Sound Therapy Induced Relaxation: Down Regulating Stress Processes and Pathologies

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Summary

The use of music as a means of inducing positive emotions and subsequent relaxation has been studied extensively by researchers. A great deal of this research has centered on the use of music as a means of reducing feelings of anxiety and stress as well as aiding in the relief of numerous pathologies. The precise mechanism responsible for these mediated effects has never been truly determined. In the current report we propose that nitric oxide (NO) is the molecule chiefly responsible for these physiological and psychological relaxing effects. Furthermore this molecules importance extends beyond the mechanistic, and is required for the development of the very process that it mediates. Nitric oxide has been determined to aid in the development of the auditory system and participate in cochlear blood flow. We show that NO is additionally responsible for the induced exhibited physiological effects. We proceed to outline the precise neurochemical pathway leading to these effects. Furthermore we explore the interrelationship between the varying emotion centers within the central nervous system and explain how the introduction of music can mediate its effects via NO coupled to these complex pathways.

Defining Stress

The term *stress* as defined in the strict biological sense is an event or stimulus that alters the existing homeostasis within a given organism [1]. Some theorists now refer to the *healthy state* as one of stability in the face of change. Multiple causes of stress add to what is called *allostatic loading*, which can be pathologic if not relieved. The state may be cognitively appraised or non-cognitively perceived. The disturbed organism may either acutely or chronically experience this stimulus. Indeed, the stressor (the stimulus) may even emerge from within the organism itself, such as in interoceptive psychiatric stress. Stress is difficult to define because there are many types of stressors, or stimuli, that can bring on this homeostatic perturbation. Through an extremely complicated homeostatic process, all living organisms maintain their survival in the face of both external and internal *stressors* [2,3].

Stress when defined as a psychological phenomenon is characterized by feelings of apprehension, nervousness and helplessness, and is commonly present in patients undergoing medical procedures. Past research demonstrates that stress induces numerous types of physiological complications. Stress has been found to cause hypertension, tachycardia and hyperventilation [4], all of which were shown to be linked with ischemia and can cause fluctuations in body temperature, urinary urgency, enlarged pupils, and loss of appetite [5]. Furthermore it has been demonstrated that stress leads to increased cortisol levels, depressing the immune system. Lastly, conditions that arouse stress may actually increase pain [6]. An overwhelming amount of research has been conducted into methods of alleviating the stress response, as well as exploring possible mechanisms by which these methods act.

Stress and its Relation to Music:

The use of music has consistently been found to reduce stress levels of patients in clinical settings. Mulooly et al. [6] investigated the use of music for postoperative stress and found that patients who underwent an abdominal hysterectomy reported lower stress levels after listening to music when compared to patients who were not exposed to this treatment. Studies [7] have contrasted music to verbal distraction, concluding that although the methods were comparable for the reduction of stress, music was more effective in the reduction of blood pressure. Further studies find [8] that adult patients that listened to music during dialysis were found to have significantly lower blood pressure before and after their treatment. In further studies the effectiveness of music in the reduction of stress has been measured in myocardial infarction patients [8], and in coronary care units [9]. Music has been paired with other therapeutic techniques to reduce stress as well. In a study of pediatric patients, group music therapy sessions, including singing, and instrument playing, were found to decrease observed stress in children before surgery [5]. Guided imagery and music together were found to decrease pain and stress in patients undergoing elective colorectal surgery [4].

How Emotions Cause Stress and How Music Alleviates it: CNS Processes

Music and its calming effects have been demonstrated to have a large emotional component [68]. When pleasant music is heard the brains motivation and reward pathways are reinforced with positive emotion mentally linked to the music (see [69] for full review). This emotionalized memory includes many *somatic markers*, i.e., bodily sensations that accompany emotion and set the feeling tone, *feels right* to the person [10]. Clearly, music and the emotion it imparts can be viewed as a process reinforcing a positive belief so that rational thought can not hinder the strength of the belief (see Refs. [11 and 12]). Indeed, belief in regard to a therapy and/or doctor and/or personal religion, may in fact stimulate physiological processes, enhancing naturally occurring health processes by augmenting their level of performance. Conversely, emotional stresses such as fear and anxiety can induce cardiovascular alterations, such as cardiac arrhythmias [13, 14 and 15]. These cardiovascular events can be initiated at the level of the cerebral cortex and may involve insular as well as cingulated, amygdalar and hypothalamic processes. Clinically we may see this as elevated cortisol levels and in some instances can induce sudden death in patients with significant coronary artery disease [16]. In addition, heart rate is often altered under stressful conditions. Neurons in the insular cortex, the central nucleus of the amygdala, and the lateral hypothalamus, owing to their role in the integration of emotional and ambient sensory input, may be involved in the emotional link to the cardiovascular phenomenon. These include changes in cardiac autonomic tone with a shift from the cardioprotective effects of parasympathetic predominance to massive cardiac sympathetic activation [13]. This autonomic component, carried out with parasympathetic and sympathetic preganglionic cells via subcortical nuclei from which descending central autonomic pathways arise, may therefore be a major pathway in how belief may affect cardiovascular function. The importance of music and the elicited emotional response (and therefore limbic activation) was further demonstrated in ischemic heart disease when patients with frequent and severe ventricular ectopic rhythms were subjected to psychological stress [13]. The frequency and severity of ventricular ectopic beats increased dramatically during emotional activation of sympathetic mechanisms but not during reflexively-induced increased sympathetic tone.

The hard-wiring of emotion/music and cardiovascular neural systems probably involves many subcortical descending projections from the forebrain and hypothalamus [17, 18, 19, 20, 21 and 22]. Cardiovascular changes were observed in experiments where the motor cortex surface was stimulated, eliciting tachycardia accompanied by and independent of changes in arterial blood pressure [23]. The *sigmoid* cortex [24 and 23], frontal lobe [25, 26 and 27], especially the medial agranular region [28], subcallosal gyrus [29], septal area [30 and 31], temporal lobe [32], and cingulate gyrus [32, 33 and 34] appear to be involved. The insular cortex in cardiac regulation is important because of its high connectivity with the limbic system, suggesting that the insula is involved in cardiac rate and rhythm regulation under emotional stress [35-38].

The amygdala, with respect to autonomicñemotional integration [39 and 40], is composed of numerous subnuclei, which the play a major role in the elaboration of autonomic responses [41]. There are profuse inputs to this region from the insular and orbitofrontal cortices, the parabrachial nucleus, and the nucleus tractus solitarius [42 - 44]. Amygdalo-tegmental projections are viewed as a critical link in cerebral cortical control of autonomic function [45, 46,].

The medial hypothalamus is also implicated in cardiac arrhythmogenesis [47]. Beattie and colleagues [47] suggested that hypothalamic projections that descended into the midbrain periaqueductal gray matter, reticular formation, and intermediolateral nucleus of the spinal cord mediate the response. Magoun and colleagues [48] demonstrated that the lateral hypothalamus and wide areas of the lateral tegmentum are also important for autonomic function. The lateral hypothalamus has long been recognized for its role in the regulation of motivation and emotion and the autonomic concomitants of related behaviors [49]. The densest cortical projection to the lateral hypothalamus arises from the infralimbic cortex [50]. Pressor sites within the insular cortex project more heavily to the lateral hypothalamus than do depressor sites and are represented at caudal levels. Anatomical studies of the lateral hypothalamus demonstrate projections to the periaqueductal gray matter, the parabrachial region, parvicellular formation, dorsal vagal complex, and spinal cord [51, 52]. Furthermore, descending projections of the lateral hypothalamus terminate as a capsule around the dorsal motor nucleus of the vagus nerve, which provides secretomotor fibers to the stomach wall, pancreas, and small intestine. These neural patterns might account for the close association of cardiac and gastric responses.

Nitric oxide:

The very origin of music as a method of stress release has its roots in the early development of the auditory system. In a study by Fessenden and Schacht [53], it was found that the nitric oxide (NO)/cGMP pathway is thoroughly involved in the development and function of the sensory systems, and specifically in the development of the cochlea. Thus NO is involved in the stimulated relaxation from the very development of the organism, to the mechanism by which the relaxation occurs [81]. Cochlear nerve fibers enter the brainstem and are routed through the thalamus to the auditory cortex. It has been demonstrated that it is along this path that the emotion centers within the limbic system are activated (as depicted in figure 1. the sensation of music enters the diagrammatic neuronal pathway at the limbic system) [83,84,85]. Furthermore this neuronal pathway from auditory nerve to cortex was found to be mediated by NO [82].

When we examine NO signaling, we notice two components the constitutive NO synthase (cNOS) endothelial (e) and neuronal (n) isoforms. Constitutive NOS (cNOS), as the name implies, is always expressed. When cNOS is stimulated, NO release occurs for a short period of time, but this level of NO can exert profound physiological actions for a longer period of time.

NO is not only an immune, vascular and neural signaling molecule, it is also antibacterial [73,74], antiviral [73,74] and it down-regulates endothelial and immunocyte activation and adherence, thus performing vital physiological activities, including vasodilation.

Thus NO release subsequent to music listening, has the potential to protect an organism from microbes and physiologic disorders such as hypertension, and also diminishes excessive immune and endothelial activation ocuring largely because of vasodilation modulated by NO [54].

The endocannabinoids, anandamide and 2-arachidonyl glycerol, are naturally occurring cNOS-derived NO-stimulating signaling molecules that are also constitutively expressed. Anandamide, an endogenous endocannabinoid, can also cause NO release from human immune cells, neural tissues and human vascular endothelial cells. Anandamide can also initiate invertebrate immune cell cNOS-derived NO. Estrogen can also stimulate cNOS-derived NO in human immune and vascular cells.

We believe that each signaling system performs this common function under different circumstances. Morphine, another naturally occurring animal signal molecule given its long latency before increases in its levels are detected, arises after trauma/inflammation and, through a NO mechanism, down regulates these processes in neural and immune tissues. Anandamide, as part of the ubiquitous arachidonate and eicosanoid signaling cascade, serves to maintain and augment tonal NO in vascular tissues. Estrogen, through NO release, provides an additional pathway by which the system can down-regulate immunocyte and vascular function in women. This may be due to both the immune and vascular trauma associated with cyclic reproductive activities, such as endometrial buildup, when a high degree of vascular and immune activities are occurring. Given the extent of proliferative growth capacity during peak estrogen levels in this cycle, NO may function to enhance down-regulation of the immune system to allow for these changes.

Clearly, therefore, enhanced cNOS activity would be a beneficial effect within the concept and time framework of music and the subsequent relaxation it induces. Thus, these signal molecules, especially endocannabinoid and opiate alkaloids [70] have the potential to make you ìfeelî good and relax [72], also release NO, which may be a vital part of this complicated process.

Signaling molecules leading to relaxation:

As noted above, once individuals undergo a very mild form of work/activity such as music listening, they experience peripheral vasodilation, warming of the skin, a decrease in heart rate and an overwhelming sense of well-being [7, 72].

In examining a potential mechanism for the music induced relaxation, besides the over-riding central nervous system output via the autonomic nervous system, peripheral neuro-vascular processes would appear to be important. We surmise NO to be of fundamental importance in this response because of the increase in peripheral temperature, i.e., vasodilation. For a complete review of possible related mechanisms see [61,63,64,65,66,54].

We also surmise, based on current studies, that endothelial derived NO, released through normal pulsations, due to vascular dynamics responding to heart beat [54] as well as ACh stimulated endothelial NO release, may contribute to the effect of NO in inducing smooth muscle relaxation [71]. Furthermore, vascular pulsations may be of sufficient strength to also stimulate nNOS derived NO release, limiting any basal NE actions [71]. Interestingly, nitrosative stress, mediated by involvement of the reactive nitrogen oxide species, N2O3 does inhibit dopamine hydroxylase, inhibiting NE synthesis and contributing to the regulation of neurotransmission and vasodilation [67].This system may provide an autoregulatory mechanism involved in the neuronal control of peripheral vasomotor responses.

Conclusion:

In summary, the music induced relaxation peripherally appears to be mediated by a system of regulation involving NO, as neurotransmitter and as a locally acting hormone. Contingent on the preliminary vasoconstriction and depolarization of the membrane, vasodilation is mediated by NO liberated from vasodilator nerves that activate guanylate cyclase in smooth muscle and produce cGMP. During this stage, NO and NE exist simultaneously. Due to the characteristics of NO, NE no longer mediates vasoconstriction; instead NO activates guanylate cyclase, which produces vasodilation and the relaxation under a depolarized membrane state (see Refs. [30,54,71].

In conclusion, the above findings demonstrate that music has a profound relaxing effect [4,5,6,68] we believe that this occurs via NO, opiate and the above mentioned hormonal system. Furthermore NO has been shown to be a necessary molecule in the development of the auditory system, [53] which is required to enable music to act as a relaxant. Taken together we believe that the complex nitric oxide signaling system is the primary and fundamental (from development to mechanism) method by which music acts as a relaxation device.