

Effects of Radiation on Brain Microvasculature and Cognition

Previous studies indicate clearly that brain irradiation can lead to functional impairments months to years after treatment. Whole brain irradiation (WBI) leads to a progressive dementia in approximately 20-50% of brain tumor patients who are long-term survivors after treatment. At the present time, there are no successful treatments for radiation-induced brain injury, nor are there any known effective preventive strategies. The need to both understand and minimize the side-effects of brain irradiation is exacerbated by the ever-increasing use of large field or WBI in the treatment of secondary brain metastases. Approximately 20-40% of the >1,300,000 new cancer patients diagnosed in 2004 will develop brain metastases, making this the 2nd most common site of metastatic cancer, the most common neurological manifestation of cancer, and a cancer problem more common in incidence than newly diagnosed lung, breast, or prostate cancer. Currently, some 200,000-cancer patients/year receive large-field or WBI. Radiation-induced brain injury is a particular problem at middle-age when melanoma, breast cancer and lung cancer increase and the earliest signs of age-related changes in cognitive function become evident in normal subjects. We, and others, have proposed that the decline in cognitive function after WBI is exacerbated by increasing age and part of the mechanisms contributing to these impairments is a decrease in cerebrovascular density, and function of endothelial cells and the blood brain barrier.

Administration of angiotensin converting enzyme inhibitors (ACEI) or Ang II Type 1 receptor antagonists (AT₁RA) has proven highly effective in mitigating the severity, or preventing the development, of late radiation-induced injury in the kidney and lung. However, the mechanistic basis for this finding remains unclear. Evidence for an increase in systemic levels of angiotensin II (Ang II) after radiation is lacking. However, both the kidney and lung possess a functioning paracrine (local - organ based) renin-angiotensin system (RAS), as does the brain, raising the possibility that increases in local RAS activity may be part of the etiology for radiation-induced damage. The brain RAS is involved in many functions including cognition, memory, pain perception, and stress (in addition to cardiovascular and fluid-electrolyte homeostasis). Elevated

Ang II increases anxiety, inhibits acetylcholine release, and impairs cognition. In contrast, Ang II blockers decrease anxiety and attenuate age-dependent cognitive impairment. In this application, we hypothesize that fractionated WBI results in cognitive impairment by exacerbating age-related cerebrovascular rarefaction resulting in a decline in cerebral blood flow and impairments in glucose metabolism; these alterations together with impairments in VEGF secretion are a contributing factor in the decline in cognitive function and can be modulated by inhibition of brain RAS.

The following aims are proposed:

1. Assess whether irradiating the brains of 12 month old Fisher 344-Brown Norway rats results in rarefaction of brain microvasculature and a corresponding decline in local cerebral blood flow (LCBF) in brain regions specifically associated with learning and memory. A cranial window approach will be used to determine the initial time-course (4, 12, 26, 39 and 52 weeks post-irradiation) and the extent of the effects of WBI on vessel rarefaction using a clinically relevant protocol (5Gy twice weekly for 4 weeks – 40Gy total). Subsequently, microvessel density (arterioles, capillaries, and venules in specific brain regions e.g. CA1, CA3, dentate gyrus, subiculum, entorinal cortex, retrosplenial and anterior cingulate cortex) and local cerebral blood flow (LCBF - using [¹⁴C]iodoantipyrine) will be assessed under basal and maximum dilatory conditions and correlated with the decline in measures of hippocampal-dependent learning and memory. Local cerebral glucose utilization will be used as an additional functional measure and these alterations will be correlated with tests of hippocampally dependent learning and memory.
2. Determine whether trophic factors (e.g. VEGF) produced by the vasculature and glia and found to be necessary for hippocampally-dependent processes of learning and memory are reduced in the hippocampal microenvironment of irradiated animals. Basal, learning-induced and hypoxia-induced secretion of VEGF and related receptors will be assessed in irradiated and sham-treated animals (using a clinically relevant protocol - 5Gy twice weekly for 4 weeks – 40Gy total) 6 and 12 months after treatment.

3. Determine whether microvascular endothelial dysfunction (apoptosis, decreased VEGF expression and response to VEGF and increased generation of oxidative stress) and disruptions in blood brain barrier integrity occur in response to irradiation and whether the effects of irradiation are ameliorated by the ACE inhibitor, ramipril, or the AT₁ receptor antagonist, L-158,809.
4. Assess whether administration of an ACE inhibitor (ramipril) or an AT₁ receptor antagonist (158,809) ameliorate the radiation-induced decline in vascular density, LCBF, glucose metabolism and these endpoints will be associated with improved cognitive status.

The significance of this application is that the effects of a clinically relevant fractionated dose of WBI will be used and dependent variables assessed in animals of known cognitive status. These procedures will allow us to make more precise conclusions related to the etiology of cognitive impairment that occurs in response to WBI and assess the efficacy of interventions to reduce cognitive impairment after radiation.