The Niacin Flush Pathway in Recovery from Schizophrenia and how Arginine and Glutamine may Provide Added Benefit

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Abstract *A reduced niacin-mediated flush is increasingly accepted today as a positive diagnostic indicator for schizophrenia. Schizophrenics that were successfully treated with high dose niacin (nicotinic acid) therapy by Dr. Abram Hoffer in the 1950s recovered from their otherwise previously reduced flush response simultaneous with recovery from schizophrenia. Significantly, some schizophrenics also recovered after high dose nicotinamide treatment, a different nicotinamide adenine dinucleotide (NAD) precursor that does not cause a flush response. Whether the niacin-flush response is first due to replenishment of NAD deficiency or due to a restoration of polyunsaturated fatty acid levels thus restoring niacin-flush competence is not mutually exclusive. It is possible that nicotinic acid is first dedicated to intracellular NAD synthesis at the expense of the flush response until the schizophrenic's immediate needs for NAD are finally met. Then the nicotinic acid, rather than entering the cell through transporters, instead becomes available to bind GPR109a, on the surface of the cell thus mediating the flush pathway. Moreover the restored NAD levels may also revive the biosynthetic pathway required for generation of the known niacin-flush vasodilatory molecules PGD_2, PGE_2, PGI2, and thromboxane A_2. The schizophrenic patient may potentially benefit by additional supplementation with arginine to aid in restoration of the vasodilation, and glutamine to increase NAD synthesis. Arginine increases the amount of nitric oxide (NO) synthase substrate available towards more sustained niacin-NO-vasodilation pathways, while glutamine increases the amount of required substrate available for conversion of nicotinic acid adenine dinucleotide to NAD. The addition of these two amino acids with high-dose niacin therapy has the potential to provide significant additional therapeutic benefits when treating schizophrenia, especially the chronic cases.*

Introduction

Nicotinic acid (commonly known as niacin) is largely used for controlling dyslipidemia. Niacin raises high-density lipoprotein (HDL) to a greater extent than any known cholesterol-associated drug while also lowering triglycerides, total cholesterol, and very-low-density lipoprotein. However, there are many more uses for niacin, which have been overlooked by conventional medi-

cine in spite of clinical proof and repeated anecdotal evidence, perhaps in part because many other therapies are not as clearly quantifiable. Nonetheless, the amazingly varied benefits of niacin treatment are actually to be predicted. Niacin serves as a precursor to endogenous biosynthesis of nicotinamide adenine dinucleotide (NAD), a molecule that is required in a greater shear number of protein catalyzed reactions than any other vitamin-derived molecule (>450 reactions1). NAD as a part of NAD, NADH, NADP, or NADPH is essential to all life ranging from bacteria to man. NAD functions in most biochemical homeostasis: catabolic and anabolic. Dietary precursors to NAD are termed vitamin B_3. Similarly, the observation that niacin helps with a wide variety of therapeutic benefits is unsurprising because the most devastating dietary deficiency disease ever observed naturally occurring in modern human history were the pellagra epidemics that happened just after the development of milling technology that would introduce white rice and flour to the masses. Over 125,000 United States southerners would die due to pellagra in just the first two decades of the 20th century! This all indicates the human animal's particularly great susceptibility to NAD deficiency arising from unfortunate dietary habits.

Schizophrenia, however, seems likely to involve an even greater susceptibility to NAD deficiency states due to genetic reasons. Entire mental asylums in the United States were full of pellagrans with dermatitis during the height of the epidemics of the 1920s. Shortly after the discovery of niacin in 1939, the government began the mandatory fortification of bread, flour, and rice. By the 1950s, Drs. Abram Hoffer with Humphry Osmond experimented with using niacin as a means of treating schizophrenics. This was initiated based on the observation that pellagrans so resembled their schizophrenic patients. Hoffer had originally been a PhD that was studying fortification of grains. Then he decided to become a MD after becoming frustrated with the lack of respect he was receiving regarding his fortification recommendations. Together, Hoffer and Osmond would discover that treating acute schizophrenics with gram quantities of niacin or niacinamide frequently resulted in dramatic complete recoveries from the disease.[2-4] So the theory was born that perhaps acute schizophrenics have a greater genetic dependency for niacin. Today this theory remains plausible. Hoffer treated over 10,000 patients using gram quantities (typically 3g) of niacin or niacinamide (nicotinamide). Most interestingly, he discovered that schizophrenics do not flush as much as non-schizophrenics. Since Hoffer's discovery other investigators have repeatedly confirmed his observation of reduced flush response in multiple studies published within our current decade (this is just a sampling[5-8]).

Most interestingly, Dr. Hoffer observed complete recovery of his patients from acute schizophrenia after high-dose niacin treatment. However chronic schizophrenics frequently did not recover after niacin treatment. Similarly, first episode schizophrenics have a reduced niacin flush response, while reduced niacin flush is not observed with multi-episode schizophrenics.[7] Now niacin skin flush-based diagnostic tests are being developed and marketed. Moreover entire expensive investments into genetic studies based on the flush response phenotype are being performed to better understand this quantifiable phenotype.[9,10]

In this article, we describe the signal transduction pathway starting from ingestion of nicotinic acid and proceeding to the physiological flush response, while relating this to schizophrenia. In the end we find that there are still significant gaps in our understanding of these pathways, but that additional supplemental strategies are predicted to potentially improve the weakened schizophrenia pathways, thus possibly promoting recovery. Novel therapeutic emphasis is placed on fulfilling these rate-limiting molecules to support recovery from schizophrenia-associated NAD/vasodilation-deficits. Specifically, this involves high doses of arginine and glutamine, since these combinations have the potential to exert therapeutic benefits in the treatment of acute schizophrenia and perhaps even among chronic schizophrenia.

Nicotinic Acid Pathways to Vasodilation and NAD

The niacin-mediated flush response is well known to be reduced in schizophrenic patients.[5-8,11-14] Conversely, recovery of the flush response has been directly correlated with recovery from acute schizophrenia.[15] The flush is first evidenced in the skin by a redness that is sometimes accompanied with an itchy sensation and perceptibly noticeable changes in body temperature as the warm blood moves more distal. A slight flush response is most therapeutically desirable for correcting dyslipidemia (either too high or too low cholesterol/lipids) – no flush is observed with high dose niacinamide treatment and no correction of dyslipidemia is observed either.

In order for the suffering schizophrenic to optimally benefit from the modern understanding of the niacin-flush, we must consider both of these distinct separate pathways starting from nicotinic acid and going either: (1) Straight to the intracellular synthesis of NAD; or (2) To the membrane-activated nicotinic acid-mediated flush response (**Figure 1,** p.7). Here, we focus on NAD biosynthesis. While nicotinic acid serves an essential function as dietary precursor used for biosynthesis of NAD, there are also several other dietary precursors to NAD. However, none of these cause a flush response. These are nicotinamide (commonly known as niacinamide or no-flush niacin; NAM), tryptophan (W), or nicotinamide riboside (NAMR). In order to make NAD starting from niacin, your body also requires thiamine for making phoshoribosylpyrophosphate, (PRPP). This PRPP combines with nicotinic acid in the first reaction to make nicotinic acid mononucleotide. Then, ATP is needed to make nicotinic acid adenine nucleotide (NaAD). Finally, glutamine is required to convert the nicotinic acid to nicotinamide, thus creating NAD and liberating glutamate. The therapeutic benefits of increased NAD are nearly incomprehensible and limitless given NAD's role in general cellular metabolism and energetics. The specific potential therapeutic effects of additional glutamine supplementation are considered in the next section.

Of the NAD precursors, nicotinic acid is uniquely distinguished as the only NAD precursor for which there is a specific high affinity G-protein coupled receptor, GPR109a and GPR109b (**Figure 1,** p. 35; upper & right boxes). Tremendous advances in our basic understanding of the molecules involved in the nicotinic acid flush pathway have been made just over the past decade.[16,17] The pathway from nicotinic acid to flush response involves multiple ligand:g-protein coupled receptor interactions, multiple secondary signaling molecules, and several different specific tissues. At the end of the signal transduction pathway from niacin to physiological flush response, there are two distinct pathways, both of which converge to promote vasodilation. These are briefly a niacin-mediated massive release of prostaglandins, and a niacin-mediated increase in endothelial nitric oxide synthase (eNOS/NOS_3) expression. The former pathway has been much more actively studied. Nicotinic acid activation of the nicotinic acid G-protein coupled receptors GPR109a and GPR109b leads to a massive release of a wide array of prostaglandins (PGD-PGH) from a combination of dendritic cells (Langerhans) and keratinocytes.[11,18-21] The vasodilatory molecules PGD_2, PGE_2, PGI_2, and thromboxane A2 are all increased after niacin treatment. PGE_2, PGD_2, and PGJ_2 are most appreciated currently, where PGD_2 is believed to exert the most dramatic flush response effects.[22] PGE_2 and PGD_2 bind to specific G-protein coupled receptors (GPR109a and GPR109b) on other cells, while PGJ_2 binds to and activates the nuclear transcription factor, peroxisome proliferator-activated receptor gamma, the drug target of the thiazolidinedione class of drugs used to control lipodystrophy/diabetes.

Niacin increases phosphorylation of eNOS to increase its half-life in the brain. Here eNOS promotes angiogenesis so critical to stroke recovery.[23] Endothelial NOS controls basal vascular dilation.[24] Elimination of eNOS does not prevent overt niacin flush in mice studies, thus suggesting a mi-

nor role for eNOS in niacin-mediated flush response.[20] Nonetheless, we still expect a role for niacin-eNOS-dilation that may even be more sustained but less acutely intense. The nitric oxide enzyme requires arginine for production of nitric oxide, which also increases vascular dilation. In fact vasodilation can overcome erectile dysfunction where viagra/sedenifil work via increasing nitric oxide production. Most interestingly, the addition of niacin and arginine to PED_5 inhibitors like viagra has been shown to improve sexual satisfaction.[25-27] HDL stimulates NO production through eNOS,[28] and no other drug increases HDL more than niacin. This seems likely to promote vasodilation in the brain that is perhaps crucial to its varied benefits to mental health. Niacin has been shown to decrease inducible nitric oxide synthase isoform (iNOS) expression,[29,30] where iNOS activity is associated with inflammation and eNOS activity is associated with vascular dilation via endothelial relaxation. As a means of increasing the desired flush response in schizophrenics, it makes sense to also consider using arginine since is the substrate used by nitric oxide synthase. In the end both the prostaglandin-GPCR-cAMP-PKA and the NOS-NO pathway converge to dephosphorylate the contractile protein myosin light chain kinase that ultimately mediates the mechanics of vasodilation. The two substrates, glutamine and arginine are discussed later in the manuscript as potentially useful additions to high dose niacin therapy for treating acute and possible chronic schizophrenia.

Explanations for the Simultaneous Recovery from Acute Schizophrenia and the Niacin-Flush Response

Hoffer observed that treatment with high doses of the non-flush NAD precursor, nicotinamide, also frequently resulted in recovery from acute schizophrenia similar to recovery from pellagra dementia. While restoration of the nicotinic acid-mediated flush response does correlate with niacin-mediated recovery from schizophrenia, it does not necessarily mean that this effect was primarily the result of the flush response. It seems much more likely that the restoration of NAD levels is central to recovery, where NAD as NAD+, NADP+, NADH, and/or NADPH, may be restoring prostaglandin-flush pathways by one or a combination of the >450 reactions that require NAD for activity. There are several possible explanations for the observed reduced flush response. In this section we give consideration to each explanation and ultimately come to the conclusion that the reduced flush response is firstly an NAD deficiency, where PUFA reductions are likely to be secondary to this effect. This analysis concludes that schizophrenia is most likely not an essential fatty acid deficiency disease, but more of a NAD deficiency disease.

Firstly, the reduced niacin flush response observed in schizophrenia likely involves niacin receptor ligand mediated desensitization. A metabolic study of schizophrenia indicates a general increase in PUFA catabolism.[31] Beta-hydroxybutryate levels were found to be elevated 2.6 fold. Beta-hydroxybutyrate is proposed to be the naturally occurring endogenous ligand for the high affinity nicotinic acid G-protein coupled receptor.[32] Decreased levels of the GPR109a protein are observed in the brains of schizophrenics, as are increased GPR109a transcripts.[33] Such ligand dependent receptor down-regulation (a.k.a., receptor desensitization) is a common theme with the G-protein coupled receptor protein superfamily. Thus, NAD may be simply restoring PUFA metabolism such that the levels of the beta-hydroxybutyrate ligand for the high affinity nicotinic acid G-protein coupled receptor are returned to normal levels. The GPR109a protein may then be expressed at correct levels, thus restoring the niacin-flush response to normal as well. This general alteration is surely a major contributor to the reduced flush response seen in schizophrenics.

Prostaglandins are synthesized starting from arachidonate - the predominant PUFA. Thus it would make perfect sense if arachidonate levels were reduced in schizophrenics resulting in a reduced flush response. However, metabolite studies of schizophrenia

indicate that arachidonic acid levels are not altered in schizophrenia.[34] Instead, increased levels of the related molecule, adrenic acid (2 carbons added to arachidonate, i.e., 22:4), are inversely correlated to the niacin flush response, with its levels being elevated in schizophrenics by 20%. This means that the rate of elongation for arachidonic acid is severely altered in schizophrenics. Elevated adrenic acid has also been correlated with diabetes incidence in schizophrenics[35] and also in patients with increased schizotypal personality traits.[36] Adrenic acid is a curious molecule with higher levels occurring in early development, but then reduced levels with aging. Decades ago adrenic acid research determined that it was metabolized to dihomoprostaglandins by cyclooxgenase.[37] More recent research confirms this finding,[38] but the activities and physiological significance of this remains to be determined. It appears that the increased adrenic acid might compete with arachidonate. Moreover, the dihomoprostaglandins produced from adrenic acid may then interfere with the other prostaglandins, which clearly has the potential to interfere with prostaglandin-dependent inflammatory pathways and perhaps mental health. We simply do not know.

Another potential contributor to the reduced flush may involve hyper-delivery of nicotinic acid to cells at the expense of nicotinic acid availability for binding the nicotinic acid receptor. In other words, the schizophrenic individual is particularly deficient in NAD and thus a greater amount of nicotinic acid is quickly soaked up by cells for use in NAD synthesis, thus leaving less extracellular nicotinic acid available for activation of the GPR109-flush response pathway. Once the needs for NAD synthesis are satisfied, then the nicotinic acid becomes available to cause the flush response, as was observed in Hoffer's recovering schizophrenics. This explanation does not seem likely to be the major contributor of the reduced flush response based on metabolic studies, but it may in part contribute to a reduced flush response.

Finally, whether the nicotinic acid effect on schizophrenic physiology is in part due to vasodilation-increased delivery of NAD to hard to reach critical brain tissues or to some other unique aspects of schizophrenic physiology is unknown. We do not even know whether niacin causes dilation in the brain blood vessels, but with the known increase in brain endothelial nitric oxide expression, we assume this is the case. The majority of basic niacin research has been focused on cardiovascular disease/lipid profiles, and not on mental disease/brain tissues. More research should be dedicated to understanding the niacin-flush response biochemistry as related to schizophrenia. In summary, the data suggests that schizophrenia is more of a NAD deficiency disease than an essential fatty acid deficiency disease.

Potential Additional Benefits with Glutamine and Arginine

Hoffer's positive results with high dose niacin treatment were primarily limited to cases of acute schizophrenia. Chronic schizophrenics generally did not recover. Perhaps something else in the pathway from niacin to NAD and/or the flush response is limited in the more chronic schizophrenic that has not completely suffered an otherwise apparently irreversible neurodegenerative fate. Assuming schizophrenia is primarily a NAD deficiency disease that is particularly responsive to high doses of nicotinic acid, what other molecules may be rate-limiting in this pathway to recovery? What is the practical import of the current knowledge of the niacin-mediated flush biochemical pathways? On first glance of these pathways, it appears that glutamine and arginine are potentially therapeutic molecules worthy of greater consideration in treating schizophrenia.

Glutamine is required for the last step in the conversion of niacin to NAD when starting from either tryptophan or nicotinic acid/niacin (**Figure 1,** p. 35). Glutamine is a conditionally essential amino acid for uncertain reasons. It is particularly important in proliferating tissues, where gliomas have been described as "addicted" to glutamine.[39,40] Undoubtedly, this means that glutamine is essential to some cancer cells and other nor-

mal proliferating cells. Interestingly enough, transformed cancer cell are well known to be exceptionally dependent on high NAD levels.[41-43] In fact, chemotherapy is one of the most common situations today where the NAD deficiency disease pellagra is actually recognized and diagnosed in the clinic.[44] There are several chemotherapeutics currently being considered that specifically cause NAD depletion via inhibition of either the rate limiting enzyme for conversion of nicotinamide to NAD or they target the rate-limiting enzyme in the pathway-mediated conversion of tryptophan ultimately to NAD (indoleamine 2,3-dioxygenase; IDO).[41,42,45,46] IDO is exceptionally highly expressed specifically in tumor cells.[47,48] The conversion of tryptophan to NAD ultimately requires the presence of glutamine in the final step. Since IDO inhibitors have repeatedly been shown to kill tumor cells, IDO is today a very exciting and active molecular target focus area in chemotherapeutic research.[49-56] In summary, many cancer cells are known to essentially require high IDO activity, high NAD levels, and glutamine levels. Since glutamine is required for the IDO-mediated conversion of tryptophan to NAD, it is highly likely that glutamine plays an important role in facilitating the completion of the conversion of tryptophan to NAD in proliferating cells in general. Crude pharmacologic data supports a role for the alpha-ketoglutarate bioenergetic pathway of glutamine in gliomas.[40] However, the former possibility for a role of glutamine specifically in the production of NAD starting from tryptophan is unexamined. Furthermore, the fact that this addiction to glutamine is seen in a form of brain cancer makes one wonder whether there are similar important roles related to schizophrenia since it can also be considered a disease of the brain. The bottom line is that glutamine is almost certainly essential to certain types of brain cells perhaps due to glutamine's role in the synthesis of NAD starting from nicotinic acid or tryptophan. Ultimately, the addition of glutamine to a high doses regimen targeting schizophrenics may thus provide additional therapeutic benefit.

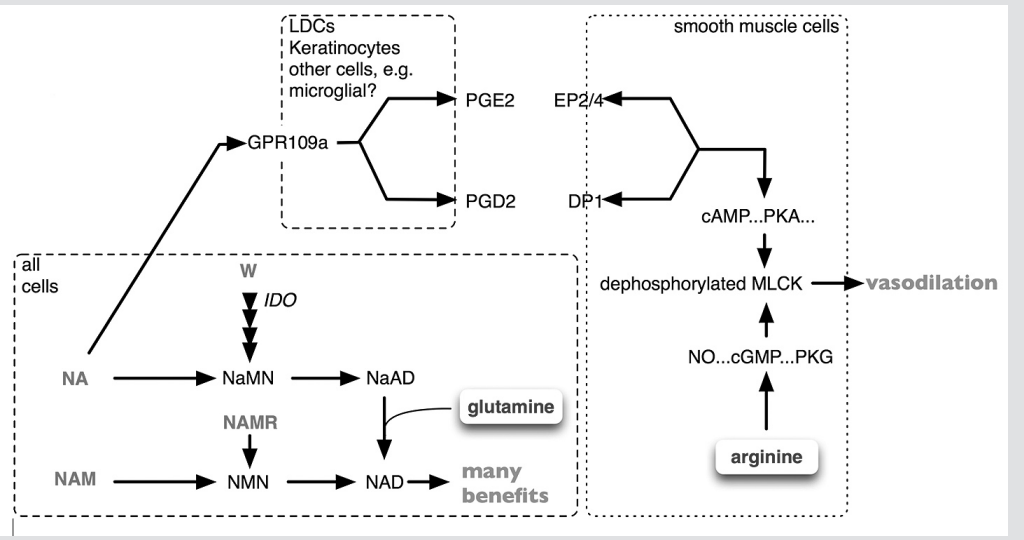
If the niacin-mediated flush response is most important in recovery from schizophrenia, then additional supplementation with arginine, the substrate used by the nitric oxide enzymes to begin nitric oxide-mediated vasodilation, may provide added therapeutic benefit. Arginine is well known to promote vasodilation during exercise[57] or hypercholesteremia.[58] Niacin increases brain endothelial nitric oxide synthase protein expression which is known to cause increased basal vasodilation and angiogenesis.[23] Thus it would be reasonable to include additional arginine to sustain the vasodilation. Nitric oxide physiology is quite complicated. NO is involved in many physiological processes. NO is most well known for its roles in fighting infections, vasodilation as opposed to vasoconstriction, and poorly understood neurological roles including neurotransmission/gastrotransmission. There are three nitric oxide synthase genes that are regulated at the transcriptional level to express their respective proteins in specific tissues. These three genes are the neuronal ($nNOS/NOS_1$), inducible ($iNOS/NOS_2$), and endothelial ($eNOS/NOS_3$), which are expressed respectively in vascular endothelial cells, neural tissues, and immune cells. The inducible nitric oxide synthase isoform is made particularly in response to infection, environmental toxins, and a variety of other stimuli. In this role, NO functions as a highly reactive molecule in killing microbes. NO radicals are elevated as measured post-mortem brains of schizophrenics.[59] Given the complex roles of iNOS, nNOS, and eNOS, it is difficult to say which one is contributing to the observed increase in NO. If schizophrenia is a disease involving brain inflammation, then perhaps iNOS activity is dysregulated and causes excessive production of nitric oxide. In fact, studies do reveal a dramatic increase in expression of the glial inflammation-associated protein S100b in schizophrenics,[60] thus supporting the idea that the increased nitric oxide observed in schizophrenic brains is most likely due to increased iNOS activity, but not so much changes in eNOS or nNOS. The role of eNOS in cardiovascular health is well known and studied intensely particularly as

related to the disease of atherosclerosis, while the role of nNOS is less understood with respect to various diseases. By supplementing with arginine, we can potentially increase vasodilation, circulation, delivery of NAD precursor, and angiogenesis. Whether this is likely to help in schizophrenia is unknown but given that there are few reported side effects for high doses of arginine or glutamine it seems there is little to risk with potentially much to gain by including these two amino acids in any high dose niacin therapeutic approach to treating schizophrenia.

Dosage

The average US diet provides 4-5 g of arginine a day. Cardiovascular benefits are clearly observed in clinical trials when providing additional supplementation of 3-10 g three times daily.[61,62] High doses have been administered in many clinical trials with numerous therapeutic benefits observed. Thus 3-10 g arginine three times each day may be worthy of consideration for treating schizophrenia for the reasons described in this manuscript. Glutamine is the most abundant amino acid in the body. To date glutamine studies have

Figure 1. The pathways from niacin to NAD and flush response are shown with the potentially therapeutic modifiers, glutamine and arginine. Niacin as nicotinic acid (NA) is converted to nicotinamide adenine dinucleotide (NAD). NAD ultimately as NAD(H(P)) participates in over 450 reactions as either a co-factor or substrate. NA however, also can bind to a high affinity G-protein coupled receptor, which leads to the vasodilation response and many other effects most prominently including the effects on lipodystrophy: lowers cholesterol, triglycerides, and VLDL, while raising the beneficial HDL in individuals for which these measures are badly overloaded in the opposite direction. PGE_2 & PGD_2 are prostaglandins, while EP_2/EP_4 & DP_1 are g-protein coupled receptors specific to PGE_2 and PGD2 ligands respectively. LDCs, Langerhans dendritic cells; NA, nicotinic acid/niacin; NAM, nicotinamide; NAMR, nicotinamide riboside mononucleotide; W, tryptophan; IDO, indoleamine 2,3-dioxygenase enzyme; NaMN, nicotinic acid mononucleotide; NMN, nicotinamide mononucleotide; NaAD, nicotinic acid adenine dinucleotide; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; MLCK, myosin light-chain kinase; NO, nitric oxide; cGMP, cyclic guanosine monophosphate



mostly focused on treating severely burned patients, those experiencing cancer cachexia, or undergoing chemotherapy.[63] Therapeutic benefits were observed for all of these situations. The most effective doses were seen after administration of 10-15 g three times each day with the biggest responses seen closer to the 45 g per day dosage. Adverse events generally have not observed for either amino acid.[64] However, since nothing is known with respect to doses for treating schizophrenia specifically, extra attention should be made to monitoring the response in all cases. In summary, 3-10 g of arginine three times each day, and 10-15 g of glutamine three times each day may additionally provide therapeutic benefit to the schizophrenic.

Conclusion

There does not appear to be any downside to the simultaneous application of supplemental arginine and glutamine in combination with high dose niacin as a potentially beneficial treatment for schizophrenia. There may be additional therapeutic benefit when this pathway is further strengthened towards more NAD biosynthesis, and more sustained vasodilation via additional glutamine and arginine respectively.

Competing Interests

The author declares that he has no competing interests.

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