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LETTER TO THE EDITOR

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Norepinephrine may be an underlying factor in chemobrain

Dear Editor,

Chemotherapy is a widely used and effective treatment for many types of neoplasms, but it is also frequently accompanied by psychological deficits that are referred to as chemotherapy-related cognitive impairment (CRCI), or colloquially as "chemobrain."[1] The pathophysiological processes that underlie CRCI are only beginning to be elucidated. This letter briefly explores the hypothesis that norepinephrine (NE), which is a neurotransmitter in the brain that is also released peripherally by the adrenal glands and sympathetic nervous system, is a prominent factor underlying CRCI. If this hypothesis is correct, it would not only provide basic information on the neurochemical basis of CRCI, but also suggest various neuropharmacological treatments with existing noradrenergic drugs.

While a number of factors besides just chemotherapeutic agents have been suggested to play a role in various cases of CRCI, such as radiation therapy or psychological stress associated with cancer diagnosis, this letter focuses only on the older agents that have been used clinically for decades in many cases. There is evidence that a number of these drugs modulate NE release in the brain and periphery, particularly in animal models. For example, there are data suggesting that vinblastine, vincristine, cyclophosphamide, and doxorubicin can *increase* release of NE in the brain,[2] peripheral organs, and blood plasma,[3,4] whereas data from other agents suggest *decreases* in NE release or destruction of noradrenergic sympathetic terminals.[5,6] The possibility that these agents typically increase peripheral NE is reinforced by findings that fatigue and nausea, which frequently accompany chemotherapeutic administration, have been correlated with changes in blood plasma NE.

Since many chemotherapeutic agents do not readily cross the blood-brain barrier, and neither does NE itself, an important question is how intravenously or otherwise peripherally delivered agents could affect brain NE to produce CRCI? One possibility is that since chemotherapy can induce a hyperinflammatory state that may disrupt the blood-brain barrier, this could allow circulating NE (or various inflammatory molecules) to enter the brain to some degree.[7] It should be noted that chemotherapy has recently been suggested to be accompanied by an inflammatory "cytokine storm,"[8] which itself has been linked with catecholamine signaling such as NE.[9] Another way that peripheral chemotherapy could influence NE in the brain is through the vagus nerve, where this pathway may also be modulated by changes in the intestinal microbiome produced by chemotherapy.

It is indeed plausible that brain NE could play a role in CRCI, since this neurotransmitter is distributed in circuits throughout the brain and is strongly associated with multiple forms of memory (e.g., working, navigational, declarative memory) that can be impaired in CRCI, as well as with depressive symptomatology that may accompany CRCI. Accumulating evidence, both in human subjects and in animal models, suggests that NE has a u-shaped or janus-faced "dose-response" function in various forms of cognition, such that either too much or too little noradrenergic signaling is pathological.[10] In this scenario, if some chemotherapeutic agents boost brain NE and others deplete it (perhaps in a subregion-specific manner), then either situation could be pathological and result in CRCI. Alterations of brain NE have also been suggested to play a role in neurodegenerative disorders such as Alzheimer's and Parkinson's, so it may also be plausible that NE could be a factor underlying neurodegeneration in CRCI.

In summary, older chemotherapeutic agents can in some cases alter peripheral noradrenergic signaling, by either increasing or decreasing it, which may translate into brain alterations of NE either through a disrupted blood-brain barrier or via signaling of the vagus nerve. If brain noradrenergic signaling is increased (perhaps in a long-term manner) by these chemotherapeutic agents, then the widely clinically used and relatively safe noradrenergic transmission-reducing drugs may ameliorate symptoms of CRCI: alpha-2 agonists (clonidine, guanfacine, dexmedetomidine), alpha-1 antagonists (prazosin, terazosin), beta-blockers (propranolol, carvedilol, nebivolol, atenolol). Histone deacetylase (HDAC) inhibitors such as valproic acid and vorinostat may also reduce NE transmission and could be effective against CRCI. The latter drugs are also already being used clinically against various types of cancer. On the other hand, if some cases of CRCI are characterized by deficits in noradrenergic signaling, then antidepressants that selectively boost NE may be therapeutic: tricyclics (desipramine, nortriptyline), atomoxetine, reboxetine.

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CONFLICT OF INTEREST

The author declares no potential conflict of interest.

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