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Neural Basis of Mindfulness Interventions that Moderate the Impact of Stress on the Brain

The scientific study of mindfulness has skyrocketed. Mindfulness can be defined as 'non-judgmental attention to present-moment experiences' and is thought to comprise several complex processes, including attentional control, emotion regulation, and self-awareness (Tang *et al*, 2015). Although the neuroscience underlying mindfulness is at an early stage, there are some intriguing findings that begin to unravel the effects of mindfulness on mental health, stress, and resilience. For example, those individuals who rated themselves as more mindful, i.e. had greater 'dispositional mindfulness', generally report lower levels of perceived stress (Prakash *et al*, 2015). This is important because the level of stress is strongly related to physical and mental health as well as cortical thinning. In comparison, dispositional mindfulness has been related to structural and functional differences in several neural structures, including the medial prefrontal cortex, hippocampus, amygdala, anterior and posterior cingulate, and orbitofrontal cortex (Tang *et al*, 2015). Therefore, dispositional mindfulness may prove to be an important construct to examine individual differences that can help to predict risk for and relapse to mental disorders.

Mindfulness-based stress reduction (MBSR) has been proposed for almost every psychiatric condition. In a meta-analysis (Sedlmeier *et al*, 2012), mindfulness interventions had medium to large effect sizes for changes in emotionality and relationship issues, medium effect sizes for measures of attention, and small effect sizes for cognitive measures. MBSR has been associated with increased cortical thickness in the insula and somatosensory cortex, which can be associated with reduction of worry, state anxiety, depression, and alexithymia (Tang *et al*, 2015). Moreover, changes after mindfulness training in the insula have been related to increase in interoceptive awareness, i.e. the ability to monitor afferents from inside the body, which is emerging as an important construct for anxiety disorders and addiction (Paulus and Stewart, 2013). Thus, some of the same brain systems that have been implicated in dispositional mindfulness are also affected by mindfulness-based interventions and show a certain degree of plasticity of these systems.

Our understanding of the molecular mechanisms of mindfulness and changes induced by mindfulness-based interventions is at its infancy. Recent studies have reported that MBSR training results in a smaller post-stress inflammatory response (Rosenkranz *et al*, 2013), which includes interleukin-6. MBSR also increased telomerase activity and those individuals with the greatest increase also reported the greatest reductions in chronic stress, anxiety, dietary restraint, dietary fat intake, cortisol, and glucose (Daubenmier *et al*, 2012). These findings suggest that mindfulness interventions affect both inflammatory and epigenetic mechanisms, which are important for mood and stress-related disorders, respectively. Therefore, elucidation of the molecular substrates that underlie individual differences in mindfulness may be one of the most fruitful areas for future research. Taken together, mindfulness and mindfulness-based interventions have profound effects on mental health, affect brain systems that are important for emotion regulation and self-awareness, and alter inflammatory and epigenetic responses, yet much needs to be done to make these interventions a part of precision psychiatry.

FUNDING AND DISCLOSURE

The author declares no conflict of interest.

ACKNOWLEDGMENTS

This study was funded by the William K Warren Foundation.

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Neuropsychopharmacology Reviews (2016) **41,** 373; doi:10.1038/npp.2015.239

Dynorphin, Dysphoria, and Dependence: the Stress of Addiction

The hypothesis that the dynorphin-kappa opioid receptor system may be a key component of the neuroplasticity associated with stress-induced mood disorders and the 'dark side' of

addiction (withdrawal-negative affect stage) continues to gain preclinical and clinical experimental support. The endogenous kappa opioid peptides derived from prodynorphin encode the dysphoric, anxiogenic, and cognitive disrupting responses to behavioral stress exposure (Bruchas *et al*, 2010; Carroll and Carlezon, 2013). Drugs of abuse are also profound activators of the brain stress systems, and dynorphin release following a binge of consumption contributes to the dysphoric and anhedonic responses experienced during withdrawal (Koob *et al*, 2014). Behavioral studies using rodents in multiple laboratories have now consistently demonstrated that kappa antagonists do not block the 'euphoric-like' effects of drugs but rather block the stress-induced potentiation of drug reward, block stress-induced reinstatement of drug seeking behavior, and block escalation of drug consumption in long-access models (Whitfield *et al*, 2015). We predict that kappa antagonists will promote stress resilience and disrupt the addiction cycle by reducing the dysphoria-driven cravings that trigger a subsequent round of drug seeking.

However, very exciting preclinical findings too often fail to deliver on their promises, particularly in CNS drug development, which is notoriously expensive and difficult. Progress is being made with a kappa antagonist (LY2456302) developed by Eli Lilly scientists, which passed initial safety testing and has been licensed for development by Cerecor (Lowe *et al*, 2014). Another key to this translational effort will be the further development of selective kappa opioid PET imaging in normal and affected human subjects, which is still at a nascent stage. A more 'out of the box approach' is to take advantage of "creative" pharmacology. Buprenorphine is not only a mu partial agonist, but is a potent kappa antagonist having antidepressant activity (Karp *et al*, 2014). A recent open label clinical trial by Alkermes demonstrated that the nonselective KOR antagonist buprenorphine when combined with a mu opioid antagonist significantly reduced depressive symptoms in a population of individuals having treatment resistant depression (E. Ehrich, Kappa-2015 conference proceedings). Dr Andrew Saxon (Seattle, VA) also reported results from the NIDA-funded CURB study, which showed that while cocaine consumption was not significantly reduced by buprenorphine combined with a long acting mu antagonist, secondary analysis of the data from cocaine-using subjects showed a highly significant reduction in nicotine and ethanol use. Additional, recent findings in the dynorphin-kappa domain reported at the '*3rd Conference on the Therapeutic Potential of Kappa Opioids in Pain and Addiction*' can be found at (http://depts.washington.edu/nidactr/kappatherapeutics2015.html).

Human laboratory studies are an efficient means of bridging the gap between preclinical studies and clinical trials, and we encourage additional validations using more selective kappa antagonists, nevertheless, these early findings are provocative. In summary, the initial results using animal models of psychiatric diseases followed by early validation in human trials support the prediction that individuals unable to control their drug consumption because of overwhelming feelings of dysphoria or anxiety during the abstinence phase, may find kappa antagonists helpful by promoting stress resilience.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work is supported by United States Public Health Service Grants from the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism.

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Neuropsychopharmacology Reviews (2016) **41,** 373–374; doi:10.1038/npp.2015.258

RiboTag: Not Lost in Translation

Measuring RNA from a defined subset of cells derived from a complex tissue is an important challenge that has confounded the field. Two recently developed tools have simplified this issue. The RiboTag and BacTRAP (Translating Ribosome Affinity Purification) methods allow for immunoprecipitation of ribosome-associated RNA from specific cells within complex tissues by expressing tagged ribosomal protein in desired cell types (GFP-tagged RPL10 for TRAP and hemagglutinin-tagged RPL22 for RiboTag) (Doyle *et al*, 2008; Heiman *et al*, 2008; Sanz *et al*, 2009). More specifically, these methods allow analysis of the 'translatome'—ribosome-associated mRNA—which may be particularly sensitive to event-dependent regulation of protein translation. For example, RiboTag-expressing transgenic mice were recently used to compare differential gene expression responses to cocaine in striatal neurons expressing D_1 and D_2 dopamine receptors (Chandra *et al*, 2015).