

specific information regarding patients with SAH. Considering the large number of individuals who have TBI and SAH each year, post-traumatic hypopituitarism is an important public health issue. TBI and SAH pose substantial risks to hypothalamopituitary dysfunction. Hypopituitarism after TBI and SAH might contribute to a delayed or hampered recovery during rehabilitation. However, in both adults and children, a large number of patients with hypopituitarism after TBI or SAH remain undiagnosed and untreated.

Possible causes of hypopituitarism include hemorrhage, infarction, ischemia, necrosis, fibrosis, swelling, stalk transaction, or direct trauma to the hypothalamus, stalk, and/or pituitary region. The severity of TBI seems to be an important risk factor for developing hypopituitarism, however, post-traumatic hypopituitarism can also manifest after even mild TBI. Whereas hypothalamopituitary dysfunction occurred without regard to the severity of SAH.

The signs and symptoms associated with hypopituitarism are often nonspecific and mimic the sequelae of TBI and SAH such as depression, neuropsychological deficits, or personality changes. They are likely to be overlooked if endocrine dysfunction is not actively assessed. Moreover, hormonal deficits may contribute to the

chronic disability and the physical, cognitive, health, and social sequelae in patients with TBI and SAH. Therefore, accurate endocrine evaluation and long-term follow-up of TBI and SAH patients are necessary in order to detect the occurrence of hypopituitarism, regardless of clinical evidence for hypothalamopituitary dysfunction. In order to improve outcome and quality of life of TBI and SAH patients, adequate hormone replacement therapy may be necessary in those who develop hypopituitarism. It is necessary for physicians as well as patients and family members to know that hypothalamopituitary dysfunction following TBI and SAH may occur long after the initial trauma. A close collaboration among neurosurgeons, neurologists, rehabilitation specialists, internists, pediatricians, and endocrinologists is essential to achieve a coordinated approach to the care of patients with TBI and SAH. The consensus guidelines for assessment and for clinical practice of such patients have been published.^{2,3}

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References

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FTO Gene Association with BMI and Obesity

Frayling et al and Dina et al have both linked a common variant in a set of single nucleotide polymorphisms (SNPs) in the first intron of FTO (fat mass and obesity associated gene; OMIM 610966, chromosome 16q12.2) with early onset of severe obesity in children and adults of European ancestry. FTO has 9 exons; its product and function are as yet unknown. In the report of Frayling et al, a genome-wide association study of 490,032 SNPs and their relationship to type 2 diabetes mellitus (T2DM) was conducted and 10 SNPs in intron 1 of FTO (designated A allele) was found to be closely related to this disorder. Further analysis revealed an even stronger association between BMI and the FTO intron 1 SNPs variant. In adults of all ages and both genders, each A allele was associated with an increase in BMI of 0.10 z-score units (~0.4 kg/m²). Adult carriers of one A allele had an odds ratio of 1.31 for being overweight (BMI >25 kg/m²) and of 1.18 for being obese (>30 kg/m²); subjects homozygous for the A allele had 1.38 risk of being overweight and a 1.67 risk of obesity. Similar studies in children and adolescents between 7 to 14 years of age revealed that those with one A allele had an odds ratio of 1.27 for being overweight and of 1.35 for being obese. Waist circumference, skin-fold thickness, and DEXA measurement of fat mass were increased in children with the A allele. Frayling and co-workers found no functional variants in the exonic

sequences of FTO relative to the SNPs variation in intron 1. Thus, the manner in which this variant of FTO affects weight accumulation is as yet unknown. Dina et al also associated the A allele with severe obesity in adults (BMI >40 kg/m²) as well as with early-onset obesity in children, but found no mutations in the coding regions of FTO. Both groups concluded that a variant in SNPs in intron 1 of FTO is associated with an increased risk of obesity in children and adults, but the mechanism of the effect remains unexplained at present.

Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007;316:889-94.

Dina C, Meyre D, Gallina S, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. Nat Genet. 2007;39:724-6.

Editor's Comment: Experimentally in mice, deletion of the chromosome segment in which FTO is located is embryonically lethal in the homozygotic animal and is marked by fused toes and thymic hyperplasia in the heterozygotic mouse that is of normal weight. Therefore, the composition, structure, and functional properties of the product(s) of FTO variants may need to be identified by methods other than those that attenuate (or enhance?) expression of FTO in experimental animals. If these goals can be successfully accomplished and the

functional relationships between variants of *FTO* and the regulation of energy metabolism and conservation elucidated, then it may be possible to design agents that can be directed to sites of *FTO* action that will ultimately lead to improved methods of weight control.

Interestingly, the presence or absence of the *A* allele was not associated with birth weight.

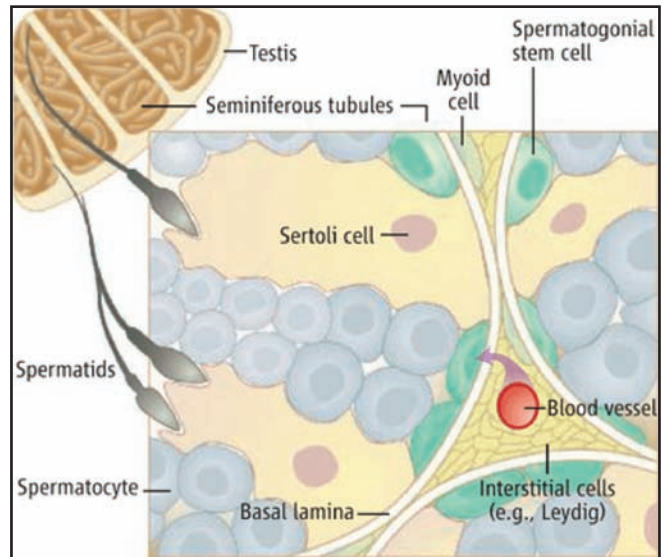
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A Niche for Undifferentiated Spermatogonia

In human males, spermatogenesis proceeds over several decades. Scattered throughout the spermatogenic tubules of mammalian testes are spermatogenic stem cells (cells that are able to self-renew and to differentiate into cells with more specialized functions) that appear to be localized to specific regions within the tubule (Figure). In mice, undifferentiated spermatogenic stem cells constitute less than 1% of testicular cells and periodically differentiate into primitive type A single (As) spermatogonia that then give rise to daughter cells—A paired (Apr) and A aligned (Aal)—chains of 4 to 32 cells—that in turn evolve into more mature spermatogenic cells.¹ The tubular regions that harbor the most primitive and undifferentiated spermatogenic stem cells are termed “niches” and are deemed important because of the environment provided therein that enables the undifferentiated A cells to survive and from which daughter cells migrate and populate the spermatogenic tubules permitting the decades-long process of spermatogenesis. Yoshida and co-workers have identified the sites of As localization by labeling undifferentiated A cells with green fluorescent protein (GFP) expressed in response to a regulatory sequence of a gene (*Ngn3*) expressed in spermatogenic cells. Utilizing time-lapse imaging to follow the course of GFP cellular expression in intact mouse testes, they localized the earliest mouse spermatogenic stem cells (As) to specific regions in spermatogenic tubules; these cells reside in a basal tubular compartment adjacent to the interstitium and across from blood vessels that are surrounded by interstitial cells (including Leydig cells); these sites are characterized by turns in the spermatogenic tubule and by branching of their associated blood vessels. As As cells transitioned to Apr and Aal cells, they migrated from the site of origin and spread throughout the basal tubular compartment giving rise to more differentiated spermatogonia, spermatocytes, spermatids, and sperm. The investigators confirmed these observations by transplantation of testicular fragments from donor testes that had been cleansed of vessels and interstitium to sites beneath the tunica albuginea of recipient testes in vivo. Three months later, the grafts had revascularized, the interstitium had been reconstituted, and spermatogenesis was normal; As cells were again localized to turns in the tubules across from branch points of the blood vessels that were themselves encased in interstitial cells. The authors suggested that the niche for As cells by proximity of the tubular basal compartment to the branch point of blood vessels and to abundant interstitial cells provides



At home, in small narrow places. Spermatogonial stem cells localize to interstitial regions between seminiferous tubules in the mouse testis. This implies that interstitial cells and branching blood vessels secrete factors (arrow) that influence stem cell fate.

Credit: Adapted by P. Huey/Science, Reprinted with permission DiNardo S, Braun R. Science.2007;317:1696-7. Copyright © AAAS 2007. All rights reserved.

a microenvironment in which “signals” from these cells recruit, nourish, and stimulate differentiation of spermatogenic stem cells. The biochemical nature of these signals is unknown but likely include testosterone, a factor known to be important for the earliest stages of spermatogonial differentiation, as well as products of the Sertoli cells. That niches can be reconstituted (as demonstrated by the testicular graft experiments) indicates that new niches can be developed, a process that would support long-term spermatogenesis.

Yoshida S, Sukeno M, Nabeshima Y-I. A vasculature-associated niche for undifferentiated spermatogonia in the mouse testis. Science. 2007;317:1722-6.

Editor’s Comment: Identification of the sites within the spermatogenic tubule that harbor undifferentiated spermatogenic stem cells may prove beneficial in isolating such cells. Inasmuch as these are cells with the diploid number of chromosomes (ie, prior to the first meiotic division), spermatogenic stem cells may ultimately provide a source of pluripotential stem cells.¹

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