study in 2002 demonstrated that supplementation with acetyl-carnitine and ALA help restore mitochondrial structure and function.[35] A reasonable starting dosage of acetylcarnitine is 500 mg twice/day and of ALA, 300 mg/day of the sustained-release formulation.

SLEEP

A 2002 review establishes that sleep deprivation brings on headaches in those with headache disorders and those without. [36] In a more recent study, sleep deprivation is listed as one of the "principal precipitating factors" in migraine.[37] In the presence of obstructive sleep apnea, 80 percent of patients who treated their apnea were relieved of their headaches.[38] Further research is needed to clarify possible sleep deprivation related-mechanisms that may underlie migraine. The reader is encouraged to examine sleep habits and evaluate the potential for any sleep disorder. The chapter on sleep will guide this process.

HERBS IN MIGRAINE

The traditional, primary herbs for migraine are feverfew and butterbur. Feverfew, a name derived from the Latin word *febrifuge,* or fever reducing, has been part of the European herbal tradition for centuries. Used for fevers, arthritis, migraine, and a number of other indications, feverfew has anti-inflammatory properties. An early study in 1982 demonstrated inhibition of platelet phospholipase by feverfew.[39] The enzyme phospholipase releases arachidonic acid from membrane phospholipids resulting in pro-inflammatory prostaglandins. Feverfew's inhibition of phospholipase results in reduced pro-inflammatory prostaglandins. Researchers from Yale reported on a study of parthenolide, a sesquiterpene lactone, the active ingredient of feverfew. Parthenolide was found to bind to and inhibit the molecule IkappaB kinase beta (IKKbeta).[40] IKKbeta is directly involved in allowing NF-kappaB to move from the cytoplasm into the nucleus initiating a cascade of pro-inflammatory events. NF-kappaB is an essential nuclear transcription factor found in all cell types. It turns on pro-inflammatory genes and

is involved in cellular responses to stress, free radicals, and infection. A 2002 study at Harvard Medical School demonstrated increased activity of NF-kappaB in the initiation of migraine and its attenuation by parthenolide. Reduction in NF-kappaB levels preceded reduced inducible nitric oxide synthase levels in response to parthenolide.[41] The enzyme nitric oxide synthase produces nitric oxide, a highly diffusable gas involved in numerous biological processes including inflammation. Finally, a 2005 Italian study of parthenolide revealed, in an animal model, that it inhibited the activation of Fos by nitroglycerin in the trigeminal nucleus. As noted in the section above on Leao's spreading depression, Fos, or C-Fos, is a transcriptional protein in the trigeminal nucleus. Its presence indicates activation of neurons in the trigeminal nucleus responsible for transmission of pain signals from the meninges. Parthenolide also reduced activation of nuclear factor-kappaB in their study.[42]

Although a Cochrane Database review of feverfew trials found insufficient evidence for prophylactic efficacy,[43] several well-conducted trials did show significantly positive results. A German randomized, double-blind, placebo controlled study of one hundred seventy patients in 2005 was positive. The migraine frequency decreased almost in half in the experimental group.[44] Two older British studies also showed positive results for feverfew, both being double-blind, placebo-controlled studies.[45,46] A study in 2003 established that parthenolide is effectively absorbed through the intestinal mucosa.[47] The cause for negative studies may relate to variable amounts of parthenolide in commercial products. A British study in 1992 demonstrated that the parthenolide content of products declined during storage and that products varied widely in their parthenolide content. Some products had no detectable parthenolide content.[48] Based on the evidence discussed above, an adequate, standardized parthenolide content is essential for the efficacy of a feverfew product. Dosage of feverfew, standardized to 1.2 percent parthenolide is 80–240 mg twice/day.

Another herb that has efficacy in migraine is butterbur (Petasites hybridus). It is a perennial shrub that has been used for centuries for inflammatory disorders, including the plague, fever, cough,

asthma, and skin wounds. Butterbur appears to have at least two anti-inflammatory mechanisms of actions. It is a selective COX-2 inhibitor. COX-2 is the enzyme responsible for the formation of inflammatory prostaglandins. In addition, butterbur extracts inhibit a mitogen-activated protein kinase (MAPK) named p42/44MAPK. Protein kinase enzymes modify other proteins by phosphorylation, the addition of phosphate groups. They serve important modulatory functions in cells since up to 30 percent of all proteins can be modified by protein kinases. In particular, protein kinases affect the transmission of signals or information in cells including the regulation of gene function. The p42/44MAPK is involved in an enzymatic cascade that affects gene transcription of inducible nitric oxide synthesis and COX-2. This may be how butterbur downregulates COX-2.[49,50] As noted above, since nitric oxide may play a role in causing migraine, downregulation of the gene responsible for the enzyme leading to its formation may be another pathway for the beneficial effect of butterbur. Finally, there are studies on another species of butterbur that demonstrate the inhibition of calcium channels.[51–53]

At least three studies have demonstrated a prophylactic effect of butterbur in migraine. All were randomized and placebo controlled, and one was double blind. The butterbur was well tolerated and all three studies show significant benefit of butterbur. Dosage was 50–75 mg twice/day.[54–56]

CANNABINOIDS

Discussing the role of cannabinoids in migraine is somewhat problematic. The basic research reveals that cannabinoids can interrupt a number of the pathogenic mechanisms in migraine, discussed above. There is also significant historical precedent for its use. Unfortunately, and somewhat curiously, there are no clinicals trial articles of cannabinoid in migraine available through PubMed. An article in the *Journal of Cannabis Therapeutics* by Ethan Russo discusses the extensive history of the usage of cannabis in migraine. A number of ancient cultures including the Chinese, Indian, Egyptian, Assyrian, Greek, Roman, and the

Islamic world used cannabis for both symptomatic and prophylactic use in migraine. Russo states, "the most prominent physicians of the age in the century between 1842 and 1942 preferred cannabis to other preparations in migraine treatment, and it remained part of western pharmacopoeias for this indication throughout the period."[57]

The following is a summary of some of the research findings that support the potential efficacy of cannabinoids in migraine. An older study from 1985 reports on a statistically significant reduction of 14C-serotonin release from platelets when the patient's plasma, obtained during an attack, was incubated with phytocannabinoids. The same effect was not seen when the plasma was obtained from the patient in a headache-free period of time. Plasma serotonin appears to play a significant role in acute migraine including vasoconstriction and stimulation of perivascular pain fibers.[58]

Another interesting finding was reported from Italy in 2008. The authors measured two endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), as well as serotonin levels in the platelets of twenty chronic migraine patients, twenty patients with medication-overuse headaches, and twenty control subjects. AEA and 2-AG were significantly reduced in the chronic migraine and medication-overuse patients compared to the control group. In addition, serotonin levels were also significantly reduced in the two patient groups compared to control, and the levels correlated with 2-AG levels. The authors conclude, "These data support the potential involvement of a dysfunctioning of the endocannabinoid and serotonergic systems in the pathology of CM (chronic migraine) and MOH (medication-overuse headaches). These systems appear to be mutually related and able to contribute to the chronification of both CM and MOH."[59]

It is known that endogenous cannabinoids inhibit trigeminovascular activation, a migraine mechanism discussed above. In 2009, a British group reported on variations in the cannabinoid receptor 1 (CB1) gene, CNR1, in migraine patients versus controls. Significant variations were found in the CB1 gene of migraneurs versus controls. The authors state, "These results suggest a significant effect of CNR1 on migraine headaches that might be related to the alteration of peripheral

trigeminovascular activation."[60] It should be noted at this point that researchers have coined the term "endocannabinoid deficiency syndrome" as an etiology in migraine, fibromyalgia, irritable bowel syndrome, and other clinical conditions.

An interesting Iranian study published in 2012 looked at the effect of cannabinoids on cortical spreading depression (CSD), a putative mechanism causing migraine aura and subsequent pain. The researchers found that delta9-tetrahydrocannabinol (THC) as well as the CB1 agonist WIN 55, 212-2 mesylate, significantly suppressed CSD in rat neocortical slices. They conclude, "Suppression of CSD by activation of CB1 receptors points to the potential therapeutic effects of cannabinoids in migraine with aura."[61]

As noted above, at this time PubMed does not contain any clinical studies of cannabinoids or other exogenous cannabinoids in migraine. If historical usage is considered as part of evidence-based medicine, then there is a long history of efficacy of phytocannabinoids in migraine. Based on the basic research and historical clinical precedent, as well as the safety of use, it would appear appropriate to try cannabinoids for migraine. The dosing would be more variable in migraine than in the other disorders discussed in this book. In particular, a patient might consider using a high cannabidiol (CBD) tincture or vaporized or smoked cannabis at the onset of migraine. This might be problematic in that the migraine mechanism may be well on its way before clinical symptoms are apparent. If the patient finds that cannabinoids are ineffective to use at the onset of headache, or if the migraines are frequent, at least two times/month, the migraneur may want to consider daily oral dosing with a high CBD preparation. The dosing would be individualized and after starting at a low dose, titrated upwards until a therapeutic response is noted. This process should be done with the supervision of a medical practitioner experienced in the use of medical cannabis. The reader is referred to the section dealing with cannabinoids in the "What These Six Disorders Have in Common" chapter of this book for further discussion of the pharmacology of cannabinoids and its implication for proper dosing in any individual.