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Modulating the modulators: Interaction of brain norepinephrine and cannabinoids in stress

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One of the most pressing issues in current neuropsychopharmacology is the search for new and more effective therapeutic agents for the most prevalent and serious psychiatric disorders, including schizophrenia, anxiety and depression. As a case in point, antidepressants that block the reuptake of monoamines, in particular serotonin and norepinephrine, are only partially effective, as only ~50–65% of depressed patients who seek treatment achieve successful clinical response from currently available drugs, and "successful response" is typically defined as 50% improvement in symptom severity (Janicak, et al., 1997). This is clearly unacceptable, and a new approach to treating such disorders is sorely needed. A recent article by Reyes et al. (Reyes, et al., 2012) addresses the interaction of norepinephrine and cannabinoid receptors in the prefrontal cortex as a potential mechanism involved specifically in stress-related psychiatric disorders such as depression, and also considers the potential utility of targeting cannabinoid CB1 receptors as a novel therapeutic strategy.

Since the elucidation of endocannabinoid signaling processes in the brain in the 1990's, the endocannabinoids and related pharmacological compounds have been investigated both for a potential role in depression, and as potential antidepressants (Ashton and Moore, 2011, Gobbi, et al., 2005, Hill, et al., 2009, Parolaro, et al., 2010). Perhaps this has been fueled in part by the atypical mode of endocannabinoid neurotransmission. Derived on demand from phospholipids intrinsic to the plasma membrane, endocannabinoids signal via activity-dependent non-vesicular retrograde transmission, acting on pre-synaptic cannabinoid receptors (primarily CB1 receptors in the brain) to regulate neurotransmitter release from afferent terminals innervating the neuron from which they were released (Freund, et al., 2003, Wilson and Nicoll, 2002). The widespread distribution and abundant expression of cannabinoid receptors in the brain, and the prospect of exploiting novel modes of interaction with monoamine neurotransmitters have made the endocannabinoid system an attractive and potentially viable new therapeutic target. This is supported by reports that CB1 receptor activation exerts antidepressant-like effects in the rat forced swim test (FST), a widely used and well-validated screen for agents possessing putative antidepressant efficacy (Hill and Gorzalka, 2005, Morrish, et al., 2009). Moreover, there is evidence of a specific interaction between endocannabinoid signaling and the brain noradrenergic system in this test, as the antidepressant-like effect induced by CB1-receptor agonist administration included a reduction in immobility and an increase in climbing behavior, similar to that induced by NE reuptake blockers, and it was dependent upon activity of both α_1- and β-adrenergic receptors as well as CB1 receptors (Morrish, et al., 2009).

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Stress is a risk factor for depression (Anisman and Zacharko, 1982, Caspi, et al., 2003, Kendler, et al., 1999, Kessler, 1997), and NE has been implicated in mechanisms underlying the etiology of stress-related psychiatric disorders and their treatment (see Morilak and Frazer, 2004). Our group and others have shown that acute stress activates the noradrenergic system, increasing NE release in stress-responsive brain regions (see Morilak, et al., 2005). In the paper by Reyes et al (Reyes, et al., 2012), the authors extend their previous work characterizing the effects of the CB receptor agonist, WIN 55,212-2, on the activity and function of the forebrain-projecting noradrenergic system originating in the locus coeruleus (LC)(see Carvalho and Van Bockstaele, 2012). In this latest paper, they focused on CB1 receptor modulation of noradrenergic activity in the medial prefrontal cortex (mPFC) of the rat, and examined changes in that interaction induced by exposure to acute stress.

The mPFC is an important region for understanding mechanisms underlying stress-related neuropathology, and potential antidepressant effects. The mPFC has consistently been shown to be dysregulated in depression, and it is involved in a number of cognitive and executive processes that are characteristically disrupted in depression (Austin, et al., 2001, Disner, et al., 2011, Fossati, et al., 1999, Murphy, et al., 1999, Rogers, et al., 2004, Sheline, 2003). Further, in some of our own work, we have shown that increasing noradrenergic neurotransmission in the mPFC can facilitate cognitive processes mediated in this region, and can also improve such processes that have been compromised by chronic stress (Bondi, et al., 2010, Bondi, et al., 2008, Lapiz and Morilak, 2006). Reyes et al conducted an elegant series of studies combining *in vivo* microdialysis to measure norepinephrine (NE) release in the mPFC; behavior on the FST, a mildly stressful assay for antidepressant-like behavioral activity; and *in vitro* electrophysiology to assess changes in the effects of post-synaptic α_2-adrenergic receptor activation on the excitability of pyramidal cells in mPFC slices. The major observations reported in this paper were: a) WIN alone increased NE efflux in mPFC; b) by contrast, WIN reduced the increase in NE release normally induced in the mPFC by acute swim stress; c) consistent with the reduction in NE release, WIN increased immobility and reduced climbing behavior during the swim test; d) in mPFC slices, acute WIN administration blocked the increase in excitability of layer V–VI pyramidal cells induced by the α_2 receptor agonist, clonidine (CLO). Both the CLO-induced activation of pyramidal cells and the blockade of that effect by WIN treatment were independent of exposure to acute FST stress shortly before recording; e) following a regimen of chronic repeated WIN administration, acute WIN similarly blocked the effect of CLO when recording was not preceded by an acute FST stress; f) however, after chronic WIN treatment, acute WIN administration failed to block the effect of CLO when recording was preceded by an acute FST stress, i.e., acute stress reversed the inhibitory effect of chronic WIN treatment on α_2-adrenergic receptor activity.

The increase in NE efflux in mPFC following systemic treatment with WIN is consistent with the previous demonstration by this group that WIN activated LC neurons, the source of NE innervation of the cortex (Foote, et al., 1983). As the primary effect of pre-synaptic CB1 receptors is to inhibit neurotransmitter release, the most logical explanation, as the authors suggest, for the activation of the LC and increased NE release in mPFC is disinhibition, i.e., by inihibiting the release of GABA from interneurons. However, the fact that WIN alone attenuated the effects of CLO in mPFC slices also suggests that CB1 receptors may interact more directly with post-synaptic α_2 receptors. CB1 receptors are coupled to $G_{i/o}$, as are α_2 receptors, so these two receptor systems may converge on the same signal transduction pathways in cells where they are co-localized, making cross-regulation possible. And because WIN appears to inhibit the activity of post-synaptic α_2 receptors directly, it may also attenuate the effects of other α_2-adrenergic receptors, including terminal or somatodendritic autoreceptors, which could also contribute to the activation of LC and increased NE release. Thus, the net effect of such activation of the noradrenergic system by

WIN may be functionally similar to activation of the noradrenergic system by α_2-adrenergic autoreceptor blockade with drugs such as yohimbine or atipamezole.

Functionally, acute elevation of noradrenergic neurotransmission could represent an enhanced capacity for stress adaptation. In our own work, we have shown that acute release of NE facilitates behavioral and physiological response mediated in the brain regions in which it is released, contributing to effective coping and stress adaptation (Bondi, et al., 2007, Cecchi, et al., 2002, Morilak, et al., 2005). We have also shown that acutely increasing NE release by α_2-adrenergic autoreceptor blockade enhanced cognitive flexibility mediated specifically in the mPFC, through the actions of post-synaptic α_1 receptors (Lapiz and Morilak, 2006). However, enhancing behavioral-emotional processes that are normally elicited by stress could also manifest as anxiety, which can be pathological if it occurs in the absence of a relevant reference stimulus. For instance, blocking α_2 receptors with yohimbine can exaggerate or provoke anxiety in individuals prone to anxiety, or suffering from anxiety disorders such as PTSD or panic disorder (Charney, et al., 1987, Southwick, et al., 1993). Similarly, the authors of the Reyes paper have shown previously that CB1 activation induces anxiety and place aversion, at least part of which was dependent on noradrenergic innervation of the limbic forebrain (Carvalho, et al., 2010). However, the literature is mixed, with reports indicating that CB1 receptor activation can have anxiogenic effects, anxiolytic effects, and biphasic effects (see Hill, et al., 2009).

In the Reyes study, NE release was increased during the FST, confirming the stressful nature of this test. However, by contrast with the activating effects on LC and the increase in NE efflux induced by WIN alone, WIN administration preceding the FST *reduced* the acute increase in NE release induced in the mPFC during swim stress. It seems unlikely that this results from direct pre-synaptic inhibition of NE release, as this effect would also then have been evident when WIN was administered in the absence of stress. Rather, because this inhibitory effect is specific to NE release induced by acute stress, it is likely to represent an inhibitory influence exerted on excitatory afferents that are recruited to activate NE release specifically in response to stress. One interpretation of this effect is that it may buffer the impact of stress, but given the beneficial effects of NE release in the context of acute stress, reducing it could also be maladaptive. In this regard, the blunted noradrenergic response to acute stress seen after WIN administration is similar to the blunted noradrenergic response to acute stress we have observed in WKY rats, a rat strain that is particularly vulnerable to stress-pathology (Pardon, et al., 2002).

Thus, WIN administration alone resembled α_2 antagonist drugs in its effects on the NE system, which could facilitate acute stress adaptation, but could also be anxiogenic in non-stress contexts. However, when administered in the context of an acute stress, WIN prevented the potentially adaptive increase in NE efflux. Consistent with this, WIN increased immobility and reduced climbing in the FST. Climbing is considered an active, adaptive behavioral response on this test, related to NE release and reflecting the antidepressant efficacy of NE reuptake inhibitors. Thus, the behavioral effect following WIN administration is consistent with the reduction in NE release during the FST. Notably, this is in distinct contrast with previous reports that enhancing cannabinoid signaling induced antidepressant-like responses on the FST (Hill and Gorzalka, 2005, see Hill, et al., 2009). The authors emphasize that the swim stimulus was used in this study as an acute stressor rather than as the behavioral screen for antidepressant efficacy for which it has been validated, because they did not employ the typical pre-swim priming session the day before testing. However, this modified version of the FST, using only a single swim exposure, has also been shown to detect antidepressant efficacy, measured as a reduction in immobility, and the same neurotransmitter-specific coping behaviors (climbing and swimming) have been associated with elevated noradrenergic and serotonergic neurotransmission,

respectively, following both acute and chronic drug treatment (Cryan, et al., 2005, Furmaga, et al., 2011). Thus, despite the specified use of the swim test as a stressor, the relevant and valid behavioral indices of coping and antidepressant efficacy were nonetheless measured, and we can't ignore the fact that the observed changes in both NE release and coping behavior in the FST after WIN administration were consistent with a potentially depressogenic effect.

The potentially dual effect of WIN on anxiety and behavioral stress reactivity is reminiscent of the dual role described previously for cannabinoid signaling in acute stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis (Hill, et al., 2010, McLaughlin, et al., 2009). CB1 agonist administration activates the HPA axis by elevating noradrenergic transmission at α_1- and β-adrenergic receptors (McLaughlin, et al., 2009). At the same time, CB1 signaling also modulates glutamate transmission to curtail HPA activity, and participates in negative feedback inhibition (Hill, et al., 2010). Whether the net effect of such a dual modulatory influence is ultimately beneficial or detrimental to stress adaptation and pathology would seem to depend on the initial and current response capacity of the system to effectively mitigate the stress. If the response is either insufficient or disproportionate to the context, CB1 receptor activation might be beneficial. But if the response is adequate, the same modulatory mechanism might then be detrimental.

Of course, these intriguing observations reported by Reyes et al. only pertain to a single acute stress exposure. While NE release may be beneficial in facilitating adaptive responses to acute stress, we also have evidence that the effects of repeatedly and persistently invoking NE-mediated facilitation could be damaging in the long run, and contribute to the detrimental consequences of chronic stress (manuscript in preparation, see Jett, et al., 2008). It remains to be seen whether the buffering effect of WIN treatment on acute noradrenergic stress reactivity might in fact have beneficial effects on the development of a depressive- or anxiety-like phenotype over the course of a chronic, severe or repeated stress treatment.

The most interesting and at the same time most perplexing results in this paper were in the *in vitro* slice electrophysiological experiments. Both acute and repeated WIN administration blocked the effect of CLO in increasing the excitability of mPFC layer V–VI pyramidal cells. However, while the acute effects of both WIN and CLO were unaffected by acute exposure to the FST stress just before the rats were sacrificed for recording, acute FST stress *reversed* the inhibitory effect of WIN, after chronic treatment, on CLO-induced excitation of pyramidal cells.

Thus, in this experiment, acute swim stress interfered with a component of CB1 receptor function that had been specifically primed by prior chronic WIN treatment, and which is distinct from the mechanism of CB1-α_2 interaction engaged by only a single WIN administration. Perhaps chronic CB1 receptor activity preferentially desensitized one CB1-induced signaling pathway relative to others (e.g., inhibition of adenylate cyclase vs activation of MAP kinases, see Turu and Hunyady, 2010), thereby shifting the mechanism by which CB1 receptor activity interfered with α_2 receptor signaling, from an acute process that was unaffected by stress to one that was sensitive to modification by acute stress. Thus, chronic WIN treatment engaged an active and dynamic, but reversible inhibition of α_2 receptor function, rather than a structural change or protein modification resulting in stable desensitization, down-regulation or internalization of α_2 receptors. The authors suggested from these results that stress can derail the protective effects of acute CB1 receptor activation. However, that was only the case after chronic WIN treatment, as stress alone did not change the effects of acute WIN, so another way to interpret these data is that chronic WIN treatment rendered the protective effect of acute WIN administration vulnerable to

stress. In this sense, then, the data perhaps more tellingly suggest that chronic WIN pre-treatment derailed the protective effects of acute CB1 receptor activation.

One caveat to the interpretation of these results is the lack of specificity of WIN 55,212-2, which acts as an agonist at TRPV1 receptors as well as CB1 and CB2 cannabinoid receptors (Campos and Guimarães, 2009). The extent of CB2 receptor expression in the brain is unclear, but TRPV1 receptors are expressed on noradrenergic neurons in the LC, and also on pyramidal cells in the mPFC (see Steenland, et al., 2006). Therefore, it is possible that chronic treatment with WIN could have selectively desensitized one receptor responsible for the acute modulation of α_2 receptor signaling by WIN that is not affected by acute stress, unmasking a similar acute modulatory effect mediated by a second receptor that is impacted by acute stress. The authors used a CB1 receptor antagonist, SR 141716A, to block the effects of WIN on NE release. Unfortunately, this was not done in the cortical slice electrophysiological experiments, which would have allowed them to address the receptor specificity of the complex effects that both chronic and acute WIN administration had, perhaps through different mechanisms, on both noradrenergic and cannabinoid modulation of pyramidal cell activity in the mPFC.

In the end, like many of the most interesting scientific observations, the paper by Reyes et al answers some questions, leaves others unresolved, and provokes many more. The major question prompted by this paper, and left unresolved, is whether cannabinoid CB1 receptor activity can be beneficial or detrimental to coping and stress adaptation, as evidence supporting both interpretations is presented. Increasing noradrenergic efflux and increasing noradrenergic reactivity could be adaptive, but in the absence of a provocative stimulus it could also be anxiogenic. Preventing acute stress-induced NE efflux could reduce the impact of stress, or especially in light of the behavioral results, could compromise an important adaptive component of the response to acute stress. As the authors suggest, preventing NE-mediated activation of mPFC pyramidal cells might protect cortical circuitry during stress. However, the α_2-receptor activation of pyramidal cells was released from that CB1-mediated inhibition specifically by exposure to stress.

Noradrenergic signaling in the mPFC is a component of arousal and attention (Aston-Jones, et al., 2000). NE enhances cognitive flexibility, a process essential to effective adaptation to the demands of a changing environment, and to the challenges imposed by a stressful environment (Bondi, et al., 2010, Lapiz and Morilak, 2006). Perhaps it is inherent to the nature of such modulatory systems that there can be no clear answer as to their overall function, nor to whether modifying their activity pharmacologically is helpful or harmful, beneficial or detrimental. By definition, there is no absolute “optimal level” of modulation, as that constantly changes relative to the demands of the immediate context, and with changing levels of activity in the circuits to be modulated. Too much or too little can both be detrimental, as can interventions that alter a system that is otherwise working well. And in the case of endocannabinoid-noradrenergic interactions, the complexity is amplified, as these are processes that modulate the activity of modulatory systems. The paper by Reyes et al adds to our understanding of the complexities of these interactions, and the important role they can play in plasticity and flexibility, and in matching the operating characteristics of response circuits in the brain to a relevant context. But before we can begin to predict whether drugs that alter such interactions may be beneficial or not in treating major psychiatric disorders such as depression or anxiety, we must first unravel the neuropathological mechanisms underlying those disorders, and understand how these pathological mechanisms might disconnect the adaptive processes that regulate optimal modulation from the demands of a changing and challenging environment.

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