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Review

The Mystery of Chemotherapy Brain: Kynurenines, Tubulin and Biophoton Release

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Abstract. *The majority of patients receiving chemotherapy experience post-chemotherapy cognitive impairment, sometimes referred to as "chemo brain" or "chemo fog." The cognitive impairment associated with this syndrome can be severe, and can sometimes last for many years after therapy discontinuation. Despite extensive investigations, its etiology is unknown. We argue that chemo brain results from damage to tubulin within microtubules. This damage can occur directly from tubulin inhibitors such as taxanes, epothilones or vinca alkaloids. Other chemotherapies stimulate increased mitochondrial activity and biophoton release. This results in abnormal tryptophan metabolism and excess production of neurotoxic kynurenines, which, in turn, damage microtubules.*

Chemotherapy drugs can have severe toxic effects on any organ in the body and the mechanisms by which most of these toxicities occur are well understood. The exception is "chemotherapy brain" (chemo brain). Up to 75% of patients receiving chemotherapy experience some degree of neurocognitive impairment (1), a clinical syndrome which manifests as difficulties with concentration, decision-making and learning, memory loss, and problems with comprehension. This is the so-called chemo brain (2-9). This general "slowness" of neurocognitive activity without other symptoms is characteristic of chemo brain. Auditory, tactile or visual hallucinations, signs of dementia, tremors, sensory impairments and problems with motor strength are not considered part of this syndrome. The "fog" these patients experience is the defining feature of chemo brain. Despite numerous investigations into the etiology of this syndrome, the cause is unknown.

Although the mechanism by which chemo brain occurs is not understood, it occurs commonly. For example, Iyer *et al*. reviewed ten studies of 509 children with acute lymphoblastic leukemia (ALL) who had received chemotherapy but not cranial radiation. The protocol of treatments for ALL patients almost always includes drugs of the vinca alkaloid (primarily vincristine) and anthracycline (doxorubicin or daunorubicin) classes (4). Children who received these chemotherapies demonstrated decreases in memory and information processing speed, as well as a reduction in IQ by 6-8 points compared to that of 555 age-matched controls. Kessler *et al*. studied breast cancer patients who had received doxorubicin-containing regimens, chemotherapy regimens without doxorubicin or no chemotherapy. Both chemotherapy groups demonstrated greater memory and other cognitive impairments compared to women who had not received chemotherapy, with greatest impairments in women who had received doxorubicin (9). Similar results have been reported in breast cancer patients receiving cyclophosphamide, methotrexate and 5-fluorouracil (10), or various chemotherapy regimens for adults with either lymphoma or breast cancer (11). There is also experimental evidence that documents the deterioration of cognitive functioning after chemotherapy. Rendeiro *et al*. observed cognitive impairments, similar to those in patients, in C57BL/6J mice treated with cyclophosphamide, doxorubicin and 5-fluorouracil (12).

There is no clear explanation why patients experience these cognitive changes, why these symptoms may be so severe or persistent, or why they occur in the absence of other impairments. Seemingly obvious explanations, such as that these symptoms are due to the psychological stress of cancer diagnosis, are not consistent with the fact that the symptoms can persist years after treatment. More importantly, cancer patients who receive adjuvant chemotherapy after surgery have a higher incidence of chemo brain than those who undergo surgery alone. It is also important to note that most chemotherapy drugs strongly associated with chemo brain do not cross the blood

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brain barrier or cross only in low concentrations. Although some studies have suggested that treatments can themselves open up the blood brain barrier, other studies do not support this conclusion (13). This suggests that the mechanism of chemo brain is unlikely to be a direct effect on neurons, but, rather, that chemotherapy acts indirectly.

Pro-inflammatory Cytokines

Chemotherapy is well-known to increase production of pro-inflammatory cytokines. Reers *et al*. demonstrated that head and neck cancer cell lines exposed to 5-fluorouracil and cisplatin increased their secretion of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta) and IL-6 (14). Edwardson *et al*. showed that multiple chemotherapy agents, including docetaxel, increased the release of TNF-alpha and CXCL1 from breast and ovarian cancer cells (15). Penson *et al*. showed that another taxane drug significantly increased IL-6, IL-8 and MCP-1 (16). Pusztai *et al*. studied 90 breast cancer patients who received either FAC chemotherapy (5-fluorouracil, doxorubicin and cyclophosphamide) or paclitaxel monotherapy. Marked increases in IL-6, IL-8 and IL-10 were observed (17). In another study, women with breast cancer had increased levels of TNF-alpha and IL-6 at 6 and at 18 months after completion of therapy compared to controls (18). Jones *et al*. described how these chemotherapy-induced cytokines mediate resistance to treatment, and accelerate tumor growth and development of metastases (19). IL-6 and other cytokines predispose to development of cancer stem cells, which are resistant to further chemotherapy and radiation (20). Others have also described how cancers stimulate cytokines to insure their survival (21-23). Antineoplastics such as oxaliplatin, fludarabine, lenalidomide, rituximab and nivolumab can sometimes even cause a potentially fatal cytokine storm with massive releases of TNF-alpha, IL-1 beta, IL-6, IL-8, interferon gamma, IL-5, IL-13 and IL-10 (24-26).

There is a close association of the increase in pro-inflammatory cytokines with chemo brain (27). Ganz *et al*. and others have suggested that TNF-alpha may be the cause of chemotherapy brain, since higher levels of this cytokine correlate with greater neurocognitive symptoms, and improvements in neurocognitive symptoms parallel with decreasing TNF-alpha levels (28). Tangpong *et al*. studied mice treated with doxorubicin and obtained no evidence that this drug crossed the blood brain barrier. However, there was strong TNF-alpha immunoreactivity within the brain, and there was also evidence of damage to brain mitochondria and increased expression of pro-apoptotic proteins like BAX and p53 (13). Others have suggested that increased levels of IL-1 beta, IL-6 or interferon gamma, or decreased levels of anti-inflammatory cytokines like IL-4 or IL-10 may be causally involved in chemo brain (29-30). For example, Cheung showed that higher levels of IL-1 beta and IL-6 were associated with greater cognitive impairments, while higher levels of the anti-inflammatory cytokine, IL-4, were protective (31). Dunlop and Campbell have discussed how chemotherapy-induced cytokines can cause symptoms of chemo brain and other poorly-defined symptoms like generalized pain and malaise (32). There is also direct evidence that cytokines can cause a clinical syndrome like chemo brain. Capuron *et al*. performed neurocognitive tests on 47 patients who had received IL-2 or interferon-alpha as cancer treatment. Patients who received these treatments developed impaired spatial memory, longer latencies in reaction time and decreased accuracy in planning tasks (33).

Cytokines have been shown to cause damage to the brain and other tissues in multiple ways (34-36). Unlike most chemotherapies, cytokines can freely cross the blood brain barrier (37, 38). They may accumulate massively after infections or injury; and although cytokines can have beneficial effects, they can be responsible for damage to the brain tissue beyond that caused by the initial insult (39-41). For example, cytokines stimulate matrix metalloproteinases, which are zinc-based enzymes which digest tissue. These enzymes are linked to the development of many diseases, including Alzheimer's (42-45).

Mitochondrial Biophoton Emission

There is an important mechanism by which cytokines may cause neurocognitive impairments by dramatically increasing (and are increased by) reactive oxygen species (ROS) (46, 47). ROS are involved in countless metabolic processes that are essential for life, including adenosine triphosphate production, response to pathogens, cellular homeostasis and cell signaling (48-50). ROS have also been postulated by many to be causally involved in chemo brain (38, 51). Anthracyclines like doxorubicin have been shown to result in the production of extremely high levels of ROS (37, 38, 52). Anthracycline-induced TNF-alpha secretion has been shown to cause damage to mitochondria (13). Tangpong *et al*. studied doxorubicin-induced nitration of manganese superoxide dismutase, resulting in a reduction in mitochondrial anti-oxidant activity in the mouse brain. The mice developed symptoms similar to those of patients with chemo brain (53). Likewise, Keeney *et al*. showed that doxorubicin induced TNF-alpha and caused similar symptoms through oxidative stress (54). Cisplatin also markedly increases ROS levels, and this is a mechanism by which this drug may destroy cancer cells (55, 56). The cytokines TNF-alpha and IL-1 beta have been shown to cause mitochondrial DNA damage in chondrocytes (57). Lopez-Armada *et al*. demonstrated that mitochondrial activity in chondrocytes is regulated by these two cytokines (58). Many other chemotherapeutic agents, including alkylating agents, arsenic, topotecan and irinotecan, also increase ROS (48, 51, 59).

Reactions involving ROS in living tissues, including all animals and plants, have been shown to cause the continuous release of photons from mitochondria, which are emitted as excited electrons return to the ground state (60-69). These biophotons are primarily in the ultraviolet and visible ranges (100-800 nm), but may also extend to the infrared (70, 71). Measurements of photon release have been used to monitor ROS production (72). These biophotons can then be absorbed and emitted at different wavelength by chromophores like flavins, collagen, NADH and tryptophan (Table I). Significant release of biophotons occurs at 280 nm, which corresponds to the peak absorption wavelength of the essential amino acid, tryptophan, a highly fluorescent chromophore (66, 73).

Table I. *Key biomolecules with corresponding absorption and emission peak maxima (nm).*

Biomolecule	Absorption (nm)	Emission (nm)
Tryptophan	280	340
Collagen	339	380
NADH	340	440-460
Flavins	375	525
Tyrosine	275	303

Tryptophan Fluorescence

Exposure of materials containing tryptophan to ultraviolet (UV) light will result in the metabolism of this amino acid along the kynurenine pathway (Figure 1). Photoyellowing of wool products after exposure to light results mostly from the stimulation of the metabolism of tyrosine and (primarily) tryptophan, and production of metabolites such as kynurenine, hydroxykynurenine and N-formylkynurenine (74). Schafer *et al*. showed again that photo-generation of kynurenines from tryptophan and photoyellowing of wool entails a key role for oxygen (75). Other studies have demonstrated that these metabolites are major ultraviolet-photooxidation products of tryptophan (76). Hamdy *et al*. exposed tryptophan to various light sources and demonstrated that UVB light markedly increased metabolism along this pathway (77). Sheipouri *et al*. have shown that UV skin damage correlates with production of kynurenines from tryptophan (78). The damage to the lens of the eye with sun exposure is caused primarily by UV light. Andley *et al*. showed that UV light stimulates the generation of superoxide anion (O_2-) and hydrogen peroxide. The authors also found a decrease in tryptophan fluorescence and an increase in fluorescence by tryptophan metabolites, consistent with stimulation of the kynurenine pathway (79). Linetsky *et al*. showed that metabolites of tryptophan through the kynurenine pathway modify proteins in the lens after exposure to UV light (80). This same mechanism also occurs within the brain, and is associated with the cytokines, interferon gamma and TNF-alpha, which stimulate excess production of the enzymes, indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase. Increased cytokines levels result in greater release of biophotons from mitochondria in the brain. Toxic levels of kynurenines are associated with the development of many neurological diseases, including Parkinson's disease (81, 82), Huntington's chorea (83), amyotrophic lateral sclerosis (84) and Alzheimer's (85), as well as glioblastoma resistance to treatment (86, 87). IL-1 beta has also been shown to regulate this important pathway (88). Metabolites formed by excessive kynurenine pathway activity have major neurotoxic effects on brain tissue. Quinolinic acid can cause axonal degeneration, acute brain cell death (89, 90), hallucinations, delusions and bizarre behavior. Quinolinic acid is also known to have important effects on microtubules. Quinolinic acid plays a role in Alzheimer's disease pathogenesis by affecting Tau phosphorylation and causing disassembly of microtubules (91). This results in death of neurons and memory loss (92). Excess levels of quinolinic acid have been linked to Huntington's chorea, AIDS dementia, cognitive decline of aging, malaria-associated neurotoxicity and multiple sclerosis (93, 94). Rats receiving intrastriatal injections of quinolinic acid experience alterations of microtubule-associated protein-2 and cytoskeletal disruption (95). Another tryptophan metabolite, 3-hydroxykynurenine, can cause hallucinations and is thought to play a role in the development of schizophrenia and bipolar disorder (96, 97). High levels of 3-hydroxykynurenine correlate strongly with increased schizophrenic symptoms. 3-hydroxykynurenine may also cause increased beta-amyloid accumulation in the brains of patients with Alzheimer's disease (98). Both of these neurotoxic tryptophan metabolites have been linked with the development of major depressive disorders (99). Importantly, abnormal levels of kynurenines are associated with cognitive impairments in individuals without these diseases. Solvang *et al*. studied 2174 adults, aged 70-72 years old, living in an adult community. They found that increasing kynurenine/tryptophan ratios correlated with greater impairments of cognitive functions (100).

Microtubules

Microtubules are cylindrical structures in the cytoskeleton of eukaryotic cells. They are composed of polymers of alpha and beta-tubulin, and are key to proper functioning of multiple cellular processes, including intracellular transport and cell movement. Most importantly, microtubules are important for both mitosis and meiosis (101-106). For this reason, tubulin has become a major target of chemotherapy drugs. Abnormalities in microtubules have long been associated with cognition and memory problems (107), and damage to microtubules correlates with numerous neurological diseases. Microtubules play a key role in neurocognitive development and abnormalities in

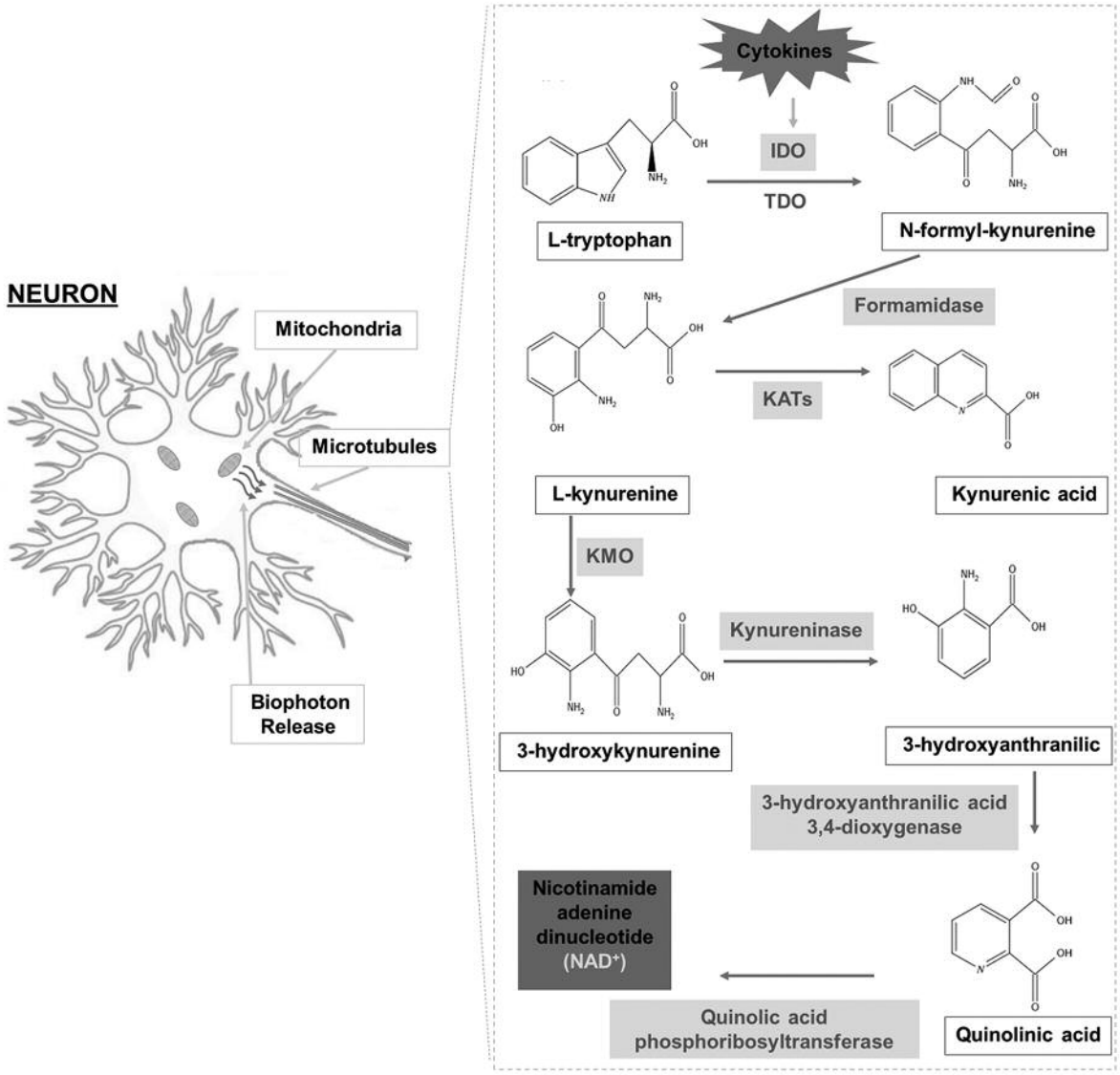

Figure 1. *Neuron with mitochondria (biophoton release) and microtubules (not to scale). Tryptophan metabolism (in the microtubules) in the kynurenine pathway. IDO: Indoleamine 2,3-dioxygenase; TDO: tryptophan 2,3-dioxygenase; KAT: kynurenine aminotransferases; KMO: kynurenine 3-monooxygenase.*

microtubules may result in intellectual impairments and autism (108). The enzyme, NAD-dependent deacetylase sirtuin 2 (SIRT 2), which concentrates in neural tissue and is associated with diseases like Alzheimer's, Huntington's chorea and Parkinson's, deacetylates tubulin (109). NAD is a major metabolite of quinolinic acid and is produced through the activity of quinolinate phosphoribosyltransferase (110).

Numerous studies have demonstrated that these mitochondrial biophotons, including those that originate in neural cells, have profound effects on microtubules (66). Both mitochondria in the cytoskeleton and closely-associated microtubules have a much higher refractive index than surrounding tissues, and these systems can act like optical waveguides (111, 112). There is also evidence that, while a physiological level of mitochondrial ROS and normal biophoton release correlates with normal brain functioning, including synaptic plasticity and memory consolidation (112-114), increased or decreased photon release is associated with neural pathology. It is notable that increased biophoton release can alter the orientation of microtubules. The greatest alteration in the orientation of the microtubules occurs when the wavelength of the biophotons is at 280 nm, which is the peak absorption wavelength of tryptophan (66, 73, 115).

Table II. *Commonly-used chemotherapeutics which act as tubulin inhibitors.*

Drug	Indication
Paclitaxel (Taxol)	Breast, non-small cell lung, ovarian, pancreatic and head and neck carcinoma, Kaposi's sarcoma
Docetaxel (Taxotere)	Breast, non-small cell lung, prostate, head and neck, gastric and ovarian carcinoma
Nab-paclitaxel (Abraxane)	Breast, non-small cell lung and pancreatic carcinoma
Ixabepilone (Ixempra)	Breast carcinoma
Erbulin Mesylate (Halaven)	Breast carcinoma, liposarcoma
Vincristine (Oncovin)	Acute lymphoblastic leukemia, Hodgkin's disease, multiple myeloma, Wilm's tumor, Ewing's sarcoma, neuroblastoma, lymphomas, adult soft-tissue sarcomas, thyroid carcinoma
Vinorelbine (Navelbine)	Rhabdomyosarcoma, breast and non-small cell lung carcinoma
Vindesine (Eldisine)	Non-small cell lung and breast carcinoma, lymphoma, leukemia
Vinblastine (Velban)	Hodgkin's disease, bladder, testicular and non-small cell lung carcinoma

Not only is there evidence that excess biophoton release can cause neurological impairments, the correlation of photon release measurements with other brain function measurements provide additional support for this hypothesis. Kobayashi *et al*. have shown a correlation of the levels of photon release with cerebral energy metabolism (61). Isojima *et al*. reported similar results (116). Van Wijk *et al*. have shown there is a correlation between the level of photon emission with the strength of alpha rhythms observed on the electroencephalogram (EEG) (117). Further, it has been reported that synchronous EEG patterns correlate with various neurocognitive states. Melloni *et al*. demonstrated that EEG readings showing synchronization of neural activity across areas of the cerebral cortex correlate with conscious perception (118). Synchronization of oscillatory phases between different brain regions promotes neural plasticity and correlates with long-term memory (119). Fries showed that neuronal gamma-band synchronization correlates with cortical computation (120).

Post-anesthesia Cognitive Impairment

The clinical syndrome of post-anesthesia cognitive impairment (PACI), sometimes referred to as post-surgical cognitive impairment, includes difficulties in concentration, comprehension and memory that occur after anesthesia, and is remarkably similar to the chemo brain. It is thought to be a separate clinical entity than post-operative delirium, and is listed in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) as such (121). In the absence of other factors (advanced age, pain medications, alcohol abuse), it does not involve hallucinations or delusions or other signs of dementia. Furthermore, it does not involve tremors or gross sensory or motor impairments (122-124). PACI can last for months or years, while post-operative delirium is usually short-lived (121). As with chemo brain, pro-inflammatory cytokines are thought to have a role in the causation of PACI. Cibelli *et al*. performed tibial surgery on knockout mice lacking the IL-1 beta receptor and on wild-type mice. PACI developed only in the knockout mice. Mice treated with IL-1 beta receptor antagonist also did not develop PACI (125). Terrando *et al*. reported that TNF-alpha could stimulate release of IL-1 in the brain and thus cause PACI (126). The anesthetic isoflurane has been shown to increase brain levels of TNF-alpha, IL-6 and IL-1 beta (127). Schneemilch and Bank showed that pro-inflammatory cytokines, especially IL-6, were increased immediately after induction with balanced inhalational Trapanal/sevoflurane anesthesia and before surgery (128). Wakabayashi *et al*. reported that sevoflurane anesthesia markedly increased the levels of IL-6 and IL-8 (129). Kumakura *et al*. showed that IL-1beta, IL-6 and MCP-1 were increased after anesthesia with nitrous oxide and sevoflurane (130). Other studies have shown similar results (131, 132). Craddock *et al*., in an extensive review, have described the numerous actions by which anesthetics may affect tubulin (133).

Tubulin Inhibitors and Other Chemotherapies

Most chemotherapy drugs profoundly affect microtubules, because of their effects on mitochondrial ROS and biophoton release. Other commonly-used agents are direct inhibitors of beta-tubulin (Table II) (134-136). Taxanes, such as docetaxel and paclitaxel, are tubulin depolymerization inhibitors. Agents of the epothilone class, such as the breast cancer drug ixempra, function through the same mechanism. Vinca alkaloids, vincristine, vinblastine and vinorelbine, inhibit tubulin polymerization. Neural cells may be especially sensitive to these agents. For example, Huff *et al*. showed that treatment with vincristine caused disappearance of tubulin from neural cells, while cancer cells and other normal cells were not affected (137). Drugs from the halichondrin class, such as erbulin, are also polymerization inhibitors. Other chemotherapy agents have been shown to cause destruction of microtubules. In fact, a large majority of patients have received chemotherapies which have been demonstrated to

destroy microtubules. Topoisomerase inhibitors, like tubulin inhibitors, cause apoptosis by the formation of topoisomerase I cleavage complexes (138). Topoisomerase I inhibitors such as topotecan and irinotecan are known to profoundly increase ROS (48). Doxorubicin, a topoisomerase 2 inhibitor which induces the largest increase in mitochondrial activity and is closely associated with the development of chemo brain, causes fragmentation of microtubules in cultured motor neurons (139, 140). Other anthracycline compounds may also disrupt microtubule organization and affect the ability of tubulin to form microtubules (141). DNA is thought to be the primary target of cisplatin, yet this agent and its analogs (carboplatin, oxaliplatin) have also been shown to enhance microtubule depolymerization and have other effects on tubulin (142). These platinum compounds cause deacetylation of alpha-tubulin and hyperphosphorylation of microtubule-associated protein tau (143). Mitomycin C and etoposide have also been shown to affect tubulin (144, 145). Yokomizo *et al*. have shown that these four important chemotherapies, doxorubicin, cisplatin, mitomycin C and etoposide, increase superoxide anions, while tubulin inhibitors (vincristine) do not (146). Estramustine, an estrogenic derivative of nitrogen mustard, inhibits microtubule assembly (147). Both actinomycin-D, which binds to DNA and inhibits transcription, and 5-fluorouracil, which blocks DNA synthesis, have destructive effects on tubulin (148-150). In addition to these "classic" drugs, many newer classes of chemotherapeutic agents, such as proteasome inhibitors and tyrosine kinase inhibitors, also damage tubulin (151-155). As noted, reversal of tubulin deacetylation caused by cisplatin has also been reported to reverse symptoms of chemo brain associated with cisplatin use (143). BMS-241027, an agent which stabilizes microtubules, reverses cognitive impairments in mice (156). The selective serotonin reuptake inhibitor, fluoxetine, reverses depressive symptoms by suppression of the proinflammatory cytokines, TNF-alpha, IL-1 beta, IL-6 and IL-17 (157). Fluoxetine has been shown to reverse cognitive impairment caused by the chemotherapy drug methotrexate (158). Gaman *et al*. have demonstrated the causative role of oxidative stress in chemo brain induced by doxorubicin, carmustine, methotrexate or cyclophosphamide and suggested that chemo brain could be reversed by anti-oxidants (159). Konat *et al*. have shown that doxorubicin and cyclophosphamide could increase oxidative stress and cause severe attention and memory deficits in Sprague-Dawley rats, and these cognitive impairments could be reversed by anti-oxidants (160).

Conclusion

We argue that post-chemotherapy cognitive dysfunction (chemo brain) is caused by chemotherapy's damage to tubulin within microtubules. Chemotherapy drugs cause a marked increase in pro-inflammatory cytokines, particularly TNF-alpha, IL-1 beta, IL-6 and interferon gamma. These, in turn, stimulate reactions involving ROS production by brain mitochondria, resulting in an increase in emission of biophotons. While normal levels of biophoton release are physiological, and, in fact, may partially regulate normal biological functions, increased release is linked to neuronal pathology. For example, the peak wavelength in the ultraviolet range where biophotons cause a change in microtubule orientation is at 280 nm, which is also the peak absorption wavelength of tryptophan. Biophoton release at this wavelength results in excess tryptophan metabolism along the kynurenine pathway, and the production of increased levels of neurotoxic metabolites. There is much evidence that microtubules are key to neurocognitive development, and abnormalities of microtubules are linked to deficiencies in cognition and memory. Anesthetics, which frequently cause a post-anesthesia cognitive dysfunction similar to chemo brain, have profound effects on tubulin. Most importantly, almost all the frequently-used chemotherapeutic drugs have destructive direct or indirect effects on tubulin. Reversal of the destructive effects on tubulin that are caused by these chemotherapies can result in alleviation of the cognitive impairments caused by these agents.

Conflicts of Interest

The Authors have no disclosures regarding this study.

Authors' Contributions

Both Authors have met all of the following four criteria: i) Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work. ii) Drafting the work or revising it critically for important intellectual content. iii) Final approval of the version to be published. iv) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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