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Rapid changes in histone deacetylases and inflammatory gene expression in expert meditators

Perla Kaliman [a,*], María Jesús Álvarez-López [b], Marta Cosín-Tomás [b], Melissa A. Rosenkranz [c,d], Antoine Lutz [c,d,e], Richard J. Davidson [c,d,f,**]

[a] Instituto de Investigaciones Biomédicas de Barcelona IIBB-CSIC-IDIBAPS, c/Rosselló 161, 6th floor, E-08036 Barcelona, Spain
[b] Faculty of Pharmacy, University of Barcelona, Joan XXIII s/n, 08028 Barcelona, Spain
[c] Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin-Madison, 1500 Highland Avenue, Madison, WI 53705-2280, USA
[d] Center for Investigating Healthy Minds, University of Wisconsin-Madison, WI 53705-2280, USA
[e] Lyon Neuroscience Research Center, INSERM U1028, CNRS UMR5292, Lyon 1 University, Lyon, France
[f] Department of Psychology, University of Wisconsin-Madison, WI 53705-2280, USA

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Summary
Background: A growing body of research shows that mindfulness meditation can alter neural, behavioral and biochemical processes. However, the mechanisms responsible for such clinically relevant effects remain elusive.
Methods: Here we explored the impact of a day of intensive practice of mindfulness meditation in experienced subjects ($n = 19$) on the expression of circadian, chromatin modulatory and inflammatory genes in peripheral blood mononuclear cells (PBMC). In parallel, we analyzed a control group of subjects with no meditation experience who engaged in leisure activities in the same environment ($n = 21$). PBMC from all participants were obtained before (t_1) and after (t_2) the intervention ($t_2 - t_1 = 8$ h) and gene expression was analyzed using custom pathway focused quantitative-real time PCR assays. Both groups were also presented with the Trier Social Stress Test (TSST).
Results: Core clock gene expression at baseline (t_1) was similar between groups and their rhythmicity was not influenced in meditators by the intensive day of practice. Similarly, we found

* Corresponding author: Instituto de Investigaciones Biomédicas de Barcelona IIBB-CSIC-IDIBAPS, c/Rosselló 161, 6th Floor, 08036 Barcelona, Spain. Tel.: +34 93 3638338.
** Corresponding author at: Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin-Madison, 1500 Highland Avenue, Madison, WI 53705-2280, USA. Tel.: +1 608 265 8189.
E-mail addresses: pkaliman@ub.edu, perlakaliman@gmail.com (P. Kaliman), rjdavids@wisc.edu (R.J. Davidson).

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that all the epigenetic regulatory enzymes and inflammatory genes analyzed exhibited similar basal expression levels in the two groups. In contrast, after the brief intervention we detected reduced expression of histone deacetylase genes (*HDAC* 2, 3 and 9), alterations in global modification of histones (H4ac; H3K4me3) and decreased expression of pro-inflammatory genes (*RIPK2* and *COX2*) in meditators compared with controls. We found that the expression of *RIPK2* and *HDAC2* genes was associated with a faster cortisol recovery to the TSST in both groups.

Conclusions: The regulation of HDACs and inflammatory pathways may represent some of the mechanisms underlying the therapeutic potential of mindfulness-based interventions. Our findings set the foundation for future studies to further assess meditation strategies for the treatment of chronic inflammatory conditions.

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1. Introduction

Poor stress-coping contributes to the development of chronic diseases and accelerated aging (Epel et al., 2009; Juster et al., 2010; Karatsoreos and McEwen, 2011). Therefore, a growing body of scientific research is devoted to understanding the neurophysiological and cellular responses induced by methods that improve stress management. Among them, mindfulness-based meditation practices, which intentionally cultivate attentional skills, have become an increasingly popular approach, with accumulating experimental evidence of beneficial effects on psychological, neurological, endocrine and immune variables (Kabat-Zinn et al., 1998; Ludwig and Kabat-Zinn, 2008; Lutz et al., 2008; Schmidt et al., 2011; Farb et al., 2012; Rosenkranz et al., 2013). However, our molecular understanding of how they can influence a broad range of biological processes, from brain networks to the immune system, remains limited.

To date, few studies have analyzed the effects of mindfulness techniques at the cellular level. Studies in blood cells have found that the mindfulness-based stress reduction (MBSR) program reduced cytokine secretion, oxidative stress and DNA damage (Carlson et al., 2003), increased natural killer cell activity and decreased interleukin secretion in women recently diagnosed with early stage breast cancer (Witek-Janusek et al., 2008), and increased CD4+ T lymphocyte counts in HIV infected subjects (Creswell et al., 2009). Some reports have also described the molecular impact of other meditation-based interventions using blood cells; for example, RNA microarray studies suggested that the expression of genes involved in cellular metabolism and oxidative stress pathways in blood cells are modulated by body–mind relaxation response training (Dusek et al., 2008; Bhasin et al., 2013). Recent bioinformatic analyses from PBMC genome-wide microarrays have suggested that yogic meditation in family dementia caregivers decreased pro-inflammatory NFκ-B signaling and increased the activity of interferon response factors (Black et al., 2013). Increased telomerase activity was detected in response to the same intervention (Lavretsky et al., 2013).

Environmental stimuli influence most body functions, including stress responsiveness and behavior, through extracellular and intracellular pathways that interact with the epigenetic machinery (Graff et al., 2011). In rodents, psychological stress during adulthood induces dynamic epigenetic events such histone acetylation and phosphorylation in the dentate gyrus as soon as 2 h after the start of exposure to a novel environment or forced swimming (Chandramohan et al., 2007, 2008) and in the hippocampus 1 h after training using a fear conditioning paradigm (Chwang et al., 2007). Rapid epigenetic changes in response to environmental exposures such as diet and physical exercise have also been detected in human peripheral tissues (Kaliman et al., 2011; Pham and Lee, 2012). However, no data are currently available regarding the possibility of an epigenetic basis for the effects of mindfulness meditation. Here we show evidence of rapid gene expression changes in chromatin regulatory enzymes, alterations in histone modifications and downregulation of proinflammatory genes after a short intensive session of mindfulness meditation in experienced subjects. In addition, we observe relations between these changes and stress-evoked cortisol responses.

2. Methods

2.1. Participants

A group of 19 long-term meditators, and a control group of 21 meditation-naïve participants with similar distributions of age, gender, race and body-mass index (S1) were studied before (8 am) and after (4 pm) an intensive day of mindfulness meditation or leisure time in the same environment.

Participants provided written informed consent prior to the study procedures, which were approved by the UW-Madison Health Sciences Internal Review Board. They were informed of the study requirements and screened through telephone interviews for exclusion/inclusion criteria.

The mindfulness meditation group was recruited in the US at meditation centers and through related mailing lists, in addition to flyers and advertisements in newspapers. Mindfulness meditation group participants had a historical daily meditation practice spanning a minimum of 3 years, with a minimum of 30 min of daily sitting meditation and had to have attended a minimum of 3 intensive retreats lasting 5 or more days. They had an average of 6240 lifetime hours of meditation practice, ranging from 1,440 to 14,730 total hours. All experienced meditators practiced both standard mindfulness-related meditations (e.g. Vipassana and concentration meditations) and compassion-related meditations (e.g. metta meditation) as taught in the Tibetan and Theravada Buddhist traditions.

The control group comprised individuals with no prior meditation experience who responded to a local advertisement, recruiting participants for research in a non-pharmacological

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