Serotonin, cytokines, p11, and depression

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For at least four decades, the field of psychoimmunology has attracted numerous investigators based on diverse hints linking the immune system to emotional behavior. The administration of cytokines for the treatment of various diseases is often associated with depression, which frequently accompanies autoimmune disease. Now, in PNAS, Greengard and colleagues (1) report a specific molecular pathway linking cytokines and the actions of antidepressant drugs. Their findings confound established wisdom, as they imply that brain cytokines exert antidepressant actions and mediate the influences of the principal serotonin-specific reuptake inhibitor (SSRI) antidepressant drugs. How the present discoveries fit into the context of our understanding of antidepressant actions can be summarized as follows.

i) Links of serotonin to depression include SSRI antidepressants potentiating serotonin, lowered levels of serotonin metabolites in some depressed patients, and antidepressant effects of serotonin precursors.

ii) The small protein p11, a member of the S100 family, is implicated in depression and actions of SSRI antidepressants, which increase brain levels of p11. Mice with targeted deletion of p11 display a depressive phenotype, and behaviors of transgenic mice overexpressing p11 mimic effects of antidepressants. Levels of p11 are reduced in murine models of depression and depressed patients.

iii) p11 binds and increases surface expression of serotonin 5HT1B receptors and interacts with 5HT4 receptors.

iv) SSRI antidepressants increase brain cytokine levels, effects blocked by nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen. Conversely, cytokines, like SSRIs, increase p11 levels. Stimulation of p11 levels by antidepressants is also diminished by NSAIDs.

v) NSAIDs prevent behavioral effects of SSRIs in rodents, and patients receiving NSAIDs display impaired therapeutic responses to the SSRI citalopram.

Several years ago, the Greengard group characterized behavioral properties of p11, a very small protein of the S100 family, also designated S100A10 (2). p11 selectively bound to the serotonin receptor subtype 5HT1B. SSRI antidepressant drugs, as well as electroconvulsive shock, increased brain levels of p11, whereas p11 levels declined in rodent models of depression as well as in the brains of human depressed patients. Transgenic mice overexpressing p11 displayed an antidepressant behavioral profile, whereas p11-KO mice appeared depressed and failed to respond to antidepressant drug therapy. In other studies, they showed that p11 is the only member of the S100 family to interact selectively with serotonin receptors and that p11 can also bind another receptor subtype, 5HT4 (3).

The Greengard study implies that NSAIDs impair the therapeutic actions of SSRIs by inhibiting the formation of brain cytokines.

The Discovery

The new study (1) focuses upon cytokines, reporting that levels of numerous cytokines in the brain are enhanced by treatment with SSRIs, with increases blocked by nonsteroidal NSAIDs such as ibuprofen. The augmentation of p11 elicited by SSRIs is abolished in mice with genetic deletion of receptors for the cytokines IFN-γ and TNF-α. Administering IFN-γ or TNF-α increases brain levels of p11. Taken together, these data delineate a pathway whereby SSRIs increase brain cytokine levels, which in turn stimulate the formation of p11. Consistent with this model, receptors for IFN-γ and TNF-α are colocalized in neuronal systems with p11. Actions of the SSRIs upon cytokines are presumably mediated by potentiation of serotonin rather than other neurotransmitters, as antidepressants that do not act selectively via serotonin generally fail to influence cytokines and p11.

The investigators have linked these biochemical findings to behavior (1). They use conventional behavioral models for antidepressant action, such as the forced swim tail suspension tests. They show that NSAIDs such as ibuprofen prevent the antidepressant actions of SSRIs such as citalopram and fluoxetine but not influences of antidepressants acting via norepinephrine or other mechanisms, such as tranylcypromine, bupropion, and desipramine. The antidepressant actions of the SSRIs are evidently mediated via p11, as they are abolished in mice with targeted deletion of p11 from neuronal rather than glial populations of the brain.

The researchers extend the link of molecules and mood to humans by incorporating clinical data (1). They have obtained access to the data of a large-scale investigation of antidepressant therapy in treatment-resistant patients and examined remission rates in patients who had received NSAIDs, analgesic agents, both, or neither. The remission rates in patients receiving NSAIDs are reduced approximately 20%, whereas the reduction is approximately 31% for patients receiving analgesic agents or NSAIDs plus analgesic agents, alterations with high statistical significance.

Implications

What do these findings teach us about molecular mechanisms of depression? They certainly point to an unprecedented role for cytokines in the brain. SSRIs, whose proximal molecular target is serotonin, somehow augment levels of cytokines in a fashion that can be prevented by drugs whose proximal target is inhibition of cyclooxygenase, with diminished formation of prostaglandins. Identifying the pathway from SSRIs, presumably through serotonin, to the cytokines will be an important task. The cytokines in turn stimulate the formation of p11 via unknown mechanisms. Pathways for the formation of the S100 family of proteins are reasonably well elucidated so that it may feasible to sort out how cytokines interface with p11. As for what p11 does in the brain, the Greengard group (1) has already established that binding of p11 to 5HT1B and 5HT4 serotonin receptors increases their surface expression.

The clinical implications of the study are considerable. The authors draw the straightforward conclusion that patients receiving SSRIs should be advised that concomitant ingestion of NSAIDs and

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related drugs may diminish the therapeutic efficacy of their antidepressant regimen. Because of the major clinical importance of such an admonition, some caveats may be in order. Although the Greengard study (1) implies that NSAIDs impair the therapeutic actions of SSRIs by inhibiting the formation of brain cytokines, one might ask whether they influence the metabolism and blood levels of the drugs. Thus far, there is no major evidence for such effects. Also, one might speculate that depressed patients receiving NSAIDs are experiencing other painful conditions that exacerbate depression and/or hinder response to drug therapy. The Greengard group (1) reviews literature indicating that pain, per se, does not interfere with response to antidepressants.

In terms of the relation between cytokines and behavior, the present findings may seem to conflict with some published literature (4). Thus, numerous studies report elevated levels of cytokines in depression (5). Also, the administration of cytokines for treatment of infectious disease and cancer is associated with depressive side effects in 20% to 50% of patients (6). Several groups have reported that antiinflammatory therapy is beneficial in depression, including observations of aspirin synergizing with fluoxetine (7), as well as celecoxib facilitating antidepressant actions (8). The TNF-α antagonist etanercept (Enbrel) is associated with diminished depression in patients receiving the drug for treatment of psoriasis (9). These discrepancies may reflect the complexity of the large body of cytokines with different populations in the periphery and the brain. The findings of the Greengard group (1) may selectively reflect the delimited pool of neuronal cytokines in areas of the brain associated with p11 and serotonin neurons.

In summary, the new findings establish a potentially important link among cytokines, p11, serotonin, and the actions of antidepressant drugs with considerable clinical implications. By meandering from molecule to mental illness with implications for clinical practice, the Greengard group (1) has reframed dialogues addressing links between the immune system and emotions.

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