The effect of tianeptine in the prevention of radiation-induced neurocognitive impairment

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Summary Radiation-induced neurocognitive impairment is an undesirable radiation-induced toxicity and a common health problem in patients with primary or metastatic brain tumor. It greatly impairs quality of life for long-term brain tumor survivors. Hippocampus is the most important brain structure for neurocognitive functions. It has been shown that radiation affects the hippocampal neurogenesis due to either induce the apoptosis or reduce the precursor cell proliferation in the hippocampus. Radiation-induced microglial inflammatory response is also negative regulator of neurogenesis. Tianeptine is a clinically effective antidepressant that induces neurogenesis. It has also been shown that tianeptine is able to reduce apoptosis and cytoprotective against the effects of proinflammatory cytokines in the hippocampus. Given the putative role of impaired hippocampal neurogenesis in radiation-induced neurocognitive impairment we think that tianeptine can be effective for preventing radiation-induced neurocognitive impairment by increasing hippocampal neurogenesis.

Introduction Cranial radiation therapy is one of the most effective treatment modality of many primary brain tumors, cancers metastatic to the brain, central nervous system involvement of leukemia/lymphoma, and head and neck cancers [1]. Unfortunately, this treatment unavoidably involves the inclusion of healthy brain tissue in the radiation field that causes radiation-induced brain injury. Histological features of the radiation-induced brain injury are diverse and not specific to radiation. Classically, two hypotheses of radiation injury in the brain have been proposed. The first one, vascular hypothesis, explains the damage as vascular endothelial cell injury which may cause altered permeability and accelerated atherosclerosis and mineralizing microangiopathy, resulting in vascular insufficiency and infarction. The second one is the glial hypothesis that posits radiation-induced ablation of glial precursors and resultant demyelinative necrosis [2]. However, neither hypothesis adequately accounts for the fact that most patients...
with significant cognitive deterioration exhibit no signs of overt vasculopathy or demyelination.

It is believed that, high doses of radiation produce overt severe structural and functional injury such as demyelination and vasculopathies within the brain parenchyma, whereas lower doses can lead to cognitive dysfunction without inducing significant morphological changes [3,4]. Such cognitive changes can occur both pediatric and adult patients and include progressive deficits in short-term memory, spatial relations, visual motor processing, quantitative skills, and attention [2]. Neurocognitive dysfunction was reported to stabilize spontaneously or to progress over time [5,6]. In some cases, subcortical dementia might result which often is associated with gait disturbance and incontinence. Due to lack of effective treatment, most patients with this severe complication die after several months or a few years [6].

Hippocampus is a major brain structure needed for neurocognitive functions. Within the hippocampus short-term learning and memory functions are associated with the principal cells of the hippocampal formation, i.e., the pyramidal and granule cells of the dentate gyrus [7]. Unlike most other structures in the adult brain, the hippocampal granule cell layer undergoes continuous renewal and restructuring by the addition of new neurons. Recent studies show that these new cells become functionally integrated into the dentate gyrus and have passive membrane properties, action potentials, and functional synaptic inputs similar to those found in mature dentate granule cells [8]. Radiation at much lower doses than that needed to injure the more resistant post-mitotic neurons and glia of the brain has been found to affect these highly proliferative progenitors severely. Recently, investigators using a hippocampal slice model showed that radiation-induced reductions in hippocampal neurogenesis were associated with an inhibition of long-term potentiation, a type of synaptic plasticity [9]. Thus any agent, such as ionizing irradiation that damages neuronal precursor cells or their progeny could have a significant impact on neurogenesis and ultimately on specific cognitive functions associated with the hippocampus. Further, investigators showed that, proliferating granule cells of dentate gyrus undergo apoptosis after irradiation, and reductions in precursor cell proliferation are still observed months after exposure [10,11].

Additionally, recent animal model studies have also demonstrated that exposure to therapeutic doses of irradiation results in a massive microglial inflammatory response which is strong negative regulator of neurogenesis in the neurogenic region of the hippocampus [12,13]. Hong et al. also showed that the levels of the proinflammatory cytokines, IL-1β, TNF-α, IL-6 increase in mouse brain within 24 h of RT [14]. Furthermore, the hippocampus has one of the highest glucocorticoid (GC) receptor concentrations in the brain, and is therefore particularly sensitive to GC effects [15]. However GC anti-inflammatory effects are well-known, in the brain GC’s feedback negatively onto the hypothalamus, thereby inhibiting their own overproduction and maintaining homeostasis [16]. In addition GCs have been found not only promote atrophy of the dendrites of pyramidal neurons in the hippocampus but also inhibit neurogenesis in the dentate gyrus of hippocampus [17,18]. Particularly sustained exposure to GCs seems to contribute to impairment of cognitive function [17].

Tianeptine is a clinically effective antidepressant with structural similarities to tricyclic antidepressants. There are compelling data that show tianeptine has a critical role of both structural and functional plasticity in the hippocampus [19]. In animal studies, tianeptine has been found to prevent and reverse stress-induced GC mediated dendritic atrophy in CA3 pyramidal neurons in the hippocampus [20,21]. In addition to normalizing the rate of cytogenesis in the hippocampus, tianeptine is able to reduce apoptosis in the dentate gyrus of the hippocampus.

Furthermore tianeptine has been shown to be cytoprotective against the effects of proinflammatory cytokines in the cortex and white matter in mice [22]. This has recently been confirmed by Castanon et al., who demonstrated that tianeptine has an antagonistic effect of IL-1β and inhibit expression in rat paraventricular nucleus [23,24].

According to our knowledge tianeptine is the only antidepressant that induces neurogenesis. In the literature, neither fluoxetine (a selective serotonin reuptake inhibitor) nor imipramine (tricyclic antidepressant) produced neurogenesis or neurocognitive improvement when hippocampal neuronal precursors were selectively reduced by radiotherapy [20].

Hypothesis

Preventing of RT-induced neurocognitive deficits is not only improving the quality of life for long-term brain tumor survivors, but also increasing their therapeutic window. Given the putative role of impaired hippocampal neurogenesis in radiation-induced neurocognitive impairment. It is proposed that tianeptine can be effective for preventing radiations-induced neurocognitive impairment by increasing hippocampal neurogenesis. This issue warrants further studies.
References


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