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Review

Mind–body medicine: Effect of the mind on gene expression

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ABSTRACT

Purpose: Positive emotions via laughter or meditation contribute to physiological and psychological health. In this review, we summarize how positive emotions affect gene expression in humans and an animal model.

Study selection and results: Our first studies demonstrated that mirthful laughter reduced a postprandial elevation in blood glucose levels in type II diabetes patients and increased the expression of genes related to natural killer cell activity. Furthermore, laughter decreased the plasma prorenin level, a marker for the progression of diabetic complications, and normalized the expression level of the prorenin receptor gene in peripheral blood leukocytes. These findings suggest a preventive effect of laughter on the exacerbation of diabetic conditions, which is accompanied by changes in the expression of discriminating genes.

Our next study examined the effects of tactile stimulation (tickling) on socially isolated adolescent rats. Evoking positive emotions by tickling influenced neurogenesis in the dentate gyrus of the hippocampus and altered the expression of genes related to feeding regulation, blood pressure control, and biological rhythms in the corpus striatum and hypothalamus. Thus, positive emotions via tickling can regulate gene expression in the rat brain in a site-specific manner.

Lastly, we review the relevant research of other groups. Meditation, a widely known healing technique, altered the expression of genes associated with cellular metabolism and oxidative stress responses, suggesting the inhibition of cell injury due to chronic stress.

Conclusions: Mind–body medicine potentially elicits positive emotions affecting gene expression.

1. Introduction

Western medicine, also called conventional medicine or mainstream medicine, is based on the philosophy that the body consists of individual parts such as organs, tissues, cells, and molecules, and that the mind is separated from the body. Western medicine differs from holistic medicine, which considers diseases local events. Conventional medical treatments, including drugs, radiation, surgery, and physical manipulation, have evolved with the development of scientific technologies. The completion of the human genome in 2003 has been described as a 'quantum leap'. Applying genomic information to the new concept of personalized medicine is expected to reap new benefits. However, genes provide only a basic outline for development. Diseases involve much more complicated mechanisms than genetic programming, and the actual causes of many diseases are still unknown. Furthermore, the questions of what makes us unique individuals and what "life" is have not been answered from a medical point of view.

Attention should now be focused on the connection between the mind and the body. A broad range of healing therapies that emphasize mind–body interaction and that are based on historical or cultural traditions have been practiced for a long time. In the 21st century, the combination of healing therapies and conventional medical treatments, a combination termed "integrative medicine," is expected to be championed to support the holistic health of individuals.

How does the mind interact with the body? Fortunately, the genome-sequencing project has brought a new insight into the understanding of gene function. The sequencing of the genome of chimpanzees, man's closest living relatives, revealed that there is only a 3.9% difference between the genomes of humans and chimpanzees. This difference is very small given that the human genome is 3.2 billion base pairs. Furthermore, despite our differences, the inter-individual genetic variation has been estimated to only 0.5%. Pääbo mentioned that the genomes of mammals are so

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similar that it is difficult to understand how similar genetic material can generate so many different living creatures [1]. We used to think that differences in gene and protein sequences defined humanity and individuality, but genome mapping revealed that the timing of gene expression and the site in the body where genes express are also important, and the regulation of on/off switches are crucial in the course of evolution and development [2,3]. It is now clear that genes possess on/off switches. These switches are not permanently fixed but can be changed by exposure to environmental factors [4].

A wide variety of environmental factors is considered to turn genes on or off. In addition to physical factors (e.g., heat, pressure, tension, training, and exercise) and chemical factors (e.g., foods, nutrients, alcohol, smoking, environmental hormones), mental factors are now being considered. Many reports have demonstrated the unfavorable gene expression effects due to negative emotional stressors, including shock, anxiety, fear, anger, and resentment [5]. In contrast, little attention has been given to positive emotional factors, such as deep emotion, excitement, joy, thankfulness, affection, belief, and prayer. In 2002, we proposed the hypothesis that "the mind and genes mutually influence each other" [5] and have been engaged in elucidating how the mental status affects gene function. The present review describes our recent approaches focusing on positive emotions (via laughter and tickling) and discusses meditation, a popular healing technique mainly in the U.S., along with recent scientific findings, demonstrating the effect of the mind on genes.

2. Laughter regulates gene expression

Laughter is the most common expression of humorous experience and typically induces a positive emotional state. Increasing evidence suggests that laughter is beneficial to human health. The first academic study of laughter was published in 1976 by Cousins, an American journalist, who conquered his own ankylosing spondylitis by using laughter as a therapeutic strategy [6]. Later studies on the physiological effects of laughter mainly focused on various immunological activities. Berk *et al.* reported that laughter increases the activity of natural killer (NK) cells and normalizes the blood levels of neuroendocrine factors associated with negative emotions, suggesting that laughter has stress-moderating effects [7,8]. Numerous attempts have been made by medical researchers to demonstrate the therapeutic value of laughter in the prevention and treatment of illness [9]. Our genetic studies provide an important opportunity to advance our understanding of the molecular mechanisms of the effects of laughter.

2.1. Studies in humans

Negative emotions such as irritability, anxiety, fear, and sorrow aggravate hyperglycemia in diabetes patients [10]. Conversely, positive emotions such as laughter may improve blood glucose levels in diabetes patients because of their stress-moderating effects [7,8]. To verify this hypothesis, we examined the effect of laughter, elicited by a comedy show, in patients with type II diabetes. Indeed, mirthful laughter reduced the postprandial elevation in the blood glucose level [11], and our report was the first to scientifically document the effect of laughter in diabetes patients.

We then assessed peripheral blood leukocyte transcriptional profiles using microarrays, a comprehensive analytical tool to monitor gene expression. In diabetes patients, laughter altered the expression of genes involved in immune reactions, cell signaling, the cell cycle, apoptosis, and cell adhesion [12]. However, the genes directly related to blood glucose metabolism were not affected, suggesting the presence of a novel mechanism regulated by laughter. Notably, of all the laughter-affected genes, those related to NK-cell activity were upregulated, and the resulting increased NK-cell activity persisted 1.5 and 4 h after the laughter intervention [13,14]. Elinav *et al.* reported that NK-cells are involved in controlling glucose metabolism in a diabetes mouse model [15]. These findings suggest that laughter may contribute to the amelioration of glucose intolerance via increased NK-cell activity due to the upregulation of genes related to NK-cell activity.

Interestingly, laughter can modulate the parameters of the renin–angiotensin system (RAS) in diabetes patients [16]. RAS has a central role in the regulation of blood pressure. It has been reported that RAS is also closely related to the development of diabetes. The most striking abnormalities of RAS in the blood of animals with diabetes are the decreased renin level and the increased prorenin level [17]. High plasma prorenin levels serve as an effective marker of diabetic microvascular complications [18]; however, the link between the renin and prorenin levels remains unclear.

In our studies on diabetes, before the laughter intervention, the blood levels of prorenin were higher in diabetes patients without nephropathy (93.4 ng/l), and even higher in those with nephropathy (196.6 ng/l), than in normal healthy subjects (32.5 ng/l). After the laughter intervention, the plasma prorenin levels were significantly decreased in both diabetes groups (60.4 ng/l in the non-nephropathy patients, 166.7 ng/l in the nephropathy patients) [16]. These findings suggest that laughter may inhibit the onset or advancement of diabetic complications by reducing the levels of circulating prorenin. Microarray analysis provided one possible approach to clarify the mechanism underlying this effect. In peripheral blood leukocytes, the expression level of the prorenin receptor gene was subnormal in diabetes patients before the laughter intervention and normal after the laughter intervention [16]. Our findings suggest that laughter can benefit by normalizing the expression level of the prorenin receptor gene in leukocytes and subsequently reduce the plasma prorenin levels in diabetes patients. Thus, we speculate that the leukocyte prorenin receptor plays a role in the clearance of circulating prorenin, thereby modulating plasma prorenin concentrations in diabetes patients (Fig. 1(A) and (B)). However, more work is needed to determine whether the prorenin receptor in leukocytes functionally binds to circulating prorenin. A recent report suggested that human T and NK-cells have a functional RAS at the cellular level, based on the expression of all RAS components [19]. Very recently, several studies demonstrated the presence of a soluble form of the prorenin receptor in plasma [20,21]. Further investigations are expected to reveal the physiological function of the prorenin receptor in leukocyte subsets.

The prorenin receptor was first identified in the human kidney in 2002 and is distributed in the mesangium and podocytes. Studies performed using animal models of diabetes well documented the pivotal role of prorenin and the local prorenin receptor in the pathophysiology of diabetic nephropathy. The binding of prorenin to the prorenin receptor triggers two major pathways: an angiotensin II-dependent pathway resulting from the conversion of prorenin to its active form through a conformational change, and an angiotensin II-independent, prorenin receptor-dependent intracellular mitogen-activated protein kinase pathway (Fig. 1(A)). The administration of a "handle-region" peptide, which competitively inhibits the binding of prorenin to its receptor, has beneficial effect in the kidneys of animals with diabetes [22,23]. Aliskiren, the first direct renin inhibitor, binds to the active site of prorenin and reduces prorenin receptor gene expression in the kidneys, resulting in renoprotection in rats with diabetes [24–26]. Consequently, renin, prorenin, and the prorenin receptor may be important therapeutic targets for the prevention and regression of diabetic nephropathy.