

Do Sauna Therapy and Exercise Act by Raising the Availability of Tetrahydrobiopterin?

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Summary

Sauna therapy has been used to treat a number of different diseases known or thought to have a tetrahydrobiopterin (BH4) deficiency. It has been interpreted to act in multiple chemical sensitivity by increasing chemical detoxification and excretion but there is no evidence that this is its main mode of action. Sauna therapy may act to increase BH4 availability via two distinct pathways. Increased blood flow in heated surface tissues leads to increased vascular shear stress, inducing increased activity of GTP cyclohydrolase I (GTPCH-I) in those vascular tissues which will lead to increasing BH4 synthesis. A second mechanism involves the heat shock protein Hsp90, which is induced by even modest heating of mammalian tissues. Sauna heating of these surface tissues may act via Hsp90, which interacts with the GTPCH-I complex and is reported to produce increased GTPCH-I activity by lowering its degradation. The increased consequent availability of BH4 may lead to lowered nitric oxide synthase uncoupling, such as has been reported for the eNOS enzyme. Increased BH4 synthesis in surface tissues of the body will produce increased circulating BH4 which will feed BH4 to other body tissues that may have been BH4 deficient. Similar mechanisms may act in vigorous exercise due to the increased blood shear stresses and possibly also heating of the exercising tissues and heart. There is a large and rapidly increasing number of diseases that are associated with BH4 depletion and these may be candidates for sauna therapy. Such diseases as hypertension, vascular endothelial dysfunction, multiple chemical sensitivity and heart failure are thought to be helped by sauna therapy and chronic fatigue syndrome and fibromyalgia may also be helped and there are others that may be good candidates for sauna therapy.

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Sauna Therapy Introduction

Sauna therapy has been reported to be helpful in the treatment of various diseases. Among these are multiple chemical sensitivity (MCS) (1-6), chronic fatigue syndrome (7), fibromyalgia (8,9), hypertension (10-13), vascular endothelial dysfunction (11-13) and heart failure (11-15). The last three of these are known to be associated with tetrahydrobiopterin (BH4) depletion (16-22) and the first three related diseases are thought to be caused by a biochemical vicious cycle, known as the NO/ONOO- cycle (23-27), with one cycle element being BH4 depletion (23-27). Thus BH4 depletion appears to be a common feature of diseases/illnesses that respond to sauna therapy, raising the question as to whether sauna therapy may act, at least in part, by increasing the availability of BH4.

In MCS but not as far as I can determine with these other diseases/illnesses, sauna therapy has been assumed to work by increasing the mobilization, detoxification and subsequent excretion of lipid soluble toxicants (1-6), a process known as depuration. However the possibility of the action of sauna therapy by increasing the availability of BH4 raises the issue of whether sauna therapy for MCS may act, at least in part by increasing such availability.

In all of these diseases, there is a reciprocal relationship between peroxynitrite and BH4 depletion as diagrammed in Fig. 1. Peroxynitrite is formed by the diffusion limited reaction between nitric oxide and superoxide (Fig. 1) and peroxynitrite formed from this reaction can oxidize BH4, thus depleting its levels. BH4 is a cofactor for all three nitric oxide synthases, and BH4 depletion leads to what is called a partial uncoupling of the nitric oxide synthases, with uncoupled enzymes producing superoxide in place of nitric oxide (27). Thus in cells and tissues with high levels of NOS activity, such partial uncoupling provides large amounts of both coupled and uncoupled NOSs, leading to production of large amounts of peroxynitrite (Fig. 1). Peroxynitrite will act to maintain the partial uncoupling through BH4 oxidation.

Such a shift away from nitric oxide and towards peroxynitrite in the vasculature will produce hypertension. While nitric oxide is a vasodilator, peroxynitrite is known to be a vasoconstrictor (28-32),

acting in part by producing increased amounts of the potent vasoconstrictor, isoprostane (28,29). Angiotensin II increases blood pressure by shifting this equilibrium by increased synthesis of superoxide (29), leading both to increased production of peroxynitrite and also BH4 depletion.

These same biochemical changes are a central part of the biochemical vicious cycle, called the NO/ONOO- cycle (Fig. 2) thought to be the central etiologic mechanism for MCS, CFS and FM (23-27).

The known or apparent roles BH4 depletion in each of the diseases that are reported to be improved by sauna therapy suggests that sauna therapy may act by increasing BH4 availability.

There are two distinct but somewhat interrelated mechanisms that may be suggested for such action of sauna therapy, both involving increased activity of the enzyme GTP cyclohydrolase I (GTPCH-I), the first and rate-limiting enzyme in the *de novo* pathway for BH4 synthesis.

Mechanism I: Blood Flow Shear Stress and Increased BH4 Synthesis

It is well known that sauna treatment produces greatly increased blood flow in the heated surface tissues of the body (33-36), with blood shunted from the inner tissues to these surface tissues (33,35). Such treatment leads, then to increased shear stress in the surface tissue vasculature.

The effects of such increased shear stress leads to induction of GTPCH-I and BH4 levels produced from the eNOS in the vasculature, as was reviewed by De Bono and Channon (37). The first such study published by Lam et al (38) studied the effects of shear stress on rat aortic endothelial tissue. They reported that such shear stress produces substantial increases in both GTPCH-I activity and in BH4 levels. The rat study responses were much smaller than were the two human endothelial studies described below and the mechanism involved, increased GTPCH-I transcription, was different from the mechanism found in the human studies. The most detailed such study was that of Widder et al (39) on the effects of laminar shear stress on human aortic endothelial cells in culture. They found that such shear stress produced a circa 30 fold increase in both GTPCH-I activity and in BH4 levels, as well as a large increase in nitric oxide production but a decrease in superoxide production. These last two observations are very important because there is a concomitant increase in eNOS

activity and these results show that the BH4 increase is greatly in excess of that needed to supply the eNOS protein with BH4. Such an excess is needed if the increased BH4 produced in response to shear stress is to supply BH4 to other tissues in the body. Mun et al (40) studied effects of shear stress on constructed human vascular epithelial tissues in culture derived from cloned human epithelial cells. They found that shear stress produced circa 4-fold increases in both GTPCH-I activity and BH4 levels under their conditions. It also produced a lowering of the oxidative stress produced by either high glucose or arachidonic acid. Their study confirms that excess BH4 is produced under these conditions, consistent with a role in possibly providing BH4 for other tissues.

The proposal here, is that increased synthesis of GTPCH-I and BH4 in the peripheral vasculature in sauna therapy may produce increased availability of BH4, which will circulate in the blood, feeding other tissues that may be BH4 deprived. In this way there may be improved function even in tissues that have no increase in blood flow during sauna therapy.

Mechanism II: Hsp90 Induction by Heating and Increased GTPCH-I

The heat shock protein Hsp90 is induced by modest heating of tissues (41-45) and such induction has been suggested to be involved in responses to sauna therapy (43). A study of protein interactions has shown that the regulatory protein that interacts with GTPCH-I has a domain that binds to a protein (Aha1) called activatory of Hsp90 (46). Aha1 presumably recruits Hsp90 into a complex of proteins including GTPCH-I, such that it is reasonable that Hsp90 may regulate GTPCH-I activity. Does this lead to heat producing increases in GTPCH-I activity and if so, does that lead to more production of BH4?

Two studies strongly suggest that it does. In one study, Hwu et al (47) reported that heating of mammalian cells in culture induced increased amounts of the GTPCH-I protein in part via an apparent Hsp90-dependent process. In another study, Whitsett et al (48) reported that Hsp90 antagonized the proteasomal degradation of GTPCH-I and that when there was excessive degradation of GTPCH-I, it led to lowered levels of BH4 and increased consequent eNOS uncoupling. This argues that Hsp90 can increase levels of both GTPCH-I and its product BH4.

Hsp90 also has been shown to produce decreased uncoupling of the eNOS form of nitric oxide synthase (48-51), suggesting that it leads to

increased availability of BH4 because of the known role of BH4 depletion, discussed above, in producing partial uncoupling of nitric oxide synthases. However, because Hsp90 interacts with the eNOS protein, this lowered uncoupling might be due to some more direct effect of Hsp90 on eNOS. In another study, Whitsett et al (52) showed that BH4 but not the Hsp90 protein produces lowered uncoupling of the eNOS enzyme. We have then, substantial evidence that heating may act through increased Hsp90 activity to produce increased BH4 product.

I am aware of some unpublished preliminary evidence that repeated sauna treatment produces increases in blood BH4 levels, but clearly we need to have some published studies on this.

Does Exercise Act to Improve Health through These Same Proposed Mechanisms?

Exercise will, of course, lead to increased blood flow to the exercising muscles as well as the heart, leading in turn to increased shear stress in the vasculature of these tissues. Vigorous and sustained exercise may also raise the temperature of the exercising tissues, possibly leading to Hsp90 induction. It is not unreasonable, therefore, that exercise may act to improve human health through increased GTPCH-I activity and increased consequent availability of BH4. This suggests an intriguing mechanism for health effects of exercise. It also suggests that sauna treatment may be, in effect, a lazy person's exercise with regard to health improvement.

Vigorous exercise has been reported to increase blood BH4 levels (53) and has also been shown to greatly lower eNOS uncoupling (54,55), providing support for these views. The notion that exercise acting through increased shear stress may be expected to increase BH4 levels is not original. For example, Widder et al (56) expressed somewhat similar views.

It should be noted that exercise in CFS/ME has a negative effect called post-exertional malaise but this is thought to act via completely different mechanisms than the apparent BH4 effect discussed above (23,26).

Summary

The possible role of sauna therapy and exercise in increasing availability of BH4 may provide a key insight into the mechanisms of

action and health benefits of both sauna therapy and vigorous exercise. These benefits may go far beyond the six diseases discussed above in the introduction to this paper. Glaucoma, a disease characterized by peroxynitrite elevation (57) and therefore possible BH4 depletion, is reported to respond to sauna therapy (58). Similarly chronic obstructive pulmonary disease is reported to respond to sauna therapy (59) and is known to involve peroxynitrite elevation (60,61). BH4 depletion has been reported to be found in Alzheimer's disease (62-65), Parkinson's disease (64,66,67), autism (68-72), asthma (73,74), pulmonary hypertension (75,76), schizophrenia (77,78), and type 2 diabetes (79-82) suggesting that these may respond to sauna therapy, as well. There is at least a superficial case to be made that the first four of these diseases (Alzheimer's, Parkinson's, autism and asthma) in the previous sentence may be NO/ONOO- cycle diseases (Chapter 14, Ref. 23) and there may be such a case for these other diseases as well.

Studies of the BH4 role in disease in general are still in the early stages and it is possible that BH4 depletion is involved in many other chronic inflammatory diseases. We may similarly be in the early stages of determining whether sauna therapy may be useful in the treatment of many additional diseases.

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