Development of an Adverse Outcome Pathway for Deposition of Energy Leading to Learning and Memory Impairment

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May 19, 2023

Abstract

The understanding of radiation-induced non-cancer effects on the central nervous system (CNS) is essential for the medical setting (e.g., radiotherapy), and occupational exposures, such as nuclear workers or astronauts. Herein, the adverse outcome pathway (AOP) approach was used to consolidate relevant studies in the area of cognitive decline for identification of research gaps, countermeasure development, and for eventual use in risk assessments. AOPs are an analytical construct describing critical events to an adverse outcome (AO) in a simplified form beginning with a molecular initiating event (MIE). An AOP was constructed utilizing mechanistic information to build empirical support for the key event relationships (KERs) between the MIE of deposition of energy to the AO of learning and memory impairment through multiple key events (KEs). The evidence for the AOP was developed through a scoping review of the literature. In this AOP, the MIE is connected to the AO via six KEs of increased oxidative stress, increased deoxyribonucleic acid (DNA) strand breaks, altered signaling pathways, tissue resident cell activation, increased pro-inflammatory mediators and neural remodeling. Deposition of energy directly leads to oxidative stress, increased DNA strand breaks, an increase of pro-inflammatory mediators and tissue resident cell activation. These KEs, which are themselves interconnected, converge through increased DNA strand breaks, altered signaling pathways and pro-inflammatory routes and directly lead to neural remodeling. Broadly, it is envisioned that the outcome of these efforts could be applied to other cognitive disorders and support ongoing work by international authorities to review the system of radiological protection.

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Figure 1: Flow chart of AOP 483 from deposition of energy to impaired learning and memory. The molecular initiating event (MIE) is the first interaction between a stressor and a biomolecule within an organism. Subsequent key events (KEs) leading to the adverse outcome (AO) were identified. Both key event relationships (KERs) and non-adjacent KERs are included in this pathway. Adjacent KERs demonstrate the causal relationship between two KEs. Non-adjacent KERs can be used to support the weight of evidence (WOE) of the whole AOP by bypassing KEs with less evidence.

Figure 2: Summary of the prominent mediators that allow for key events (KEs) (more details are provided in the AOP Wiki entries). KERs are ordered by level of biological organization. Green arrows indicate the subsequent increase in the KE, and red arrows indicate the subsequent decrease in the KE. No arrows are used to indicate the deposition of energy because the KE is measured for radiation dose in gray (Gy). Abbreviations: APOE, apolipoprotein E; BAD, Bcl-2-associated death promoter; Bax, Bcl-2-associated X protein; Bad 2 b-cell lymphoma 2; CaM, calmodulin; cFLIP, cellular FLICE-like IL-1 beta-converting enzyme; ESR1 estrogen receptor alpha; GSK3 beta, glycogen synthase kinase 3 beta; HIF-1alpha, hypoxia inducible factor 1a; IL-1b, interleukin-1 beta; IL-6, interleukin 6; JAK1/JAK2, Janus kinase 1/2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; NF-kappaB, nuclear factor kappa B; PKM2, pyruvate kinase M2; p53, tumor suppressor protein p53; PTEN, phosphatase and tensin homolog; PR, progesterone receptor; ROS, reactive oxygen species; SIRT1, sirtuin 1; TGFbeta, transforming growth factor beta; TNF, tumor necrosis factor; TLR4, toll-like receptor 4; USP, ubiquitin specific protease.

Figure 3: Systematic evidence map depicting the quantity of evidence supporting each key event relationship (KER). Key events (KEs) are represented as circles, and KERs are arrows. The size of each arrow represents the weight of evidence as determined by the number of articles supporting the relationship in the form of biological plausibility, empirical evidence and essentiality studies. Articles could be used to support multiple KERs.
Figure 4: Summary of the Bradford Hill criteria (upper panel): plausibility, incidence concordance, dose concordance, time concordance, essentiality and the stressor types supporting the AOP (lower panel). The number of studies showing with evidence stream and the number of studies using each stressor to support the AOP were determined. Note essentiality may be overrepresented relative to other evidence streams due to the multiple KEs directly linked to the MIE (essentiality) through control and treatment groups (as seen with an abundance of studies). Not all stressors support each KE. Details can be found in the AOP Wiki. Observation: % occurrence.

Figure 5: Summary of the domain of applicability and dose used in the AOP. Studies were grouped by life stage (animal studies only), taxonomy, and the dose of radiation used. Animal life stage is defined in [1]. Human studies are not included. Not all dose ranges support each KE. Details can be found in the AOP Wiki. Under taxonomic applicability, “other” refers to pigs (1%), dogs (1%), beavers (1%) and giraffes (0.0%). Studies derived from in vitro models, as well as some in vivo models, do not specify life stage.

Figure 6: Summary of findings. Visual representation of evidence supporting the AOP [AOPWiki]. Studies based on evidence charts, taxonomic applicability, low-energy particles (LET), and dose range. The AOP is predominantly supported by ionizing radiation stressors and the breakdown of the doses is as follows: low doses were defined as 0.1 Gy; moderate doses were in the range of 0.1-1 Gy; and high doses were >1 Gy. High LET radiation includes neutrons and heavy ions, and low LET radiation includes protons, X-rays and gamma rays. Not all stressors and dose ranges support each KE in the AOP; details can be found in the AOP Wiki. The size of each colored section is representative of the number of studies supporting that category.
Supplementary Figure 1. PRISMA flow diagram depicting reference screening during the scoping review as described in Koczenko et al., 2022. “Other sources” refers to papers retrieved outside of literature searches (e.g., from subject matter experts and reference sections of review articles). References could be excluded for multiple exclusion reasons simultaneously. PEOE: population, exposure, endpoint, outcome.