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Review Article

Music and Dopamine – Potential in Movement Disorders

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ABSTRACT

Most people have been deriving pleasure from music since long ago. Music is deeply associated with human communication and language. Music had also been popular as therapy in early history. How can we feel happiness or sadness when we listen to music? Scientifically, the dorsal and ventral striatum release dopamine when listening to pleasurable music. The activity in these structures is known to associate with the reward system of the human brain. Moreover, the nigrostriatal dopaminergic system regulates our motor function, and this is the very part that is damaged in the movement disorders. In this article, we review the potent role of music from the viewpoint of the dopaminergic system. We also describe the molecular mechanism of the dopaminergic pathogenesis and suggest the potent ability of music for the therapy of Parkinson's disease and related movement disorders.

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History of Music and Humanity

Most people have been deriving pleasure from music since long ago. Music is deeply associated with human communication and language [1]. Music had also been popular as therapy in early history [2]. In general, one may conclude that music was frequently employed as a part of magical rituals to control the unpredictable and unexplainable forces of nature, to calm or satisfy metaphysical forces, such as gods or demons, and to combat disease and death. In early history, as still in evidence in preliterate societies, these three realms of control of nature, control or entreaties of supernatural forces, and control of life and health, must have been highly interwoven. In this context, Nettl refers to the importance of the physical response, in addition to the emotional response, to music by the human organism [3]. Not only does the sound production create a physical behavior and general bodily attitude specific to the desired sound, but the structures within the music could also create specific physical responses.

Music and Clinical Effects

Some Ancient Greeks considered music as therapeutic in more direct ways – reflecting and projecting the harmony of the cosmos onto the mind and thus creating or reestablishing inner harmony. This process was considered not only valuable as therapy, but also for educational purposes to strengthen character and virtue. The Aristotelians added a new emphasis, explicitly introducing the therapeutic function of affective “catharsis” induced by music to relieve the mind from negative emotions. We also know from the writings of the physician Asclepiades about specific “clinical” prescriptions of music therapy for the treatment of mental disorders [2].

Music therapy has the unique ability to promote neuroplasticity through the increase of dopamine production, the synchrony of neural firing, and the production of a clear signal. Much of what is taught and inherently known in music therapy has roots in neuroplasticity. Music therapists are taught to pair non-music tasks/behavior with music. This in itself is a

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basic principle of neuroplasticity, but now there is more research supporting music as a rich neuroplasticity tool. What makes music therapy work, though, is the ability of music therapists to know how to use/manipulate music to shape the neural responses that underlie client/patient behavior [4].

Music and Dopaminergic Functions

How can we feel happiness or sadness when we listen to music? Scientifically, the dorsal and ventral striatum release dopamine when listening to pleasurable music. The activity in these structures is known to associate with the reward system of the human brain. Moreover, the striatum interacts with cortical mechanisms involved in the perception and valuation of musical stimuli. In detail, listening to music stimulates the nigrostriatal dopaminergic system, as well as the nucleus accumbens and ventral tegmental area in the mesolimbic pathway [5-10]. Additionally, listening to pleasurable music facilitates neuroplasticity, as well as movement, breathing, and heart rate, indicating the immense potential of music in the therapy for dementia and movement disorders, including Alzheimer's disease and Parkinson's disease [11-14].

Regulation of Dopamine Biosynthesis

Dopamine is biosynthesized from L-tyrosine by tyrosine hydroxylase (TH) and aromatic amino acid decarboxylase (AADC) [15, 16]. TH is responsible for catalyzing the conversion of the amino acid L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), and subsequently, L-DOPA is converted to dopamine by AADC. Tetrahydrobiopterin (BH4), which is biosynthesized by GTP cyclohydrolase I (GTPCHI), is required for the enzymatic activity of TH. Unlike other enzymes, the TH protein has its enzymatic activity strictly controlled at the rate-limiting step of dopamine biosynthesis [17, 18]. TH expression level and activity are directly involved in regulating intracellular dopamine levels. The activity of TH can be modulated by two mechanisms: medium- to long-term regulation of gene expression, for example by the effect on enzyme stability, transcription, RNA stability, alternative RNA splicing, and translation; and short-term regulation of enzyme activity, for example by feedback inhibition, allosteric regulation, and phosphorylation. Regulation of TH expression is dependent on a cAMP-dependent responsive element (CRE), AP-1, ATF-2, and Nurr1 [18-22].

Molecular Mechanism of Dopaminergic Pathogenesis

The reduction of the nigrostriatal TH protein level is a pathological feature of Parkinson's disease. Contrary to the decrease in the protein level, TH activity from parkinsonian tissue was reportedly increased by 48% compared to controls, or activity per enzyme protein of TH in the parkinsonian nigrostriatal region was elevated by 3-4-fold [23, 24]. The increased activity of residual TH in the parkinsonian brain suggests the facilitation of TH phosphorylation as a result of a compensatory increase in TH activity to compensate for the loss of dopamine caused by the disease [25]. In fact, we previously reported that dopamine or biopterin deficiency potentiates TH phosphorylation [26]. It is noteworthy that the potentiated TH phosphorylation is accompanied by degradation of TH protein by the ubiquitin-proteasome system [26, 27]. This mechanism suggests the possibility that the dysfunction of dopamine biosynthesis in dopamine-related disorders such as Parkinson's disease and dopa-

responsive dystonia leads to the induction of TH phosphorylation, which is accompanied by a reduced total TH protein level induced by degradation via the ubiquitin-proteasome system.

Consistently, phosphorylation of the N-terminal portion of TH reportedly triggers proteasomal digestion of the enzyme [28]. Phosphorylated TH also easily aggregates to form intracellular inclusions by proteasomal inhibition [27]. The activity of proteasome is reduced in Parkinson's disease [29, 30]. These phenomena support a putative mechanism in which elevation of TH phosphorylation to prevent a lack of dopamine in Parkinson's disease leads to the formation of intracellular aggregates of TH protein. Indeed, Lewy bodies are phosphorylated TH-immunopositive in the brains of patients with Parkinson's disease [31]. These data suggest that phosphorylated TH is vulnerable and that the dopamine-deficient state in Parkinson's disease and related disorders may accelerate the decrease in TH protein level through the degradation or accumulation-induced aggregation of phosphorylated TH.

Advances in Therapies for Parkinson's Disease

Fundamental therapies for Parkinson's disease are not yet well established. Almost half a century after it was first introduced, L-DOPA ($C_9H_{11}NO_4$) is still the most effective medication available for the palliative treatment of the motor symptoms in Parkinson's disease [32, 33]. Recent progress of treatment technique for Parkinson's disease is remarkable; deep brain stimulation is efficacious in the treatment of parkinsonian tremor, striatal injection of AADC-coding vectors stably restore the response to L-DOPA and contribute to a decrease of the effective L-DOPA dose, and stem cell transplantation therapies may effectively restore and replace cells in the damaged tissues [34-36]. Interestingly, music therapy is popular in medical care for Parkinson's disease, as well as pharmacotherapeutic development to potentiate dopamine biosynthesis, and the combination [37-41]. In fact, listening to music reportedly facilitates dopaminergic neurotransmission in a calcium/calmodulin-dependent manner [42, 43]. This phenomenon suggests the potential mechanism to facilitate CRE-mediated TH gene expression by the activation of calcium/calmodulin-dependent kinase II [44]. These reports mentioned above raise the expectations for fundamental therapeutics and the benefits of music in neurodegenerative disorders.

Future of Music and Dopaminergic Disorders

Parkinson's disease and related disorders are currently difficult to fundamentally cure. However, although fundamental therapies have not been established, the development of novel therapeutics is remarkable. The combination of medical therapeutics and listening to music, singing songs as well as playing instruments can improve not only the motor function, but also the emotional and cognitive system. We had spread the Kodály method-based piano culture in Japan, which is based on the musical education established by Zoltán Kodály. It is already adopted as Community Music Therapy for the social and psychological aspects of the illness [45]. We further pray for harmony for the development of pharmacotherapeutics, diagnostic tools, and musical therapies for Parkinson's disease and related dopaminergic disorders.

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