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Estrogens downregulate cyclo-oxygenase -2 *(COX-2)* gene expression

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Inflammation plays a role in neurodegenerative illnesses such as Alzheimer's disease (AD). As a distinct fact, AD predominates in post-menopausal women as compared to aged men. Together, these observations suggest that sex steroids regulate neuro-inflammatory processes. Specifically, in the premenopausal state, estrogens could have a protective effect that would be lost after the menopause. To determine whether estrogens could down-regulate an inflammatory process, an amygdalar cell line was used to determine the effect of estradiol (E2) on cyclooxygenase–2 *(COX-2)* gene expression. Estradiol (E2) reduced *COX-2* mRNA and pre-mRNA levels. Given that E2 exerts most of its known genomic effects by binding to two estrogen receptors (ERs), ER-alpha (ER-a) and ER-beta (ER-b), ER-a and -b selective ligands were used to determine the relative contributions of the two receptors. ER-b accounted for all the E2 repressive effect on *COX-2* RNA expression. Ligand-bound ERs exert activating effects by binding to palindromic estrogen response elements (EREs); however, repression may occur via a different mechanism. The proximal *COX-2* gene promoter of the *COX-2* gene lacks an ERE, and E2 treatment leads to decreased recruitment of the transcription factor NF-kB to the promoter. E2 also leads to recruitment of histone deacetylase 1 and Sin3A, members of a repressive complex. Lastly, E2 leads to increased methylation of the *COX-2* proximal promoter. ER-b accounts for some but not all of these effects. These data suggest that E2 has a neuroprotective effect by decreasing an inflammatory response through pathways that are in part regulated by ER-b.

Speaker Biography

Rosalie M Uht was awarded her MD and PhD from the State University of New York at Stony Brook in 1990. She did a combined Anatomic Pathology Residency and Neuropathology Fellowship at the University of California, San Francisco (UCSF). This was followed by Post-doctoral work as an NIH Clinical Investigator, also at UCSF. She established her first independent laboratory at the University of Virginia at Charlottesville in 2000. In 2008, she moved to UNTHSC where she established a second independent lab and helped found the CANDR Brain Bank.

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