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Improving mental health care... together

Neuroendocrinology

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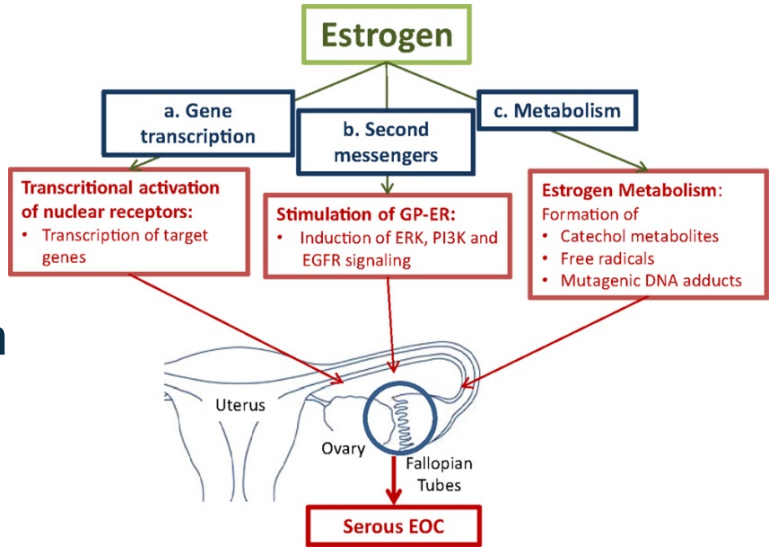
Sex differences in Schizophrenia

- Incidence of Schizophrenia ratio mean of male:female 1.42 (as defined by less negative symptoms)[1]
  - Men have earlier onset, and generally a worse prognosis
  - Females have higher incidence at older age
  - Premenopausal women have a better course of illness than menopausal women (have less negative symptoms and respond better to antipsychotic treatment)[3]
- No sex difference in prevalence[1]
- Progression of the disease and symptoms may be related to sex[1,2]
  - Men are more likely to have more psychotic symptoms than women
  - Women are more likely to have depressive symptoms and affective symptoms than men

1. Abel, KM, et al. 2010. *Int Rev of Psych.* 22 (5): 417-428
2. Hafner, H. 2003. *Psychoneuroendocrinology.* 28: 17-54.
3. Gogos, A, et al 2015; *Int J of Endocrinology*. 2015: 1-16.

Estrogens: Neuroprotection in Schizophrenia?

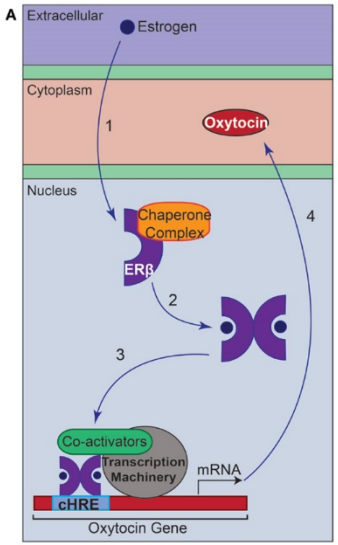
- Psychotic symptoms may be associated with estrogen levels[1,2]
  - Higher symptomology with lower estrogen levels
  - Low estrogen associated with higher hospital admissions
  - Low estrogen associated with lower cognitive performance
  - Only in females, not in males[3]
- A negative correlation was demonstrated between puberty and age of onset in women
- Data does not suggest estrogen supplementation improves schizophrenia or symptoms[1,3]
- Emerging data suggests that progesterone may be a contributor to schizophrenia, although the mechanism is not yet elucidated[4]

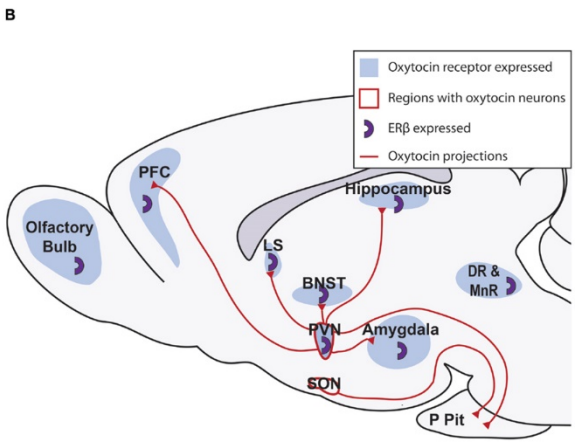


1. Abel, KM, et al. 2010. *Int Rev of Psych.* 22 (5): 417-428
2. Hafner, H. 2003. *Psychoneuroendocrinology.* 28: 17-54.
3. da Silva, TL and Ravindran, AV 2015. *Asian J of Psych* 18: 2-14
4. Sun, J, et al. 2016. *Psychoneuroendocrinology* 74: 126-140

Treatment based on Estrogen Hypothesis of Schizophrenia

- Estrogen receptor modulation has been proposed as a potential treatment (likely adjunctive) for the treatment of schizophrenia[1,2]
  - Particularly focused on cognitive impairment for schizophrenia[1, 2]
  - Concern around administration of exogenous estrogens[1]
- Selective Estrogen Receptor Modulators (SERMs) have been proposed as a potential treatment for schizophrenia[1,2]

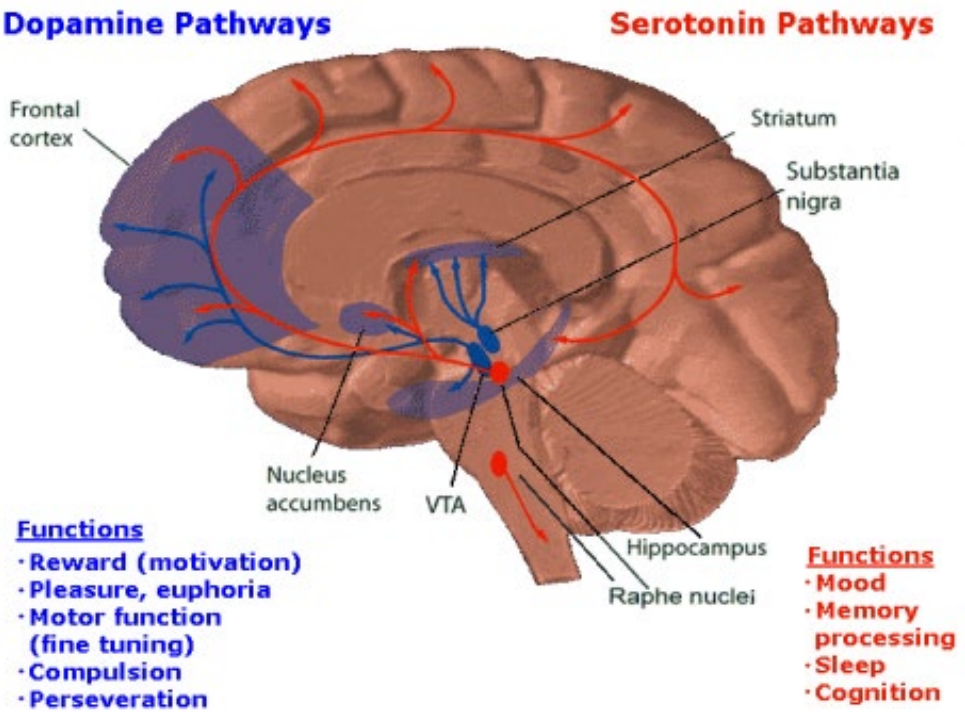




1. Kulkarni, J, et al 2013. *Int J of Endocrin and Metab* 11 (3): 129-136
2. Miller, B. 2015. *Psychiatric Times*. September 29, 2015

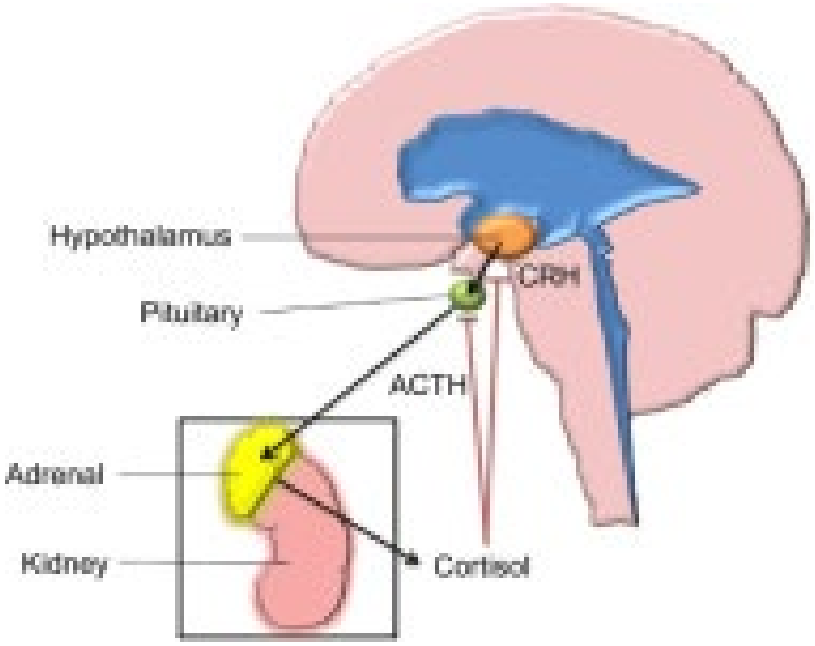
Neurotransmitter Function & Estrogen

- Animal models show:
  - Estrogen can modulate Dopamine, Serotonin, and Glutamate[1]
  - Estrogen can reduce D_2, $5HT_2$, NMDA, and GABA receptor sensitivity[1]
  - Estrogens may modulate learning and memory
  - Estrogens are neuroprotective in nature
- Taken together, estrogen is hypothesized to help protect the female brain. Dysregulation of estrogen may leave the brain open to insult (such as schizophrenia)



1. Gogos, A, et al 2015; *Int J of Endocrinology*. 2015: 1-16.

Cortisol



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- Schizophrenia symptoms may be associated with stress.[1]
  - Stress hypothesized to precipitate psychosis in schizophrenia.[1]
  - Cortisol is released as part of the stress response mediated by the hypothalamic-pituitary-adrenal (HPA) axis.[1]
  - Studies suggest stress and glucocorticoids lead to brain structural changes and neurochemical effects[1]
  - Some evidence that stress exposure impacts dopamine activity which exacerbate psychosis [1,2]
- Cortisol levels have been associated with schizophrenia.[2]
  - Cortisol levels positively correlated with positive symptoms, disorganization, and symptom severity [1,2]
  - Significantly higher cortisol levels have been observed in subjects who manifest clinical signs of psychosis risk than control subjects suggesting a relationship between increased HPA activity and risk of psychosis[2]
  - Significant lower cortisol awakening response (CAR), and higher levels of inflammatory markers, have been observed at psychosis onset in patients and may predict treatment response.[3]

1. Corcoran C, et al. *Schizophr Bull.* 2003. 29 (4):
2. Walker E, et al. *Biol Psychiatry* 2013. 74:410-417
3. Mondelli V, et al. *Schizophr Bull.* 2015. 41(5):1162-1170

Growth Hormone

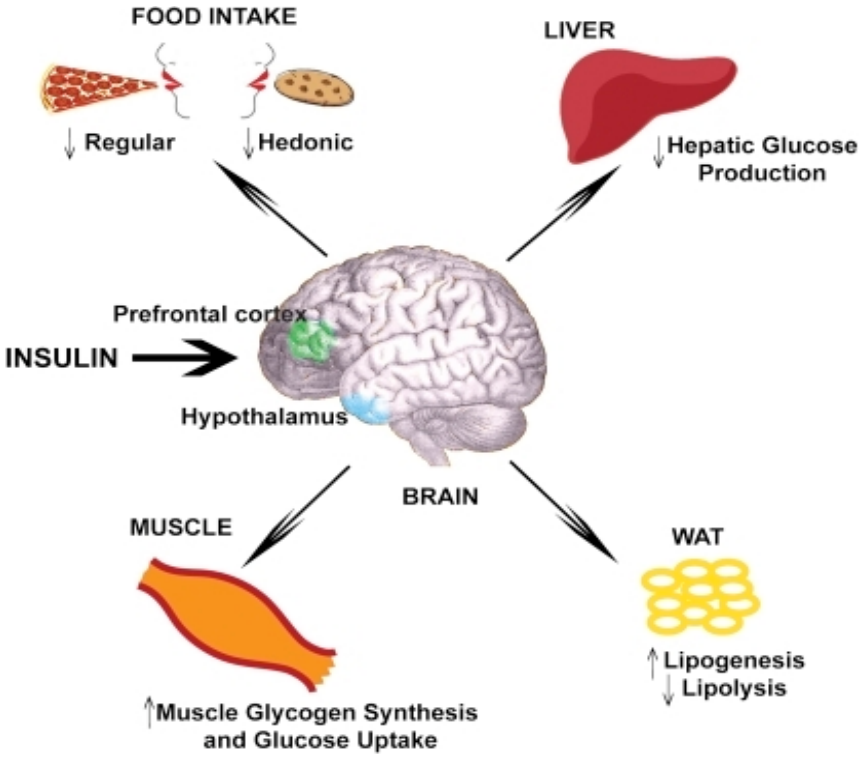
- Growth hormone (GH) has anabolic effects throughout the body, promoting protein synthesis and lipolysis while decreasing glucose utilization[1]
  - Regulated by growth hormone-releasing hormone (GHRH) and growth hormone-releasing hormone (GHIH) secreted by hypothalamus[1]
  - Neurotransmitters that stimulate GH release include catecholamines, dopamine, serotonin, and GABA[1,2]
- Abnormal GH signaling has been observed in patients with schizophrenia
  - A pattern of decreased GH plus increased insulin levels has been observed in SZ patients and their siblings compared to controls, suggesting that disturbed insulin and GH signaling pathways may be a potential risk factor for SZ[3]
  - Acromegaly has been reported in patients with SZ, possibly secondary to alterations in dopaminergic transmission associated with SZ pathophysiology and/or antipsychotics[4]

1. The pituitary hormones and their control by the hypothalamus. In: Guyton AC, Hall JE, eds. *Textbook of Medical Physiology*. 10th ed. Philadelphia, PA: WB Saunders Company; 2000:848-853.
2. Sheehan AH, Yanovski JA, Calis KA. Pituitary gland disorders. *Pharmacology: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw-Hill; 2008:1281-1283.
3. Van Beveran NJM, Schwarz E, Noll R et al. *Transl Psychiatry.* 2014 Aug 26;4:e430.
4. Iglesias P, Bernal C, Díez JJ. *Schizophr Bull*. 2014 Jul;40(4):740-3.

Metabolic Disturbances

Insulin

- Insulin functions in central and peripheral nervous systems[1]
  - glucose homeostasis and body weight[1]
  - cognition and mood[1]
- Studies in first episode, antipsychotic-naïve patients with schizophrenia show:
  - Increased circulating levels of insulin and insulin resistance[2,3]
  - Higher levels of plasma glucose, impaired fasting glucose tolerance[4]



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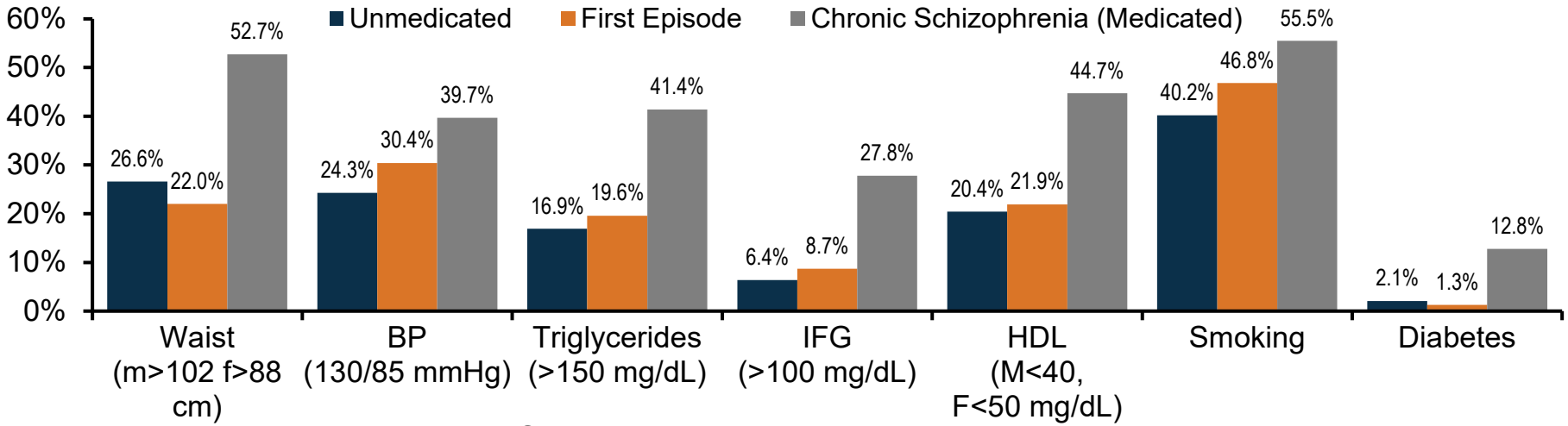
1. Lee SH, Zabolotny JM, Huang H et al. *Mol Metab* 2016 Jun29;5(8):589-601
2. Guest PC, Schwartz E, Krishnamurthy D et al. *Psychoneuroendocrinology* 2011 Aug;36(7):1092-1096
3. Dieset I, Andreassen OA, and Haukvik UK. *Schizophr Bull* 2016 Nov; 42(6):1316-1319
4. Ryan MC, Collins P, and Thakore JH. *Am J Psychiatry* 2003 Feb;160 (2):284-289

Metabolic Abnormalities in Unmedicated, First-episode, and Medicated Patients With Schizophrenia

Summary of individual metabolic syndrome risk factors in a meta-analysis of 21 studies of unmedicated SZ patients (n = 8593), 26 studies of first-episode SZ patients (n = 2548), and 78 studies of medicated patients with chronic SZ (n = 24,892)



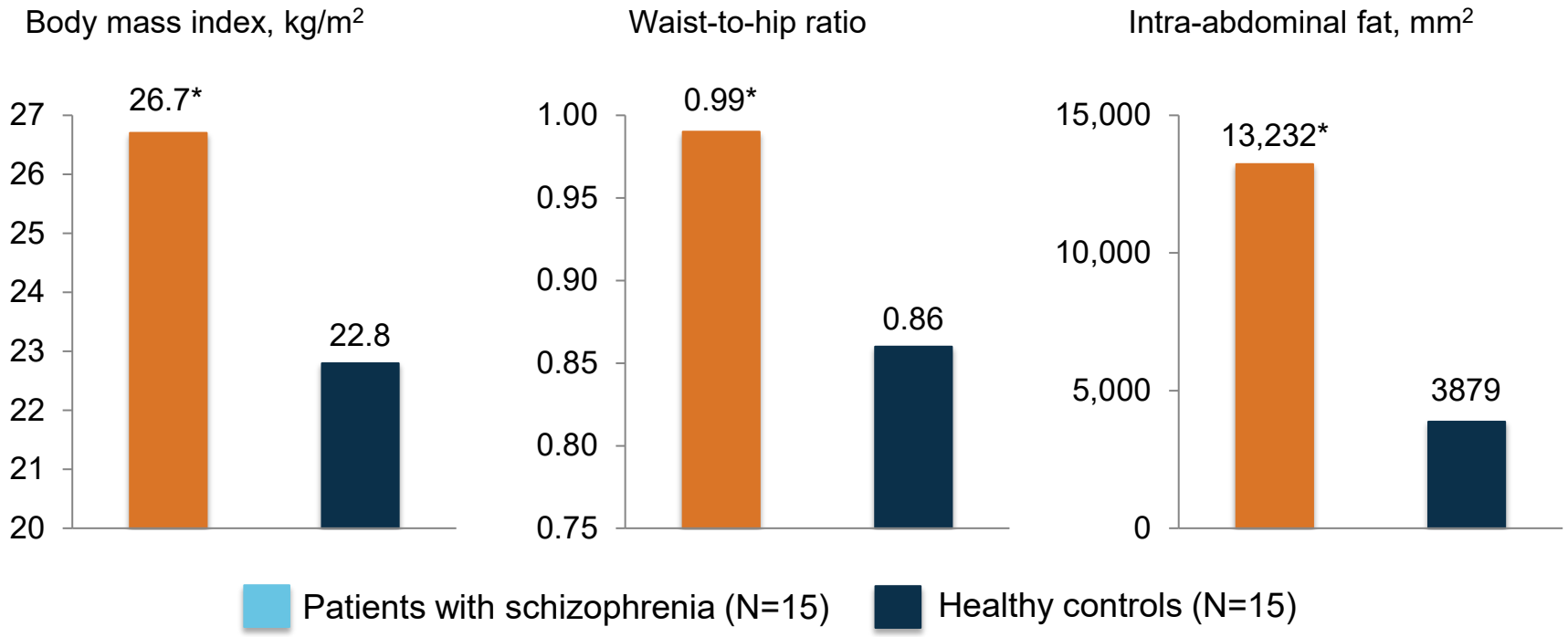
- Among patients with chronic SZ:
  - 1 in 2 are overweight (waist size: men > 102 cm, women, > 88 cm)
  - 2 in 5 have high blood pressure (>130/85 mmHg)
  - 1 in 10 have diabetes
- First-episode SZ patients had significantly fewer metabolic risk factors than those on established antipsychotic medication

*Data from a meta-analysis of 32 publications. BP, blood pressure; HDL, high-density lipoprotein; IFG, impaired fasting glucose, SZ, schizophrenia.

1. Mitchell AJ, et al. *Schizophr Bull*. 2013;39(2):295-305.

Mental Illness and Increased Obesity-Related Parameters

Patients with schizophrenia had increased levels of visceral adiposity compared with healthy controls



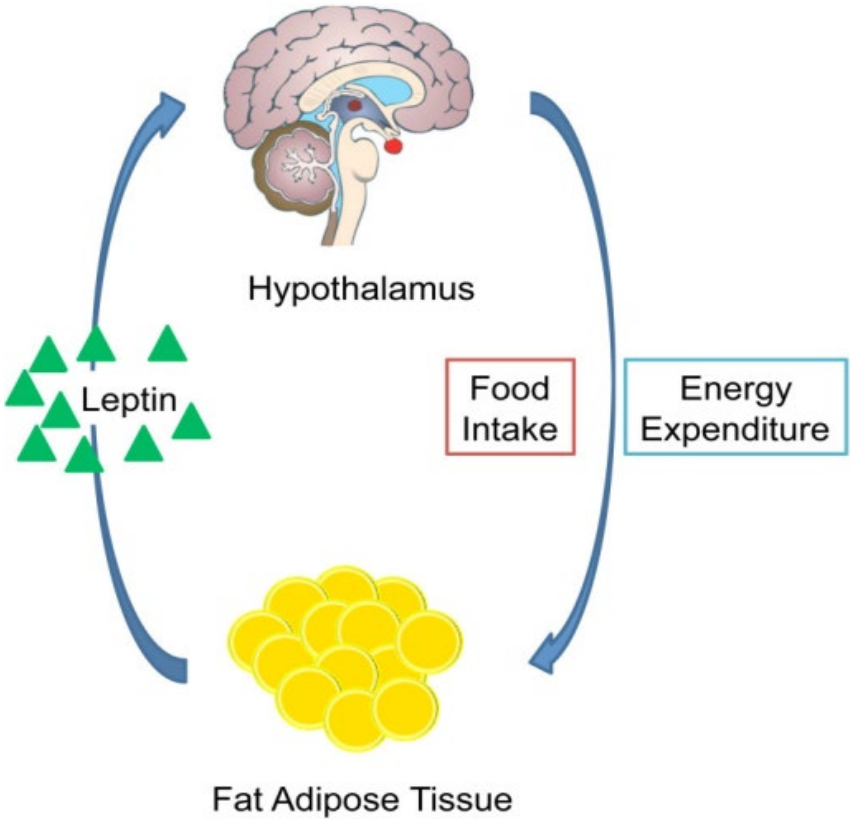
*P<0.005 vs healthy controls.

Thakore et al. *Int J Obes*. 2002;26:137-141.

Metabolic Disturbances

Adipose Tissue

- Dysregulation of adipose tissue signaling involved in pathophysiology of metabolic syndrome[1]
- Adipokines biomarker of adipose tissue metabolism[1]
  - Leptin
  - Adiponectin
  - Resistin
  - Adipocyte fatty acid binding protein (AFABP)

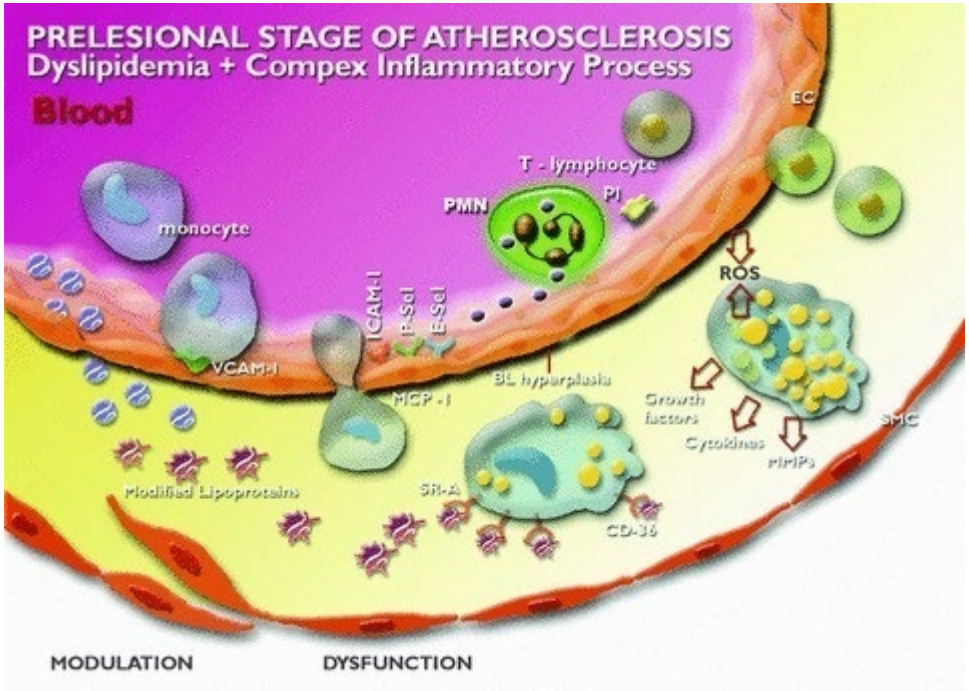


https://openi.nlm.nih.gov/detailedresult.php?img=PMC3064240_yjbm_84_1_1_g01&query=adipose+signaling+to+brain&it=g&req=4&npos=28

1. Kucerova J, et al. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2015 Jun; 159(2):208-214

Endothelial Dysfunction

- Endothelial dysfunction has been associated with both increased cardiovascular risk and impaired neurocognition in SZ[1]
- Chronic inflammation underlying SZ may contribute to endothelial dysfunction[2]
  - Cell adhesion molecules ICAM-1 and VCAM-1 facilitate leukocyte adhesion to the endothelial layer of the vasculature, promoting atherosclerosis
  - Vascular endothelial growth factor (VEGF) increases angiogenesis to restore oxygen supply
  - ICAM-1, VCAM-1, and VEGF have been strongly linked to inflammation and may be abnormal in SZ, though studies are conflicting



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1. Grove T, et al. Schizophr Rex 2015. 164: 1-3
2. Nguyen TT, et al. *Eur Arch Psychiatry Clin Neurosci*. 2017.

Conclusion

- Although there is a difference of incidence but not prevalence of Schizophrenia between males and females, sex is thought to play a role in the progression of the disease
  - The estrogen hypothesis of schizophrenia may provide some insight into the sex differences in the progression of the disease
- Other hormones including cortisol, growth hormone, and insulin may play a role in the progression and metabolic disturbances of schizophrenia
- Endothelial dysfunction, from inflammatory pathways, may contribute to the progression of the disease