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Distress Intolerance, Kynurenic Acid, and Schizophrenia

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We are all intuitively aware that when we are under stress, we think differently and often less well than when we are calmer. The study by Chiapelli et al¹ in this issue of the journal addresses some of the critical links underlying the effects of stress on cognition. In particular, their study highlights the effects of stress on circulating kynurenic acid (KYNA) levels in patients with schizophrenia, as measured in saliva, and the interaction of KYNA with persistence during cognitive testing. The main findings of the study¹ are (1) that schizophrenic patients as a group showed increased KYNA levels when performing stress-inducing cognitive tasks and (2) that the higher levels of KYNA were associated with an increased likelihood of terminating the tasks early, an effect termed *distress intolerance*.

Kynurenic acid is one of the primary metabolites of the amino acid tryptophan. At the center of the study by Chiapelli et al¹ is the basic observation, made more than 50 years ago, that stress of many kinds modulates the expression of one of the main enzymes, tryptophan 2,3-dioxygenase, that converts tryptophan to kynurenine in the liver.^{2–4} Kynurenine is then actively transported into the brain and metabolized in astrocytes to KYNA. Many other factors, including inflammation, also affect kynurenine pathway metabolism, so elevations of kynurenine and KYNA are observed in a great many inflammatory and neoplastic disorders, as well as in conditions (such as stress) that modulate kynurenine pathway metabolism via the glucocorticoid system.

Interestingly, as discussed in the study by Chiapelli et al,¹ despite deriving from a metabolic pathway totally separate from that involved in either acetylcholine or glutamate metabolism, KYNA in the brain inhibits with both $\alpha 7$ nicotinic and *N*-methyl-D-aspartate-type glutamate receptors to influence brain function.^{3,4} As expected, therefore, when elevated, KYNA impairs sensory gating and various types of cognitive functions. Over the years, many different types of stress have been used to induce KYNA metabolism, including physical manipulations, such as cold stressors,² and difficult mental manipulations, such as cognitive testing, as in the study by Chiapelli et al.¹

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A central question to this line of research is why evolution has selected for kynurenine metabolism to be sensitive to circulating glucocorticoid levels. One possibility is that the primary consequence of kynurenine pathway upregulation is the shunting of tryptophan metabolism away from serotonin synthesis, which could potentially lead to depressive behaviors. Darwin argued that depressive responses to stress may act to conserve resources when resource expenditure would not be beneficial. However, the fact that KYNA affects cognition directly argues that stress effects on KYNA metabolism may also be evolutionarily beneficial.

One effect of KYNA, for example, is to decrease cognitive flexibility.^{3,4} While reduced cognitive flexibility is usually considered a negative, when one is being exposed to an aversive stimulus such as a cold pressor, it could be that the time for deep thinking has passed and the time for immediate action has arrived. The fact that there is a glucocorticoid-sensitive element built into the promotor for tryptophan 2,3-dioxygenase may be testament to the fact that, in many situations, individuals who thought less and acted were more likely to live to think (and reproduce) another day.

The effect of stress on cognition is also not limited to psychiatric conditions. For example, it has recently been reported that stockbrokers exposed to higher market volatility show elevations in glucocorticoids and that, when induced experimentally, such elevations correlate with an increase in “risk aversion” during trading.⁵ Moreover, the effects of stress on brain function are not mediated solely through the kynurenine pathway system. For example, glucocorticoids have direct effects on glutamate transmission at both presynaptic and postsynaptic sites,⁶ providing an alternative pathway by which stress could lead to alterations in cognition.

Finally, it has been suggested that stress responses, in general, may be divided into those that are “hawklike,” which involve fight-flight decisions mediated primarily by the sympathetic nervous system, and those that are “dovelike,” which involve freeze-hide behaviors mediated by glucocorticoid effects.⁷ To the extent that distress intolerance may be viewed as an example of freeze-hide behavior, the present findings suggest that elevations in KYNA may play a role in alterations in brain function involved in glucocorticoid-induced behavioral response patterns.

As noted previously by these authors and others, both schizophrenia and bipolar disorder are associated with increased cerebrospinal fluid and postmortem KYNA levels that are associated with polymorphisms of kynurenine 3-monooxygenase, the enzyme that converts kynurenine to 3-hydroxykynurenine and away from KYNA.^{8,9} In the study by Chiapelli et al,¹ no differences in salivary KYNA were observed between groups at reset. Therefore, the relationship between stress-induced changes in salivary KYNA levels, as measured in this study,¹ and more tonic alterations in cerebrospinal fluid KYNA levels may require further clarification.

Nevertheless, there are several important take-home messages. First, the study¹ highlights that patients may be more stressed than controls, even by simple tasks such as mental arithmetic or mirror drawing. This must be taken into account when asking patients to

participate in other mentally demanding activities, such as cognitive remediation or supported employment. Patients, in general, may have difficulty reporting their emotions, including subjective feelings of stress. Monitoring salivary KYNA levels, potentially along with glucocorticoid levels, may provide additional information as to the subjective stress experienced by an individual and might help identify individuals who would benefit from additional supportive therapy.

Second, many of the enzymes involved in kynurenine metabolism are inherently “druggable.” These include not only tryptophan 2,3-dioxygenase and kynurenine 3-monooxygenase, but also kynurenine aminotransferase,¹⁰ the enzyme that converts kynurenine to KYNA. Given the complexity of these systems, it is difficult to know whether or not the net effects of such interventions would be beneficial. Nevertheless, a naive expectation is that acute alterations of behavior by stress systems may be evolutionarily advantageous but that chronic activations are unlikely to be so advantageous. Thus, for individuals with chronic KYNA elevations, whether due to genetic variation or simply to circumstance, pharmacological manipulation of the kynurenine pathway may be therapeutically beneficial.

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