which is again associated with the development of mood disorders (Stohle, 2009).

In 2015, the World Health Organisation estimated that globally 350 million people suffer from depression making it the leading cause of disability worldwide and so a substantial contributor to the global health burden (WHO, 2015). Furthermore, 63% (36 million) of all deaths worldwide in 2008 were due to non-communicable diseases, primarily, cardiovascular disease, diabetes, cancer and chronic respiratory disease (Alwan et al., 2010). With the prevalence of chronic medical conditions and mood disorders continually rising, it is essential that any potential adjunctive therapy, such as the use of probiotics and/or exercise prescription must be seriously considered.

Irritable Bowel Syndrome (IBS)

Approximately 30% of individuals with major depressive disorder have diagnosable IBS which is known to cause a reduction in intestinal *Lactobacilli* and *Bifidobacteria* (Logan and Katzman, 2005). It has been hypothesised that one factor leading to the rise of IBS in modern society is due to the decreased exposure to mud, animals and faeces, also known as the 'old friends hypothesis'. This has consequently led to a decrease in contact with microorganisms which play a vital role in developing immunoregulatory responses in humans (Rook et al., 2012). This is also known as the 'hygiene hypothesis' whereby the rise in chronic inflammatory disease such as IBS is hypothesised to be partly due to changes in the microbial

environment in developed countries i.e. the absence of 'good' bacteria which are normally able to supress the inflammatory response. Increased levels of inflammatory cytokines are common in various mental health conditions and can produce symptoms of anxiety and depression (Rao et al., 2009) with some risk factors including obesity, psychosocial stress, social isolation, sedentary lifestyle (Rook et al., 2012). Therefore, if probiotics are able to decrease inflammatory cytokines and so IBS symptoms in humans, it can be hypothesised that they could have a positive effect on mood (Logan et al., 2005).

Chronic Fatigue Syndrome

Chronic fatigue syndrome is a complex illness which is poorly understood. In addition to periods of persistent fatigue, approximately 50% of sufferers are affected by anxiety or major depressive disorder (Rao et al., 2009). Furthermore, many chronic fatigue syndrome patients have complaints of GI disturbances with over 50% diagnosed with IBS (Whitehead et al., 2002) and subsequently reduced levels of *Bifidobacteria* alongside elevated levels of aerobic bacteria such as *enterococci* (Logan et al., 2003). Therefore, if probiotics have a positive effect on mood disorders and IBS, there is the potential for them to be beneficial to sufferers of chronic fatigue syndrome.

Common Symptoms

Individuals who are affected by these various medical disorders like IBS, chronic fatigue syndrome and others such as fibromyalgia (a chronic disorder characterized by widespread musculoskeletal pain) and endometriosis (a disease in which tissue that normally grows inside the uterus grows outside it with symptoms of pelvic pain and infertility) are affected by a number of common symptoms including pain, fatigue, sleep, memory and mood issues. In particular individuals suffering from these disorders frequently have a migration of bacteria from the colon to the small intestine causing a small intestinal bacterial overgrowth which is

associated with greater levels of somatic pain (Pimental et al., 2004). Pain and discomfort is regularly associated with symptoms of depression. Although small intestinal bacterial overgrowth has not been investigated in those with major depressive disorder, Logan and Katzman (2005) have hypothesised that it is likely to occur in these individuals due to low levels of stomach acid which can lead to small intestinal bacterial overgrowth. In this situation probiotics are a potential treatment, which may have a consequential positive effect on mood (Gaon et al., 2002).

Probiotics And The Microbiota

The various inflammatory and metabolic disorders described above may be a result of dysbiosis i.e. disruption in the interactions between microbes and the host (Hermarajata and Versalovic, 2012). Probiotics may be able to partially restore the host's microbiota through various mechanisms. Bravo et al., (2012) have provided an overview of the mechanisms by which probiotics are thought to work. The network of events outlined include:

- Displacement of pathogens
- Competition of metabolic interactions with hostile bacteria
- Production of bacteriocins (proteinaceous toxins produced by bacteria to inhibit the growth of similar or closely related bacterial strains)
- Inhibition of bacterial translocation
- Enhancement of mucosal barrier function
- Effects on calcium dependant potassium channels in intestinal sensory neurons
- Induction of opioid and cannabinoid receptors in intestinal epithelial cells
- Modulation of the immune system through signals on epithelial cells and gut-associated lymphoid tissue

Probiotic bacteria are able to displace pathogens through the production of antimicrobial agents which supress the growth of other microorganisms (O'Shea et al., 2011) or through competing with other microbes on the intestinal mucosa for binding sites and receptors (Collado et al., 2007). Enhancement of mucosal barrier function may result in improved immune function; for example, *Lactobacillus* has been found to improve barrier function due to decreased translocation of bacteria across the mucosa and disease phenotypes such as IBS (Lee and Bak, 2011). However, further studies on humans are needed to enhance our understanding of the processes involved in disease phenotypes such as IBS.

Mechanisms By Which Probiotics May Influence Mood

Probiotic bacteria work through a very complex network of events, with compelling evidence to suggest that there is involvement of both anatomical connections such as the vagus nerve and humoral components such as the immune system and hypothalamus-pituitary-adrenal (HPA) axis (Bravo et al., 2012).

When activated the HPA axis releases corticotrophin-releasing factor from the hypothalamus, adrenocorticotrophic hormone (ACTH) from the pituitary and cortisol from the adrenal glands (Cryan and Dinan, 2012). Evident suggests a contributing factor linked to both depression and stress is an impaired HPA system (Belmaker and Agam, 2008). When the role of the HPA axis in stress was investigated in mice by Sudo et al., (2004) who found that restraint stress in germ-free mice caused an inflated rise in ACTH and corticosterone; however, this response was able to reversed by *Bifidobacteria infantis*.

The vagus nerve plays a key role in modulation and communication between bacteria, gut and brain, also known as the microbiota-gut-brain axis (Desbonnet et al., 2009). This axis allows bidirectional communication whereby the brain can functionally affect the gut and the gut can mediate changes in the central nervous system (CNS) (Mayer et al., 2006). Any

dysfunction or alteration of the axis can have pathophysiological effects (Cryan and Dina, 2012) which may be involved in modulating various factors including pain perception, emotion and general well-being (Rhee et al., 2009). Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS and is involved in regulating many physiological and psychological processes where any alterations in GABA receptor expression can result in symptoms of depression or anxiety (Bravo et al., 2012).

The importance of the vagus nerve in communicating changes in the GI to the CNS has been shown in rodents whose vagus nerve was cut. A strain of probiotic, *L. rhamnosus (JB.1)*, was found to reduce stress-induced elevation in corticosterone; however, these effects were not evident in the vagotomised mice (Bravo et al., 2012). This provides further evidence to support the use probiotics as a therapeutic alternative to reduce mood disorders such as stress, anxiety and depression. It is important to note that this is a brief overview of the mechanisms involved; however, within the literature the various mechanisms and pathways are discussed in greater detail e.g. Bravo et al., (2012).

The Effect Of Probiotics On Mood Disorders

In recent years there has been a substantial increase in the number of studies investigating the effects of probiotics on various mood disorders. However, the idea that probiotics may improve certain mental health disorders is not a novel concept but rather one which has been recognised for several decades. For example, in 1910 it was reported that live lactic acid bacteria improved symptoms of depression in adults with melancholia (Philips, 1910). A selection of more recent work relating to probiotics and mood disorders are outlined below. The reader should be aware that a number of the more invasive studies have, to date, only been carried on in animals, therefore the applicability to humans needs to be taken into consideration.

Human Studies

As outlined previously, there is an established link between chronic constipation and mood scores, therefore, Benton et al., (2001) investigated the impact of consuming a probiotic on mood and cognition. Results suggested that more frequent constipation was associated with a poorer mood state, in addition to, an inverse association between constipation and feelings of calmness, elatedness and agreeableness. However, the correlational nature of data prevented the conclusion of a causal relationship between constipation and mood state. Due to the continual speculation that probiotics may be a valuable adjuvant therapy for those with major depressive disorder in a more recent study, the same group of authors (Benton et al., 2007) investigated the effect of a fermented milk drink containing *Lactobacillus casei* probiotic bacteria (Yakult) on mood and cognition. Again it was suggested that reduced constipation may play a role in improving mood disorders. However, daily ingestion of the probiotic, for a period of three weeks, failed to show any improvement in mood or an increase in the number of motions passed. The authors suggested that the lack of improvements may be related to the participants having a 'good' baseline mood with low levels of constipation.

There are however, a number of studies which have found a significant improvement in mood disorders with the consumptions of probiotics. A six month study investigating the effects of a probiotic multivitamin compound on adults suffering from stress or exhaustion was conducted by Gruennwald et al., (2002). The overall conclusion to emerge from the study was that the multivitamin compound significantly improved the general condition of those who participated in the study. The authors found a 41% improvement in stress alongside a decrease of 29% in the prevalence of infection and 91% reduction in GI discomfort, both of which are indicators of stress. An intervention study investigating the effects of a lactic acid probiotic in patients with chronic fatigue syndrome and associated depression and anxiety was carried out by Rao and colleagues (2009). The intervention group consumed a probiotic

containing a strain of *Lactobacillus* three times per day. Following an eight week trial, compared to the placebo group, the treatment group were found to have a significant improvement in anxiety scores alongside an increase in faecal *Bifidobacteria* and *Lactobacillus* (73.7% and 73.7%), the changes in depression scores were not found to be significant.

Recently, Steenbergen et al., (2015) investigated the effect of a multispecies probiotic on cognitive reactivity to sad mood. The participants in this study were not diagnosed with having a mood disorder, however, compared to the control group it was found that those who consumed the probiotic over a four week period significantly reduced their cognitive reactivity to sad mood. This is important due to the risk of sad mood developing into clinical depression.

Although, there are limited human studies which have investigated the use of probiotics in the treatment of mood disorders, the current evidence suggests that it would be naïve to rule out the use of probiotics as an adjunctive therapy (Foster and McVey Nuefeld, 2013).

Animal Studies

The psychotropic properties of a probiotic formulation has been assessed in both rats and humans by Messaoudi et al., (2011). The main finding to emerge from this study was that consumption of the probiotic formula containing a combination of *L. helveticus R0052 and B. Longum R0175* mitigated psychological distress in three tests without displaying any adverse events. In humans, the formula was taken for 30 days and resulted in significant improvements on scales used to measure depression, anxiety and hostility. Within the paper it is suggested that the effects of probiotics on anxiety and depression may be due to competitive exclusion of detrimental gut pathogens, decreases in pro-inflammatory cytokines

and communication with the CNS via vagal sensory fibres, leading to changes in neurotransmitter levels or function.

The potential antidepressant properties of *Bifidobacteria infantis* in the rat were investigated by Desbonnet and colleagues (2009) and it was found that chronic administration of the probiotic protected the rats from depressive symptoms caused by stress induced through maternal separation. The results of this study suggested that probiotics may be a suitable alternative to tryptophan supplement as a therapy for depression, although the authors highlight that these findings are preliminary and further investigation would be required to establish precise mechanisms.

Alternatively, administering a pathogenic bacteria to healthy mice has been shown to stimulate anxiety behaviours within hours of infection suggesting that changes in the gut microbiota can very quickly induce biochemical changes in the CNS (Lyte et al., 2006; Goehler et al., 2008). This highlights that altering the gut microbiota can have an effect on animal behaviour and so providing further evidence for the existence of the microbiota-gut-brain-axis (Bravo et al., 2012).

Although not conclusive, both animal and human studies, present a significant claim for the use of probiotics as an alternative treatment, particularly in those individuals with pre-existing mood disorders.

The Effect Of Exercise On Mood Disorders And Chronic Medical Conditions

There is a well-established link between physical inactivity and the risk of various non-communicable diseases which coincides with an increased prevalence of mood disorders. Both epidemiological and clinical studies have shown there to be a correlation between

physical activity levels and prevalence of mood disorders, with physical activity generally having a positive effect on mood (Ströhle, 2009).

There are several studies where this link between physical activity and depression is evident; for example, a longitudinal study by Paffenbarger et al., (1994) found physical activity levels in men to be negatively correlated with depression 25 years later. This is similar to the findings of Motl et al., (2004) who found natural changing levels of physical activity in adolescents was inversely related to depressive symptoms.

Over the last 10-15 years there has been an increase in the number of controlled trials investigating the effects of prescribed exercise as a therapy for depression and other mood disorders. Dunn et al., (2005) investigated the effects of various aerobic exercise protocols on mild to moderate major depressive disorder in 20-45 year olds. The authors were able to conclude that exercise prescribed in a dosage aligned with public health recommendations was an effective treatment for mild to moderate symptoms of major depressive disorder and that greater energy expenditure is associated with larger decreases in symptoms of depression. Furthermore Blumenthal et al., (1999) was able to conclude that an exercise training programme for older adults with major depression was as effective as administering an antidepressant treatment and had a lower relapse rates.

Additional support for the role of exercise in mood enhancement comes from a study where participants attended a regular exercise class for three months. It was found that improvements in mood were significantly greater in those individuals who had reported symptoms of depression prior to beginning the exercise programme (Lane and Lovejoy, 2001).

Although there is a well-established association between exercise and mood enhancement, the physiological mechanisms underlying the relationship between mood and exercise are

poorly understood. However, it is likely that the mechanisms for exercise induced improvements in mood disorders is a complex interaction between psychological and neurobiological mechanisms (Strohle, 2009). Typically, exercise decreases inflammation which in turn reduces the activity and expression of the enzyme indoleamine 2,3-dioxygenase, which degrades tryptophan (an essential amino acid needed for the production of serotonin) (Gostner et al., 2015). This therefore allows for an increase in tryptophan which when transported to the brain can increase the production of 5-hydroxytryptomin which can subsequently lead to an increase in mood state (Strasser et al., 2015).

In an attempt to gain a greater understanding of the relationship between mood and exercise, Poole et al., (2011) investigated the effects of exercise withdrawal on mood and inflammatory cytokine response. Two weeks of exercise withdrawal in healthy participants resulted in significant increases in negative mood which was significantly related to a decrease in circulating interleukin (IL)-6 (inflammatory marker), indicating that inflammatory pathways do play a role in the development of mood disorders.

Even if exercise was found not to enhance mood, it should always be recommended whether to combat the various chronic medical conditions previously mentioned or simply to maintain a healthy lifestyle and prevent disease.

Gut Microbiota, Obesity And Diet

There is considerable evidence which has emerged from obesity studies highlighting the link between diet, obesity and a 'healthy gut microbiota'. Obesity is a worldwide epidemic in both adults and children and is a major health concern within society. It can be largely attributed to an unhealthy lifestyle consisting of an abundance of energy dense food and physical inactivity; however, there is now compelling evidence suggesting that there are differences in the gut microbiota of obese and lean individuals. This brings to light the

possibility that the development of obesity and other metabolic diseases may be influenced in some way by the gut microbiota (Marik, 2012; Serino et al., 2012). It also is interesting to note that there has been a correlation found between diet and the prevalence of specific bacteria groups; for example, a diet high in inulin and related fibres has been shown to increase *Bifidobacteria* (Marik, 2012). This suggests that diet can change both the composition and activity of the microbiota and thereby possibly having a positive impact on mood disorders.

Backhed et al., (2004) investigated the role of the gut microbiota in the regulation of fat storage in mice. The authors found the germ-free mice had 40% less body fat compared to conventionally reared mice; this was despite the germ-free mice consuming more food. However, when the microbiota was harvested from the distal intestine of the normal mice and transplanted into the germ-free mice, this resulted in a 60% increase in body fat content within two weeks. From the results, it was proposed that the microbiota promotes monosaccharide absorption resulting in *de novo* hepatic lipogenesis (conversion of surplus energy to fat in the liver). It was concluded that the gut microbiota is an important environmental factor which can affect energy storage of the host organism.

The role of the gut microbiota in the development of obesity in humans has been demonstrated by Kalliomaki et al., (2008). Investigation of the faecal matter of children revealed that *Bifidobacteria* content was higher in children of a normal weight than those who were showing signs of becoming overweight. This gives rise to the possibility that consumption *Bifidobacteria* to manipulate the gut microbiota may have a positive effect on weight control in humans.

On consideration of the preceding evidence it can be suggested that the gut microbiota may influence metabolism, consequently impacting energy storage which may be linked to the

development of chronic medical conditions such as type II diabetes and obesity, where there is significant evidence for co-morbidity with mood disorders (Turnbaugh et al., 2006).

Conclusion.

In summary, it seems reasonable to advocate the use of probiotics as an alternative therapy in the treatment of neuropathological disorders as an alternative or in addition to traditional therapies. However, it is important to realise the various strains of probiotics elicit different effects and may not have the same effect on everyone. It is possible that, in general, probiotics may be more beneficial for older adults who have less 'good' bacteria in their gut (Tiwari et al., 2012).

In terms of both psychological and physiological health maintenance it is recommended for individuals to exercise regularly, eat a balanced diet high in fibre and possibly supplement with probiotics containing strains of *Lactobacilli and Bifidobacteria*.

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