after cessation of the social choice. This protective effect was associated with activation (assessed by the activity marker Fos) of inhibitory central amygdala PKCδ-expressing neurons and decreased neuronal activity in the anterior insular cortex [6].

demonstrated the generality of food-choice voluntary abstinence to female rats and to heroin, and that surprisingly voluntary abstinence prevents incubation of heroin craving [3]. In mechanistic studies, we found a role of dorsomedial striatum neuronal ensembles in incubation of methamphetamine craving after voluntary abstinence [4], and a role of glutamatergic projections from the anterior insular cortex to central amygdala in relapse after voluntary abstinence [5].

However, the use of palatable food as the nondrug reward may limit the model's clinical translation. This is because for most humans, the rewards that compete with drugs are primarily social (family and employment). Based on this consideration, we recently introduced a newer voluntary abstinence model that involves choices between a drug and operant access to social interaction [6] (Fig. 1). We found that rats trained in established addiction models—escalation, DSM-IV-based, and intermittent access—will voluntarily abstain when given mutually exclusive choices between methamphetamine or heroin versus social interaction. This effect was independent of their 'addiction score', persisted through 4 weeks of forced abstinence, and could only be reversed by delay or punishment of the social reward. We also found that social-choice-induced voluntary abstinence prevents the emergence of incubation of methamphetamine craving, even 1 month

Central to this epigenetic framework linking neural and systemic functions is the concept of allostasis (adaptation) and allostatic load (pathophysiology) [1]. This concept emphasizes that endogenous mediators for adaptation contribute to pathologies, including MDD, when activated persistently or dysregulated under circumstances of toxic stress and associated health-damaging behaviors [1]. There is an increasing scientific consensus to support a connection between systemic illness and MDD, a disorder still primarily seen as brain based. Recently, we reported decreased plasma levels of acetyl-L-carnitine (LAC) in two cohorts of patients suffering with MDD [2]. The LAC deficiency was greater with stronger severity, earlier disease onset and treatment-resistant-depression, which was associated with childhood trauma [2]. In rodent models, targeting the deficiency in LAC by supplementation of exogenous LAC leads to antidepressant-like responses after a few days of administration, while standard antidepressants require multiple weeks [3–5]. LAC is an endogenous molecule with a plethora of biological functions important for brain plasticity and systemic metabolism relevant to stress and pathophysiology of MDD [3]. In rodent models with sustained activation of neural mineralocorticoid receptors (MR), supplementation of LAC increased acetylation of histone markers of activate gene transcription leading to increased expression of an inhibitor of spontaneous glutamate release, mGluR2, and the neurotrophin, BDNF [3, 4]. Normalizing glutamate overflow and BDNF expression ameliorated decreased dendritic branching in the hippocampus and connected brain areas important for the pathophysiology of depression [1, 3–6].

Within this framework, it is important to emphasize that, at least in rodent models, low LAC serves as a biomarker of insulin resistance (IR), which was also ameliorated by supplementation with LAC [4]. IR is a modifiable inflammatory state that is often observed in patients suffering from MDD [1]. Furthermore biomarkers of allostatic load involving imbalance in systemic stress-related physiology, and also including heightened release of proinflammatory cytokines and hypercortisolemia [1], are inversely correlated with hippocampal volume in patients with affective dysregulation [1].

These studies provide a foundation for future research of the mechanisms of LAC action related to the pathophysiological role of systemic physiology in a variety of stress-related CNS disorders, including MDD and interrelated disorders, such as Alzheimer's disease. This framework can lead to identify therapeutic targets for development of mechanism-based treatment strategies tailored to biologically defined patient populations [5].

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