Biologic effects of mindfulness meditation: growing insights into neurobiologic aspects of the prevention of depression

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A recent paper in the *Archives of General Psychiatry* confirms that mindfulness-based cognitive therapy (MBCT) "offers protection against relapse/recurrence on a par with that of maintenance antidepressant pharmacotherapy."[1] It is a tribute to the accumulated wisdom of humankind that a traditional Buddhist meditation practice going back 2500 years, which was originally designed in part to deal with the problem of human suffering, has been successfully adapted to prevent the relapse of depression in the modern era. Buddhist meditation techniques were originally adapted by Jon Kabat-Zinn, founding executive director of the Center for Mindfulness in Medicine, Health Care, and Society at the University of Massachusetts Medical School (www.umassmed.edu/Content.aspx?id=43102), for mindfulness-based stress reduction (MBSR). Reviews of MBSR studies suggest that it decreases depression, anxiety and psychologic distress in people with chronic somatic diseases[2] and that it reduces stress, ruminative thinking and trait anxiety in healthy people.[3] Mindfulness-based cognitive therapy is similar to MBSR and is designed to change some of the cognitions that are associated with depression.[4]

Mindfulness has been described as "paying attention in a particular way: on purpose, in the present moment, and non-judgementally."[5] In contrast to traditional cognitive behavioural therapy in which dysfunctional thoughts are targeted, the objective of MBCT is to help individuals learn, at times, to become aware of thoughts, feelings and bodily sensations rather than trying to modify them or acting on them. A core skill learned in MBCT is how to recognize and disengage from self-perpetuating patterns of ruminative, negative thought through sustained attention and attention-switching exercises. This self-regulation of attention is thought to help recovered depressed individuals shift attention away from the rumination about dysfunctional cognitions, which may be reactivated during transient mood lowering, and thus allows them to process depression-related information differently.[4] Dysfunctional cognitions, such as "If I do not do as well as other people in a particular task it means I am inferior," "My value as a person depends on what others think of me," or "It is important that everyone likes me,"[6] are risk factors for depression in adults[7–9] and children.[10,11] Mindfulness-based cognitive therapy targets the ruminative thinking by enhancing awareness and monitoring of thoughts. This suggests that MBCT might not only decrease relapse in depression but also prevent the onset of the first episode of depression in susceptible people. As Insel and Scolnick[12] have pointed out, "the great public health success stories of the past century are largely stories of prevention." Insights into both psychologic and biologic factors that are associated with the prevention of depression should help in the long run to develop better strategies for prevention. I describe some of the biologic factors associated with dysfunctional cognitions and what is known about the biologic effects of MBCT. Finally, I suggest some possible research directions that may provide more information on the systems that MBCT influences when preventing the onset of depression.

Different forms of meditation have been compared with various control interventions, some of which did not have similar intensity. As a result, the exact component of meditation that produces a beneficial effect is not clear, although the targeting of dysfunctional cognitions is probably the most plausible mechanism. In the rest of this editorial, different forms of meditation are assumed to have similar effects.

The idea that serotonin is related to the control of mood persists, and a small portion of the literature relates serotonin function to dysfunctional attitudes. In one of the first studies of this type, dysfunctional attitudes decreased in healthy participants when they were treated with the serotonin-releasing drug fenfluramine.[13] In depressed patients, one of the more common abnormalities reported using positron emission tomography (PET) is an increase in serotonin 2A (5-HT_{2A}) binding potential. In depressed patients, high 5-HT_{2A} binding

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potential in the cortex was positively associated with dysfunctional attitudes, and the mean value was higher in those exhibiting extremely dysfunctional attitudes than in controls.[13] In recovered depressed patients, there was also a positive correlation between 5-HT_{2A} binding potential and dysfunctional attitudes.[14] No difference in regional serotonin transporter binding potential was found between participants with major depression and healthy participants. However, in brain regions containing mainly serotonergic nerve terminals, the binding potential was significantly higher in depressed patients with highly negativistic dysfunctional attitudes. There was also a strong association between the serotonin transporter binding potential and dysfunctional attitudes in depressed patients.[15] Treatment of depressed patients with fluoxetine decreases dysfunctional attitudes.[16] Finally, the mood lowering of recovered depressed patients on medications in response to acute tryptophan depletion was related to their cognitive reactivity,[17] a measure of the extent to which dysfunctional attitudes appear when mood is low.

The biologic factors associated with mindfulness meditation have been studied using a variety of different methods. As discussed in recent reviews,[18,19] changes in brain function during meditation have been documented using electrophysiology, single photon emission computed tomography, PET and functional magnetic resonance imaging. Results differ somewhat, possibly owing to the use of different forms of meditation, but in general show increased signals in brain regions related to affect regulation and attentional control, with increased release of dopamine. Long-term brain changes are of greater interest to MBCT as a preventive strategy. Several studies have compared brain morphology of experienced meditators with matched controls, and findings include increased cortical thickness along with reduced age-related cortical thinning.[18] However, these results could be owing to pre-existing differences in those who choose to meditate and those who do not choose to do so. Two recent studies have overcome this problem by looking at brain morphology before and after an 8-week meditation program. The first study found increases in grey matter in the left hippocampus, the posterior cingulate cortex, the temporo-parietal junction and the cerebellum in those who did MBSR relative to wait-list controls.[20] The second study looked at MBSR in stressed but otherwise healthy individuals. Reductions in stress correlated positively with decreases in right basolateral amygdala grey matter density.[21]

Changes in the brain owing to mindfulness meditation could be a direct effect on the brain or could be mediated in whole or in part by an indirect mechanism. Reduced stress could decrease glucocorticoid levels and modulate the immune system (e.g., cytokines), both of which could feed back to alter the brain. A recent review concluded that there is accumulating evidence that plasma and salivary cortisol can be reduced by MBSR.[22] Several studies have looked at immune parameters. In patients with cancer, MBSR tended to return cytokine levels and natural killer cell activities toward normal levels.[23,24] In healthy people, meditation increased the antibody titer to influenza vaccine,[25] lowered the stress-induced increase in interleukin-6[26] and decreased C-reactive protein.[27]

Research on the biologic effects of meditation is relatively new, and there is scope for more work. For example, no studies have yet looked at the effect of meditation on serotonin function. Mindfulness-based cognitive therapy is designed in part to decrease dysfunctional attitudes, which are related to 5-HT_{2A} binding potential. Would MBCT alter 5-HT_{2A} receptor function? As mentioned, in recovered depressed patients on medication, the lowering of mood after acute tryptophan depletion was related to their cognitive reactivity (the extent to which they developed dysfunctional attitudes when their mood was lowered).[17] If MBCT decreases dysfunctional attitudes, would it also decrease the lowering of mood in response to acute tryptophan depletion?

If MBCT is to be tested for the prevention of the onset of the first episode of depression, and not just relapse, knowledge about how it works will be helpful in selecting participants for such a study. Prevention studies usually last years and involve a large number of participants; they are therefore very expensive. Unfortunately, medicine provides many examples of negative prevention trials. For example, a large trial of β carotene and vitamin A found no benefit after 4 years of treatment and an adverse effect on the incidence of lung cancer and cardiovascular disease in smokers,[28] whereas a study lasting 8 years found no beneficial effect of a low-fat diet on coronary heart disease.[29] A prevention study with MBCT would not be easy to carry out. The success of such a study might be influenced by how the patients were selected. Participants should have a strong motivation to practise meditation for years and a high risk for depression. People who have never experienced depression but come from a family with a high incidence of depression have a high risk for the illness and, having seen the effects of depression on their family members, would have a good motivation to practise MBCT if there were a chance that it would protect them from the illnes. In addition, if they had above-average levels of dysfunctional cognitions and cognitive reactivity, they might be expected to benefit from MBCT. The biologic measures that might be useful to help select patients must be speculative at this stage, but 1 or more serotonergic measures might be candidates. For a prevention study with a large sample size, simple measures would be important. Platelet serotonin can be measured relatively easily, and in one study, people with high trait anxiety had more dysfunctional attitudes and high platelet serotonin levels than controls with low trait anxiety.[30] Furthermore, platelet 5-HT_{2A} receptor binding was positively related to suicidal ideation in depressed patients,[31] so the idea that a simple biologic maker for response to MBCT might be discovered is plausible. Increasing knowledge about the neurobiologic effects of MBCT may foster the convergence of the biologic and psychologic aspects of psychiatry and also aid in the design of much needed primary prevention studies in mood disorders.

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