Next generation antidepressants

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Over the past 50 y, there have been few mechanistically distinct drugs for the treatment of major depressive disorders, despite the fact that nearly two-thirds of patients do not achieve full remission of symptoms on currently available antidepressants (1).

Fig. 1. Schematic describing potential cellular mechanisms for rapid antidepressant properties of L-acetylcarnitine. LAC may act within the nucleus to promote gene expression of mGlu2 receptor and BDNF by acetylation (AC) of transcription factors (TF) that promote DNA binding or of histones proteins surrounding DNA, leading to a permissive transcriptional state. LAC may act outside the nucleus on chaperone proteins, such as HSP90, to impair glucocorticoid receptor (GR) processing and limit the cellular effects of stress. LAC may acetylate microtubule proteins in dendrites to control stability of the neuronal cytoskeleton and prevent stress-induced loss of dendrites.
depression treatment in humans, these exciting results are a first step toward that goal.

There is a growing literature suggesting that chronic stress reprograms gene expression in brain regions, such as the Hipp and nucleus accumbens (NAc), and that normalization of the transcriptional machinery through posttranslational modifications of histones can correct some of the aberrant gene transcription and promote antidepressant responses (8). Histone deacetylase (HDAC) inhibitors given intraperitoneally (9, 10), as well as directly into the Hipp (11), amygdala (11), and NAc (12, 13), promote antidepressant behavioral responses following stress. In the NAc, HDAC inhibitors have been shown to normalize gene expression profiles similar to chronic imipramine-treated and control unstressed mice. Work described by Nasca et al. (5) suggests similar mechanisms of action for LAC, whereby increased histone acetylation and normalization of BDNF or mGlu2 in the Hipp and PFC promotes resilience following chronic unpredictable stress, or in the FSL rats. Interestingly, the authors show that normalization of mGlu2 receptor expression through an epigenetic mechanism is functionally related to antidepressant responses (5); HDAC inhibitors normalize mGlu2 expression in FSL rats and LAC has limited antidepressant efficacy in mGlu2 knockout mice. These findings are very interesting; however, there are some important questions to consider. For example, previous work has shown that increased BDNF in the hippocampus is anti-depressant (14), but increased BDNF in the mesolimbic dopamine system is prodepressant (15). Does peripheral administration of LAC also increase BDNF transcription in the mesolimbic dopamine system through a similar mechanism, and does this increase the possibility of unwanted side effects or limited efficacy? Furthermore, there are likely many other epigenetic targets across multiple brain areas contributing to the antidepressant behavioral effects of LAC that warrant further investigation.

Nasca et al. (5) point out the possibility that LAC may acetylate transcription factors, such as NFκB, to regulate mGlu2 transcription (Fig. 1). Their results suggest that increased acetylation of p65 by LAC is associated with its antidepressant efficacy and that pretreatment with the anti-inflammatory sodium salicylate, which nonselectively inhibits NFκB, blocks the effects of LAC on mGlu2 gene transcription, and partially blocks antidepressant behavioral responses. These findings are somewhat contrary to previous work, which shows that chronic stress increases NFκB-dependent transcription or its upstream kinase, IKK, in the Hipp (16) and NAc (17), respectively. In the Hipp, increased NFκB-dependent transcription promotes stress-impaired neurogenesis, but local administration of a selective NFκB inhibitor prevents stress-impaired neurogenesis and shows antidepressant efficacy on novelty-induced hypophagia and sucrose consumption tests (16). In the NAc, IKK inhibition reverses social defeat stress-induced social-avoidance behavior and synaptic plasticity (17). Thus, although the current findings are intriguing, they raise a number of important questions. First, sodium salicylate acts on many more targets other than NFκB. Is sodium salicylate acting through these other targets to control mGlu2 transcription and antidepressant behavioral responses? The use of more specific NFκB inhibitors or genetic knockouts will be important to determine this. Next, although Nasca et al. (5) mention that the mGlu2 promoter contains a number of NFκB binding sites, it’s unclear whether LAC promotes acetyl-p65 binding to the mGlu2 promoter in vivo and whether this increases mGlu2 transcription.

Finally, it is important to note that LAC is a nonspecific acetylation agent and it is unclear from the present work whether the antidepressant actions are solely a result of acetylation of nuclear proteins, such as transcription factors and histones, or whether it is in part a result of acetylation of other proteins outside the nucleus (Fig. 1). For example, acetylation of microtubules can influence the stability of the neuronal cytoskeleton (18). Chronic stress and genetic models of depression are well-established regulators of the neuronal cytoskeleton, and in the PFC and Hipp, depressive phenotypes have generally been associated with a destabilization of the cytoskeleton and a loss of excitatory glutamatergic synapses (19). Thus, it is tempting to speculate that LAC may affect stability of the cytoskeleton and glutamatergic synapses during times of stress or in genetically predisposed individuals. The possibility that acetylation may affect posttranscriptional processes in stress disorders is not completely speculative. Recent work has identified a role for the histone deacetylase, HDAC6, outside the nucleus through its deacetylating actions on heat-shock protein 90 (HSP90), a chaperone protein important for protein processing (20). Standard antidepressants down-regulate HDAC levels, resulting in hyperacetylation of HSP90 and subsequent impairment of glucocorticoid receptor processing, which blunts the impact of stress on serotonergic neurons in the dorsal raphe nucleus. Although these two examples highlight the diverse roles of acetylation on the function of neuronal systems, future work to determine the effects of LAC on a host of nonnuclear targets needs further investigation.

Work by Nasca et al. (5) represents the type of basic science research that can help guide the development of novel, more rapidly acting treatments for depression. The identification of rapidly acting antidepressants, like ketamine, has resulted in a much needed major paradigm shift in the discovery process that promises to lead to a new generation of antidepressant therapies.