Sex hormone

Sex steroids, also known as gonadal steroids, are steroid hormones that interact with vertebrate androgen or estrogen receptors.

Their effects are mediated by slow genomic mechanisms through nuclear receptors as well as by fast nongenomic mechanisms through membrane-associated receptors and signaling cascades.

The term sex hormone is nearly always synonymous with sex steroid. The non-steroid hormones luteinizing hormone, follicle-stimulating hormone and gonadotropin-releasing hormone are usually not regarded as sex hormones, although they play major sex-related roles.

Aneurysmal subarachnoid hemorrhage risk factors are increased in postmenopause women compared with men of similar age, suggesting a role for sex hormones. Molenberg et al. aimed to explore whether sex hormones, and age at menarche/menopause have a causal effect on aSAH risk by conducting a 2-sample MR study (Mendelian randomization).

They obtained sex-specific genetic instruments for serum estradiol, bioavailable testosterone (BioT), SHBG (sex hormone-binding globulin), and age at menarche/menopause from genome-wide association studies. The associated sex-specific aSAH risk was estimated with inverse-variance weighted MR analyses with various statistical sensitivity analyses. Multivariable and cluster MR analyses were performed for BioT and SHBG to account for a genetic and phenotypic correlation between the 2 exposures. The clusters represented (1) single-nucleotide polymorphisms primarily increasing SHBG, with secondary decreasing effects on BioT, and (2) single-nucleotide polymorphisms affecting BioT without affecting SHBG.

Results: Univariable MR analyses showed an 18% increased aSAH risk among women per 1-SD increase in genetically determined SHBG levels (odds ratio, 1.18 [95% CI, 1.05-1.34]; P=0.007). Suggestive evidence was identified for a 27% decreased risk of aSAH among women per 1-SD increase in BioT (odds ratio, 0.73 [95% CI, 0.55-0.95]; P=0.02). The latter association disappeared in cluster analysis when only using SHBG-independent variants. MR analyses with variants from the cluster with primary SHBG effects and secondary (opposite) BioT-effects yielded a statistically significant association (odds ratio, 1.21 [95% CI, 1.05-1.40]; P=0.008). No other causal associations were identified.

Conclusions: Genetic predisposition to elevated serum levels of SHBG, with secondary lower serum BioT levels, is associated with an increased aSAH risk among women, suggesting that SHBG and BioT causally elevate aSAH risk. Further studies are required to elucidate the underlying mechanisms and their potential as an interventional target to lower aSAH incidence [1].

1)
Molenberg R, Thio CHL, Aalbers MW, Uyttenboogaart M; ISGC Intracranial Aneurysm Working Group, Larsson SC, Bakker MK, Ruigrok YM, Snieder H, van Dijk JMC. Sex Hormones and Risk of Aneurysmal Subarachnoid Hemorrhage: A Mendelian Randomization Study. Stroke. 2022 Jun 2:101161STROKEAHA121038035. doi: 10.1161/STROKEAHA.121.038035. Epub ahead of print. PMID: 35652345.