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Coenzyme Q10 for Heart Disease

By Dónal P. O'Mathúna, PhD

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COENZYME Q10 (COQ10) HAS BEEN RECOMMENDED FOR A WIDE RANGE of cardiac conditions. Heart disease remains a significant cause of morbidity and mortality, in spite of recent progress in some areas (heart disease will be used here broadly to include heart failure, arteriosclerosis, ischemic heart disease, cardiomyopathy, hypertension, and other cardiac problems[1]). In a variety of patients with heart disease, serum CoQ10 levels have been found to be significantly lower compared to healthy controls, suggesting that a deficiency may exist due to insufficient intake.[2] Studies have found that CoQ10 levels decrease as the severity of heart disease increases.[1] Because of these associations between heart disease and CoQ10 levels, use of CoQ10 supplements has become widespread.[2] Various trade sources list it as having the third highest sales levels among non-herbal supplements, falling behind only glucosamine and essential fatty acids. Clinicians should be aware of the evidence currently available on CoQ10 and heart disease as many patients already may be using it or considering doing so.

Biochemistry

Coenzyme Q is the name given to a group of compounds containing a ring structure and a long chain made up of repeating five-carbon sections called isoprenoid units.[3] The coenzyme Q found in humans contains 10 isoprenoid units, hence the name coenzyme Q10, or CoQ10. It is also called ubiquinone because it is ubiquitous, being found in all eukaryotic cells.[1] It is an essential cofactor in the electron transport chain (ETC) and a potent antioxidant.[3] It carries out both roles within mitochondria, the "power houses" of all cells. CoQ10 is highly lipid-soluble and lodges within the lipid layers of the inner membranes of mitochondria. CoQ10 is especially important in cardiac muscle because energy requirements are high and therefore the cells contain many mitochondria.[4]

Mechanism of Action

Mitochondria replenish the chemical energy of cells by generat-

ing a molecule called adenosine triphosphate (ATP) via the ETC. CoQ10 plays a vital role in a number of complexes involved in this process.[3] Administration of CoQ10 has been proposed to help in heart disease by improving cardiac bioenergetics.[1] CoQ10 is a more powerful antioxidant than vitamin E and may be beneficial in cardiovascular damage caused by free radicals and superoxide.[5] CoQ10 stabilizes membranes, and in particular stabilizes calcium and other ion channels.[1] This may prevent the depletion of metabolites necessary for the production of ATP. In addition, since CoQ10 levels are depleted with heart disease, supplementation may be beneficial via other mechanisms that have not yet been elucidated.

Clinical Studies

CoQ10 was discovered in 1957 and by the 1980s was being used in studies involving heart failure patients.[6] The results of early clinical research were highly encouraging, but most of these studies were observational in design. Randomized controlled trials (RCTs) then were conducted, but tended to have small numbers of participants and to reach contradictory conclusions. A meta-analysis published in 2006 included 11 RCTs with a total of 277 heart failure patients.[2] A statistically significant increase in ejection fraction of 3.7% was found between those taking CoQ10 and controls ($P < 0.00001$). This is about half the improvement found with other heart failure medications. A sub-group analysis found that patients taking CoQ10 along with ACE inhibitors had no increase in ejection fraction; those taking CoQ10 who did not concurrently take ACE inhibitors had a 6.7% increase in ejection fraction. The reviewers concluded that the two substances should not be taken together, but that CoQ10 may be an option for patients intolerant to ACE inhibitors. Further analysis found that patients with more severe heart failure (New York Heart Association [NYHA] class III and IV) had greater improvements than those with class I and II.

A Cochrane Collaboration systematic review currently is being conducted to provide an updated evaluation of the evidence regarding heart failure.[7] One of the challenges in this area is that to detect differences in relatively infrequent events (like death), very large numbers of participants would be needed. Some have estimated it would take at least 2,000 patients per group.[6] Given the costs of such a trial, one with several hundred patients is more realistic. An international, multicenter RCT is being conducted with more than 500 patients with NYHA class III and IV chronic heart failure.[4] Called the Q-SYMBIO (Symptoms, Biomarker status (BNP), and Long-term Outcome) trial, its results should be available in the near future and will provide the best evidence to date on the long-term effectiveness of CoQ10 for heart failure patients.

The impact of CoQ10 on hypertension was reviewed in 2007.[8] The review included 12 studies, although most of them were observational studies with no control group. In that meta-analysis, the pooled results, from 362 patients, demonstrated that CoQ10 supplementation produced a reduction of up to 17 mmHg in systolic and 10 mmHg in diastolic blood pressure.

Including such divergent study designs in a meta-analysis is questionable. A 2009 Cochrane systematic review of CoQ10 for hypertension included only RCTs.[9] Three were identified, with a total of 96 patients. Statistically significant reductions in both systolic (11 mmHg) and diastolic (7 mmHg) blood pressures were found. The reviewers stated that this would indicate that CoQ10 was "a remarkably effective antihypertensive agent"—if the results "are true." They were concerned at the very high risk of bias in the studies stemming from their small size and unclear descriptions of their methods. In addition, the lead author on one of the studies has been investigated for scientific misconduct, leading *BMJ* and *Lancet* to publish "expressions of concern" about his work.[10] Others have concluded that large RCTs are needed in this area to provide high-quality evidence to guide hypertension patients and their clinicians.[6]

Because of its antioxidant properties, CoQ10 also has been used for the prevention and treatment of cardiovascular disease. A 2003 AHRQ Evidence Report/Technology Assessment identified 54 studies on a variety of cardiovascular outcomes and markers.[11] Many of these were preclinical studies, enrolled small numbers of patients, or were of short duration. The authors limited their analy-

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sis to RCTs measuring clinical outcomes with at least 60 patients and at least 6 months of follow-up. This led to discussion of 6 studies. The two earliest studies found significant benefit for those taking CoQ10, but both studies had serious methodological flaws. The four subsequent studies reported either no benefits or clinically small improvements. The report concluded that use of CoQ10 supplements in patients with cardiovascular disease was "an open question, with neither convincing evidence supporting nor refuting evidence of benefit or harm."

A series of RCTs has examined the impact of statins (HMG CoA reductase inhibitors) on CoQ10 metabolism.[6] The majority of these showed that plasma CoQ10 levels were lower when people took statins. This is believed to arise because statin inhibition of cholesterol synthesis also inhibits CoQ10 synthesis. Concerns have been raised that reduction in CoQ10 may account for muscle complaints and myopathies, which are an adverse effect reported for statins.[12] However, this remains an unproven hypothesis in part because while statins reduce circulating CoQ10 levels, reductions in muscle tissue levels have not been reported.[3] Small studies comparing the rate of muscle pain in people taking statins alone or statins plus CoQ10 have produced contradictory results. An RCT with 80 patients is currently examining this issue.[3]

Adverse Effects

One of the attractive aspects of CoQ10 administration is that few adverse effects are reported. It is widely acknowledged as having an excellent safety profile.[4] Up to 1,200 mg per day is viewed as safe, although most studies tend to use 100-300 mg per day.[3] Some studies have reported mild adverse effects, primarily gastrointestinal disturbances.

CoQ10 is chemically similar to vitamin K and may have pro-coagulant activity. A small number of cases have reported decreased effectiveness of warfarin when CoQ10 was taken concomitantly.[13] Thus, caution is warranted if those taking warfarin start taking CoQ10.

Formulation

CoQ10 supplements are most commonly formulated as oil-based capsules because of the highly lipophilic nature of CoQ10. This leads to its absorption being poor, highly variable, and strongly dependent on the contents of the stomach. Nanoparticular, solubilized, and emulsified formulations are available and have better bioavailability than capsules or powders.[3] More recent studies have found that higher serum levels are reached when ubiquinol is administered rather than ubiquinone.[1] Ubiquinol is the reduced form of CoQ10 and believed to be the active antioxidant in the body.[6] This form is absorbed eight times better than ubiquinone.[1]

Conclusion

The rationale for CoQ10 supplementation is clearly established biochemically. CoQ10 has a number of actions in the body that would be beneficial in the prevention and treatment of heart disease. However, the results from controlled clinical trials have not been as uniformly beneficial as was originally expected. Meta-analyses have generally found evidence of some benefit from CoQ10 supplementation. However, most of the studies to date have had small numbers of participants and other methodological weaknesses. Concerns also have been raised about the lack of detail on the CoQ10 formulation used and plasma levels attained in some studies. The concern is that some studies may have used formulations with poor bioavailability. Newer formulations and larger RCTs currently being conducted should help to give more conclusive evidence on the therapeutic potential of CoQ10 supplements.

Recommendation

Given the lack of adverse effects, CoQ10 can be recommended for some patients with heart disease. Although the evidence is inconsistent, beneficial effects on various cardiac parameters have been found. However, careful monitoring is essential, especially as many heart patients are likely to be taking other medications. Those taking ACE inhibitors may not derive any additional benefit from co-administration of CoQ10. Some uncertainty remains about the effectiveness of CoQ10 in heart disease, but a number of large RCTs are currently being conducted. As their results become available, greater confidence will be possible on precisely which types of conditions are most likely to be improved by CoQ10 supplementation. Further evidence is also needed on the best formulations and dosage regimens for various conditions. ■

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Probiotics Effectively Treat Irritable Bowel Syndrome in Children

ABSTRACT AND COMMENTARY

By Donald Brown, ND

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Synopsis: *Results of this 8-week clinical trial demonstrated the efficacy of* Lactobacillus rhamnosus *strain GG (LGG) in reducing the frequency and severity of pain in children with irritable bowel syndrome or functional abdominal pain. Benefits persisted for 8 weeks after cessation of treatment. Additionally, small intestinal permeability was decreased in children with IBS treated with LGG.*

Source: Francavilla R, et al. A randomized controlled trial of *Lactobacillus* GG in children with functional abdominal pain. *Pediatrics* 2010;126:e1445-e1452.

Recurrent abdominal pain (RAP) is estimated to affect 10%–15% of school-aged children.[1] The pediatric Rome criteria have proposed four categories for RAP: irritable bowel syndrome (IBS), functional dyspepsia (FD), childhood functional abdominal pain (FAP), and abdominal migraine.[2] Based on some published clinical trials indicating success using probiotics to treat IBS in adults as well as limited data in children,[3] the researchers of this randomized, double-blind, placebo-controlled trial sought to determine whether probiotic therapy could reduce the frequency and severity of pain in children with a diagnosis of either IBS or FAP. Children (5 to 14 years of age) with a diagnosis of IBS or FAP, according to the Rome II diagnostic criteria, were enrolled in the study. Exclusion criteria included chronic diseases, antibiotic or probiotic therapy within the previous 2 months, and pain history suggestive of functional dyspepsia/aerophagia/abdominal migraine.

The 20-week study was divided into three parts: 1) a 4-week run-in phase (weeks 1-4); 2) an 8-week treatment period (weeks 5-12); and 3) an 8-week follow-up phase (weeks 13-20). During the treatment period, children were randomly assigned to receive oral capsules containing either *Lactobacillus rhamnosus* strain GG (LGG; 3 x 10^9 colony forming units) or oral placebo twice per day. Throughout the 20-week study, children recorded the frequency and severity of pain using a combination of a self-reported visual analog scale and the Faces Pain Scale. Parental assessment of overall of pain relief was obtained by interviewing them just before and after the treatment period. Additionally, intestinal permeability was tested using the lactulose-to-mannitol ratio (La/Ma) test. The test was performed one day before and after the 8-week treatment period. Fifty-five children with no history of RAP were recruited to assess the normal range of La/Ma and were used as a control group. The primary outcome was the change in abdominal pain (frequency and severity) from baseline to the end of the treatment period. Secondary outcomes included at least a 50% decrease in the number of episodes and intensity of pain (treatment success), a decrease in perception of children's pain according to parents, and modification of intestinal permeability.

A total of 141 children underwent randomization and 136 children completed the study (n = 67 in the LGG group). Of the children completing the study, 80 were diagnosed with IBS (n = 42 in the LGG group) and 56 with FAP (n = 25 in the LGG group). In the children with IBS, the number of episodes of pain per week during the 4-week run-in was 3.4 ± 2.3 in the LGG group and 4.0 ± 3.5 in the placebo group. The number of painful episodes at the end of the 8-week treatment period (week 12) were 1.6 ± 0.8 and 3.2 ± 1.9, respectively ($P < 0.001$). At the end of the 8-week follow-up period (week 20), the number of episodes of pain per week were 0.9 ± 0.2 for the

LGG group compared to 1.6 ± 0.9 for the placebo group ($P < 0.001$). The severity of pain at baseline was 4.4 ± 2.1 for the LGG group and 4.6 ± 2.8 for the placebo group. After the treatment period, severity of pain was 2.5 ± 1.2 and 3.6 ± 2.2, respectively ($P < 0.001$). At week 20, severity of pain was 1.8 ± 0.3 in the LGG group compared to 3.3 ± 1.5 in the placebo group ($P < 0.001$). At week 12, treatment success was achieved in 82% of the children in the LGG group compared to 45% in the placebo group ($P < 0.01$). Treatment success at 20 weeks was 87% and 50%, respectively ($P < 0.01$). Children with a diagnosis of FAP did not show significant changes in either number of episodes or severity of pain compared to placebo. The only exception was a small improvement in pain intensity at week 20 compared to placebo. According to the researchers, LGG was well tolerated and there were no adverse effects reported.

Only 54 children participated in the intestinal permeability test (IPT). Compared with control subjects, 32 of 54 children had abnormal IPT (mean La/MA: 0.035) irrespective of whether they were diagnosed with IBS or FAP. At week 12, there was a significant reduction in intestinal permeability in children with IBS taking LGG compared to placebo ($P < 0.02$) but not in those with FAP. There was no correlation between the IPT and severity of symptoms.

■ COMMENTARY

IBS is the most common functional gastrointestinal disorder with a reported prevalence in the general population between 12%-22%.[4] Children with IBS represent 25%-50% of all patients presenting to pediatric gastroenterology clinics.[5] However, beside reassurance and counseling on managing pain, conventional therapies have shown inconclusive results in the treatment of RAP, including IBS.[6]

A 2009 meta-analysis reported on the findings of 14 placebo-controlled trials using probiotics for the treatment of IBS.[3] Although the majority of studies were with an adult population, two pediatric trials reported on the use of the probiotic strain LGG for the treatment of FAP and IBS.[7,8] Despite methodological limitations in both trials (e.g., small sample size and short treatment duration), one study found minimal efficacy (slight improvement in abdominal distension) in children with IBS[7] while the other reported efficacy in children with IBS, but not FAP and FD.[8] Interestingly, in both adult and pediatric trials demonstrating efficacy for IBS, the predominant symptom alleviated by probiotics was abdominal pain.[3]

The reviewed clinical trial improves on the design of the previous positive trial with LGG. While using the same daily dose of LGG, the study not only includes a longer treatment period (8 weeks vs. 4 weeks) but also an 8-week follow-up phase. It is interesting to note that the findings of this trial mirror those of the earlier trial. Specifically, that LGG appears to provide symptoms relief for children with IBS but not FAP. As opposed to the earlier trial, the current study demonstrated a significant decrease in both the severity and frequency of pain. Of particular interest is the finding that those subjects with IBS taking LGG continued to have significant symptom relief for 8 weeks after the cessation of treatment. Also notable was the absence of adverse events in those taking LGG.

Although only measured in a handful of children, the intestinal permeability findings are also notable in this study. Abnormal intestinal permeability has been found in adults with diarrhea predominant IBS.[9] Probiotics have been shown to decrease intestinal permeability in preterm infants[10] as well as healthy Egyptian children.[11] The current study clearly demonstrates a decrease in permeability in children with IBS taking LGG. While altered intestinal permeability still has not been established firmly as a cause or effect of IBS, there is growing evidence that it may play a role in both pediatric FAP and IBS.[12] There is also growing evidence that patients with IBS are likely to demonstrate dysbiosis (small intestinal bacterial overgrowth)[13] to argue in favor of probiotic therapy for the condition.

It should be noted that the reporting of the results of this study are confusing and bring into question the editorial rigor of the journal. There are inconsistencies between the reported numbers of children in each group included in the intention-to-treat analysis in a figure showing enrollment, assignment, intervention, and follow-up and the tables reporting the primary and secondary outcomes. Also, the outcomes reported in the Results section of the paper appear to combine both diagnoses. A closer look at the specific results by diagnosis shown in Tables 2 and 3 basically demonstrate an excellent treatment response for children with IBS and essentially none for those with FAP. The results reported in my summary of the study reflect that data as reported by specific diagnosis.

Taking off an editorial hat and replacing it with a clinical one, the reality is that while pediatric gastroenterologists may have the tools and expertise to differentiate between IBS and FAP, the division between specific diagnoses is not always clear in pediatric practice. While IBS is often a more clear-cut diagnosis in adults, children present a more complicated challenge due to the often non-specific nature of their chronic abdominal pain that encompasses a heterogeneous group of patients. The researchers chose to include children with FAP because the condition has been found to be a precursor of IBS in adults.

So, while this study certainly lays the groundwork for a follow-up trial using LGG specifically in children with IBS, it provides us with a promising and safe therapeutic option for a condition currently lacking in efficacious

treatment options. In short, a therapeutic trial with LGG may be indicated in any child meeting any of the pediatric Rome criteria for RAP. ■

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Salvia: From Grandma Anna to Hannah Montana?

By Craig Schneider, MD

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Salvia is back in the news, but is well known to healer's through the ages. At least as far back as Pliny the Elder (23-79 C.E.), *Salvia* species have been purported to have memory-sparing effects. *Salvia officinalis* (common sage), *Salvia lavandulaefolia* (Spanish sage), and *Salvia mittorrhiza* (Danshen) all have been evaluated to some degree for dementias, although there are few well-designed clinical trials in humans. As with the majority of pharmaceutical approaches to managing Alzheimer's disease, salvia appears to inhibit acetylcholinesterase (AChE) and increase levels of acetylcholine in the brain. Constituents of salvia demonstrate this both in vitro (human brain) and in vivo (rats).[1-3] "Rosmarinic acid, an active ingredient of common sage, also reduces several deleterious events induced by amyloid-β, including the formation of reactive oxygen species, lipid peroxidation, DNA fragmentation, caspase-3 activation and tau protein hyperphosphorylation."[4]

Thus far the only double-blind randomized controlled trial of salvia use for dementia was of *S. officinalis* in 2003, which was previously reviewed in *Alternative Medicine Alert (May 2003)*. This study evaluated 30 Iranian subjects (aged 65-80 years) with mild-to-moderate Alzheimer's, randomized to trial intervention over 4 months. Their current dementia medications were discontinued and replaced with 60 drops per day of an extract of *S. officinalis* (1 kg dried leaf to 1 L of alcohol) or placebo. Cognitive function was measured at baseline and every two weeks by a neurologist. At 16 weeks, those who received *S. officinalis* had significantly better scores on Alzheimer's Disease Assessment Scale (ADAS-cog) and ≤ 2 on the Clinical Dementia Rating (CDR) than subjects in the placebo group, (ADAS-cog: $F = 4.77$, d.f. = 1, $P = 0.03$) (CDR-SB: $F = 10.84$, d.f. = 1, $P < 0.003$). Side effects related to use of *S. officinalis* were related to cholinergic stimulation, primarily agitation ($P = 0.09$) as would be expected. The study was criticized for small numbers of participants, unclear exclusion criteria, and brief duration, etc.

So, why is salvia back in the news? The salvia that has stepped onto the stage of late is a different member of the genus, *Salvia divinorum*. *S. divinorum* or "divining sage" originated in Oaxaca, Mexico, where it has been

used orally for hundreds of years by Shamans for healing and divination. Over the past decade *S. divinorum* has become a popular hallucinogenic with youth in America who smoke or inhale a vaporized version. It is widely available for sale on the Internet and in drug paraphernalia shops; as of 2006, about 1.8 million people had tried *S. divinorum*, with the heaviest use among males 18-25, 3% of whom had used *S. divinorum* in the previous year.[5] Users report brief, intense hallucinogenic effects and more persistent effects as improved moods and insight.[6]

A retrospective review of California Poison Control Centers revealed 37 calls involving *S. divinorum* exposures with gastrointestinal, cardiovascular, and neurologic complaints. There are several cases of extended psychotic reactions, but interpretation is complicated by concurrent drug use,[7] or suspected genetic predisposition.[8]

Most recently *S. divinorum* swept into media consciousness as a video on YouTube revealed "tween" idol Miley Cyrus of Disney's *Hannah Montana* celebrating her 18th birthday smoking a bong filled with *S. divinorum,* resulting in "uncontrollable laughter" and "garbled speech."[9] Its use has been banned or regulated in 15 states, and there are moves to ban it in more, but the Drug Enforcement Administration currently considers it a "drug of concern" not a controlled substance. Researchers have taken an interest in its potential medical uses and are concerned that "criminalization would make it burdensome to obtain and store the plant, and difficult to gain government permission for tests on human subjects."[10] Apparently the herb's "presence on military ships and bases has even prompted the Armed Forces Institute of Pathology to develop the first urinalysis for salvia."[10]

Around the same time, an article in press reported on recent work at Johns Hopkins focusing on salvinorin A, a neoclerodane diterpene considered to be the most active component of *S. divinorum*.[11] A kappa opioid receptor agonist in the brain, salvinorin A works differently than other common hallucinogens. The researchers wanted to study this drug due to its "wide availability, continued popular use, and legal controversy" as well as the belief that "studying the effects of salvinorin A may assist in identifying new opioid receptor modulators that may have therapeutic applications in certain psychiatric disorders (e.g., Alzheimer's disease, schizophrenia, bipolar disorder, cocaine abuse)."[11]

Four participants who previously had used a hallucinogen, but had no drug or alcohol dependence and no personal or family history of mental illness were included. Their mean age was 29 and they completed a medical exam prior to participation including a physical exam, ECG, CBC, CMP, and cholesterol profile. Subjects were given 16 doses of inhaled salvinorin A isolated from *S. divinorum* leaves and placebo inhalations across 20 sessions over 8-14 weeks. An unblinded staff member monitored the sessions but blinded staff collected drug-strength ratings and other pre- and post-session data. Subjects rested in easy chairs (semi-upright or reclined), listened to "a relaxing instrumental music track, and wore eyeshades 3-5 minutes prior to and for 10-30 minutes after administration of salvinorin A. They completed questionnaires and assessments 1 hour after administration of drug. Blood pressure, heart rate, and tremor were monitored during the sessions. No tremor nor significant impact on blood pressure and heart rate was observed. Time- and dose-related effects were observed, with peak drug strength occurring at 2 minutes and then progressively weakening over 20 minutes to near baseline.

In this recent high-profile but tiny human trial, in healthy participants with histories of hallucinogen use the authors report a safe physiological and psychological safe profile, with no adverse events. They were able to demonstrate that in a comfortable and supportive environment, salvinorin A elicited a "unique profile of subjective effects" that included "changes in spatial orientation, feelings of energy or pressure on different parts of the body, and unusual and sometimes recurring themes across sessions, such as revisiting childhood memories, cartoon-like imagery, and contact with entities."[11] Unlike the online videos demonstrating "chaotic effects," these subjects remained behaviorally inactive.

Salvia, salvia, salvia. *Salvia divinorum* is a popular hallucinogenic drug among today's youth. *Salvia officinalis* has no hallucinogenic effects and might be helpful for people with mild-to-moderate dementia. We don't yet know if either will yield new approaches to dementia, but do know that people considering using salvia should become familiar with plant taxonomy. ■

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Acupuncture—The Seen, Unseen, and Adenosine

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: In this exquisite set of methodical laboratory investigations, researchers tested whether adenosine might play a pivotal role in the analgesic effects associated with acupuncture. Their results suggest that the search for a mechanism of action behind this traditional therapy may be near its end.

Source: Goldman N, et al. Adenosine A1 receptors mediate local anti-nociceptive effects of acupuncture. *Nature Neurosci* 2010;13:883-889; commentary: Zylka MJ. Needling adenosine receptors for pain relief. *Nature Neurosci* 2010;13:783-784.

The traditional explanation for acupuncture's therapeutic effects have focused on the movement of *qi*, or the life force energy within and surrounding each of us. The placement of needles in carefully detailed locations on the body for the management of different health conditions as handed down across millennia is now commonplace, but a mere 40 years ago it fell more into the realm of mystery, if not in some people's minds, voodoo. Modern research instruments and some of the great scientific minds of our time have attempted to unravel what, if anything, happens during acupuncture therapy but puzzle pieces have always been left missing. That is, perhaps, until now.

The authors of this terrific investigation extrapolated well-accepted data on the activity of the nucleotides ATP, ADP, and AMP to explore in a murine pain model whether adenosine might be important to the analgesic effects ascribed to acupuncture. They knew that the aforementioned nucleotides are acted upon by ectonucloetidases that degrade them producing adenosine, and first sought to determine whether extracellular concentrations of adenosine increase during acupuncture. Samples of interstitial fluid were collected from near the "Zusanli point," located a few mm away for the midline of the knee. Levels of adenine nucleotides and adenosine were quantified using high-performance liquid chromatography before, during, and after acupuncture in association with gentle manual rotation of the needle every 5 minutes over the course of a 30-minute session. Levels of all purine levels increased locally. Adenosine concentration increased ~24-fold (253.5 ± 81.1 nM from a baseline of 10.6 ± 6.7 nM). Extracellular ATP levels returned to baseline after acupuncture, but those of adenosine, AMP, and ADP remained significantly elevated (adenosine and AMP, $P < 0.01$; ADP, $P < 0.05$) at 60 min. Thus, the researchers showed that adenosine was released during acupuncture.

Next, they explored whether adenosine was central to the analgesic effects of acupuncture by testing the effect of a selective A1 receptor agonist (CCPA) in mouse models of chronic pain. Injection of an inflammatory compound into the right paw resulted in mechanical and thermal allodynia (pain due to a stimulus that normally does not induce pain) in the same paw. When CCPA was injected into the Zusanli point there developed a marked increase in the threshold to pain in response to touch and heat and a reduction in mechanical allodynia. Further studies included mice lacking the A1 adenosine receptor and concluded that CCPA only reduced hypersensitivity in the presence of the A1 receptor.

The study authors next created a model of neuropathic pain by ligating the sciatic nerve, with peak pain levels being reached in 5-7 days. When CCPA was injected into the Zusanli point of the ipsilateral leg, a reduction in discomfort compatible with that seen in the chronic pain model was elicited. However, when CCPA was injected into the contralateral leg there was no pain relief. Thus, the authors concluded the action of CCPA is mediated through local A1 receptors. The researchers injected saline instead of CCPA into the Zusanli point and found no change in pain threshold.

The researchers then recorded in vivo responses of the left anterior cingulate cortex (ACC) to painful stimulation of the right foot and found that high-intensity stimulation produced consistent field excitatory postsynaptic potentials (fEPSPs) in the ACC with a latency of ~40 ms, reflecting the involvement of a polysynaptic pathway. Injection of CCPA into the contralateral leg's Zusanli point

had no effect on fEPSPs, showing that CCPA did not act centrally; however, when CCPA was injected into the ipsilateral leg, a significant decrease in fEPSP amplitude was seen, occurring as soon as 6 minutes after injection. Thus, CCPA exerts its actions locally.

The researchers then employed a similar strategy to assess the effects of acupuncture on fEPSP amplitude recorded in the left ACC from painful stimulation of the right leg. Acupuncture of the left Zusanli point created no effect; however, when the ipsilateral Zusanli point was needled, fEPSP amplitude decreased. fEPSP amplitude was maximally reduced to 53.7 ± 7.2% ($P < 0.01$) of baseline at 60 min. Of note, acupuncture did not alter fEPSP in mice lacking A1 receptors. An additional study used deoxycoformycin, an established inhibitor of enzymes involved in adenosine degradation, with resultant augmentation of the acupuncture-elicited rise in adenosine levels, as well as its anti-nociceptive effect.

The authors state that combined, these observations provide direct evidence for a role of adenosine in acupuncture-mediated analgesia and suggest that adenosine accumulates slowly in the extracellular space during acupuncture. They also suggest that specific pharmaceuticals that antagonize adenosine metabolism may enhance the duration of pain relief with acupuncture.

■ COMMENTARY

In some ways it seems the search for a plausible mechanism behind acupuncture's effects was a "holy grail" of sorts. Some practitioners simply trusted in the outcome of the intervention, while others held to the traditional belief that the *qi* could be manipulated in therapeutically effective ways; some found comfort in data suggesting central opiate activity plays an important role, while others thought any response to acupuncture therapy to be placebo in nature; still others wanted a definitive answer. Across the rage of philosophies espoused by practitioners comes a potential answer that seems hard to refute.

The researchers found not just adenosine was released following acupuncture, but so were ATP, ADP, and AMP. This suggests that adenosine is produced locally by the effects of ectonucleotidases. As the author of a commentary that accompanies the study points out, it will be interesting to see if the anti-nociceptive effects of acupuncture are blocked by ectonucleotidase inhibition.

Adenosine can increase or decrease pain depending upon which receptor is stimulated. Of the four adenosine receptors (A1R, A2AR, A2BR, and A3R), only A1R has anti-nociceptive effects when activated peripherally. And A1R is blocked by caffeine; thus, it appears that people undergoing acupuncture therapy should avoid caffeinated products at least around the time of their treatment.

In sound fashion, the researchers took us through a methodical exploration into the role of adenosine and A1 receptors in acupuncture-associated analgesia. Other pathways may be involved, too, but for the first time there is an explanation to the oft-heard question, "How does acupuncture work?" that should assuage hard-core scientists, while not disrespecting traditionalists. In addition, there is the promise of an integrative approach to pain relief using a combination of acupuncture and drug therapy to extend the duration of acupuncture's effects. In this paper, science and traditional belief have come together in a meaningful way that should help our patients find even greater relief from pain. ■

Over-Energized Kids — Energy Drinks

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: A review article examining the potential adverse effects of energy drinks on kids generated a lot of buzz recently in the lay media. The beverage industry countered with information of its own, but the research referenced in the journal article lays out a solid foundation against the drinking of energy drinks, especially in children.

Source: Seifert SM, et al. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics* 2011;127:511-528.

The burgeoning energy drink market gathers a significant proportion of its steam from youngsters and adults under the age of 25 years. The drinks are marketed in attractive ways and at popular venues, and together with the hype surrounding their use (clearer thinking, better athletic performance, etc), their appeal is hard for young people to resist. Studies suggest that upwards of one-third of all middle school children partake of energy drinks, with an increasing prevalence of use as they enter into early adulthood, sometimes in combination with alcohol. Little hard data exist, but a number of high-profile reports of serious complications associated with frequent ingestion of energy drinks prompted the authors of this review to delve deeper.

The investigators searched PubMed for English language articles and abstracts relevant to the topic of energy drink use in children and adolescents, as well as Google for trade media reports. Of the 121 references identified, more than 60% were from "the scientific literature," mostly from U.S. publications.

Only recently have U.S. poison centers been able to specifically track adverse events related to energy drinks; the authors note that previously such incidents often were coded under caffeine toxicity, for example. Other countries have been able to collect specific data in this regard and report small but significant numbers of cases of liver and kidney damage, behavioral disorders, seizures, dysrhythmias, and even rare cases of death associated with extremes of intakes. The study authors do a nice job of reviewing the physiologic effects of caffeine, balancing the few positive health effects often cited (improved reaction time, exercise performance) with the untoward consequences mentioned above while adding reports of irritability, palpitations, increases in blood pressure, and the possibility of withdrawal symptoms with even mild exposure.

The authors conclude that energy drinks offer no therapeutic benefit but do offer potential for significant harm, especially in youngsters with cardiac disease, seizure disorders, and behavioral issues who are taking medications. They recommend that physicians ask their patients about the use of energy drinks, and recommend consideration of added regulation of these products.

■ COMMENTARY

The number of adverse events reported in this article is relatively small considering the number of energy beverages consumed each day around the world, but many complications surely go unreported, and even when reported are often classified, as the authors note, under general terms that do not implicate energy drinks. However low the total number of reported adverse events, the critical nature of many of the events warrants our immediate attention, and the researchers are to be applauded for this wake-up call.

The principle active ingredient found in most energy drinks is caffeine, but other compounds, including cocoa and the herb guarana (*Paullinia cupana*), provide added caffeine content that is not necessarily reported on the food label. Limits on beverage caffeine content are enforced by the FDA, but energy drinks are generally considered dietary supplements and so may escape such regulatory standards. The generally accepted adverse effect level of caffeine according to the study authors is 3 mg/kg body weight per day. Energy drinks are frequently high-calorie beverages, too, and may contain significant amounts of sweeteners.

Adults who would not offer their children coffee for fear of getting them "hooked" or developing a bad habit often have no difficulty allowing those same kids to drink caffeinated sodas and now energy drinks. Most adults rely on caffeine as a way to fend off fatigue related to inadequate sleep, and research suggests that adults are not the only ones who are sleep deprived; their children are, too. In part the answer may be to pound the message home about the importance of getting an adequate quantity and depth of sleep and to repeatedly instruct patients in the tricks of sleep hygiene that can help ensure a restorative night's sleep. The default position is to continue feeling tired in the morning, treating oneself with caffeine to "get going" in the morning and perhaps again in the early and late afternoons, followed by added difficulty getting to sleep due to the lasting effects of caffeine, and a worsening of the cycle. Certainly this is not what any parent would want for his or her children; dependence on any substance stirs deep fears within us all, but the message has not gotten out in a substantive way until the publishing of this paper.

Another part of the solution has to be countering the marketing messages that make these drinks appear cool to kids. Here's hoping that this new kind of media attention energy drinks have earned goes a long way toward the curtailing of their use by children (and their parents). ■

Meditation for Fibromyalgia: Yea or Nay?

ABSTRACT AND COMMENTARY

By Nancy Selfridge, MD

Dr. Selfridge is Associate Professor, Department of Integrated Medical Education, Ross University School of Medicine, Commonwealth of Dominica, West Indies; she reports no financial relationship to this field of study.

Synopsis: *Mindfulness-based stress reduction (MBSR) was investigated as an intervention for fibromyalgia patients in a 3-armed randomized controlled trial using health-related quality of life at the end of 2 months as the primary outcome. While the study did not support the efficacy of MBSR for the treatment of FM for this outcome, some secondary outcome variables demonstrated improvement.*

Source: Schmidt S, et al. Treating fibromyalgia with mindfulness-based stress reduction: Results from a 3-armed randomized controlled trial. *Pain* 2011;152:361-369.

Mindfulness-based stress reduction (MBSR) training often is offered as an 8-week structured program as initially created by Jon Kabat-Zinn. The program uses meditation and yoga techniques to help participants develop nonjudgmental awareness and acceptance of emotions and sensory perceptions in the present moment.[1] MBSR has been shown to improve psychological and physical

symptoms, coping, and quality-of-life measures in a number of chronic conditions.[2] Several studies have assessed MBSR alone and in combination with other techniques as an intervention for fibromyalgia. Of these, few have been randomized or controlled, but most have shown some benefit of this meditation training program for fibromyalgia patients.

Based on positive short- and long-term outcomes of a small quasi-randomized trial of mindfulness-based stress reduction (MBSR) for fibromyalgia (FM), the authors of this article decided to replicate and extend their original study.[3]

Participants in this study were women 18-70 years of age recruited from the community through news media, support groups, and physician practices. All were telephone screened and underwent an intake interview and examination to confirm their diagnoses of FM and their eligibility for this study. The 177 patients included in the trial were randomized to one of three study groups: the MBSR experimental intervention, an active control intervention, and a wait-list control group. In the two intervention arms, patients were told that two innovative treatments would be prepared: one based on mindfulness concepts and the other based on health support techniques.

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

The MBSR intervention was structured on the original 8-week program created by Kabat-Zinn and others at University of Massachusetts and was taught by two formally trained and experienced MBSR instructors. In addition to class attendance, patients were required to document home practice of the techniques for 30-45 minutes daily. Participants received pre- and post-intervention 1-hour interviews with an instructor to discuss pretreatment expectations and goals and their experiences during the course. Patients also were asked to quantify to what degree goals

CME Questions

9. CoQ10 plays an important role in energy production in which part of the cell?
a. Nucleus
b. DNA
c. Mitochondria
d. Flagellum

10. The effectiveness of CoQ10 in heart disease is currently supported by:
a. biochemical studies and clear rationale for its mechanism of action.
b. high-quality, large RCTs.
c. international clinical guidelines.
d. None of the above

11. CoQ10 formulation is important because it:
a. is highly water soluble.
b. is highly lipid soluble.
c. is produced naturally.
d. breaks down quickly.

12. A randomized controlled trial of *Lactobacillus* GG (LGG) in children with functional abdominal pain found:
a. LGG appears to provide symptom relief for children with irritable bowel syndrome.
b. patients experienced a significant decrease in severity and frequency of pain.
c. symptom relief continued for 8 weeks after cessation of treatment.
d. All of the above

13 Potential harms from ingesting energy drinks include palpitations, increases in blood pressure, and withdrawal symptoms after mild exposure.
a. True
b. False

14. *Salvia officinalis:*
a. is a popular hallucinogenic drug.
b. may be helpful for people with mild-to-moderate dementia.

15. A recent study found that adenosine, ATP, ADP, and AMP are released following acupuncture.
a. True
b. False

Answers: 9. c, 10. a, 11. b, 12. d, 13. a, 14. b, 15. a.

were met at the end of treatment.

The active control intervention was also an 8-week course consisting of social support, topical education discussions, relaxation training, and gentle stretching exercises. Homework assignments were similar in intensity to the MBSR group. The two instructors, both of whom were psychologists experienced in group therapy and relaxation training, conducted similar pre- and post-treatment interviews for individuals in this active control arm.

Wait-list control patients received no active treatment and were offered a choice of either intervention at the end of the short-term follow-up period.

Primary outcome of the study was chosen to be baseline to post-intervention change on a German Health Related Quality of Life (HRQoL) inventory called "Profile for Chronic Diseases." This validated instrument consists of a self-administered 40-item questionnaire appropriate for patients with chronic but non-life-threatening diseases. Secondary outcome measures were made using the Fibromyalgia Impact Questionnaire (FIQ) and other validated instruments to assess depression, anxiety, sleep quality, pain perception, physical symptoms and self-attribution of mindfulness.

All participants also were assessed for periods of 24 hours, while pursuing their normal activities of daily living, wearing a vest-like ambulatory psychophysiologic monitor with sensors for respiration, ECG, and physical activity. The device included a recording display, and patients were required to complete an electronic diary entry at regular intervals while they were awake. The authors intend to report the monitor data in another paper.

All data, including the monitor data, were collected at baseline, at the end of the 8-week intervention or wait period, and after an additional 8 weeks for all patients. Results were based on intention-to-treat analyses, and analysis of covariance was performed. Contrast analyses were performed; one contrast compared wait-list control vs. both active treatments and a second contrast compared MBSR vs. the active control group.

HRQoL, the primary outcome, showed a significant positive change over time for the whole cohort and was significant for the MBSR group but not the active control or wait group. The differences in effect size between groups, however, was not statistically significant. Secondary outcome results were positive and significant only for improvement in anxiety and self perception of mindfulness in the MBSR group.

■ COMMENTARY

These results were in stark contrast to the large significantly positive effect that the authors noted in their first quasi-randomized study of MBSR for FM and may illustrate some of the difficulties in devising a robust study protocol involving behavioral interventions for some chronic debilitating conditions. It is interesting to note that the pre- and post-interview data collected, which included qualitative and quantitative feedback about perceived improvement, was markedly positive in the MBSR group compared to the active control. The authors postulate that the data collection in this study may have created a large patient burden that was not present in their original study protocol. Patients complained that the in-hospital process of fitting and calibrating the vest-like monitor caused fatigue and was done at the same time they were requested to complete multiple questionnaires. Thus, some patients were allowed to take the questionnaires home and complete them over the following 24 hours during which they also received prompts every 45 minutes from the monitor to fill in the electronic diary.

There are other possible explanations for the different results observed in the two studies. In the earlier study, patients chose the MBSR course based on referral from an often enthusiastic and supportive physician or after reading a positive brochure promoting the course. In the more recent study, patients did not choose their intervention. Thus the powerful effects of patient preferences and motivation may have created different outcomes.

The authors conclude that MBSR cannot be recommended as an effective intervention for FM. However, further studies are needed that attempt to conform to what occurs under more natural conditions and that are designed to carefully consider the patient burden of study participation in this population. ■

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