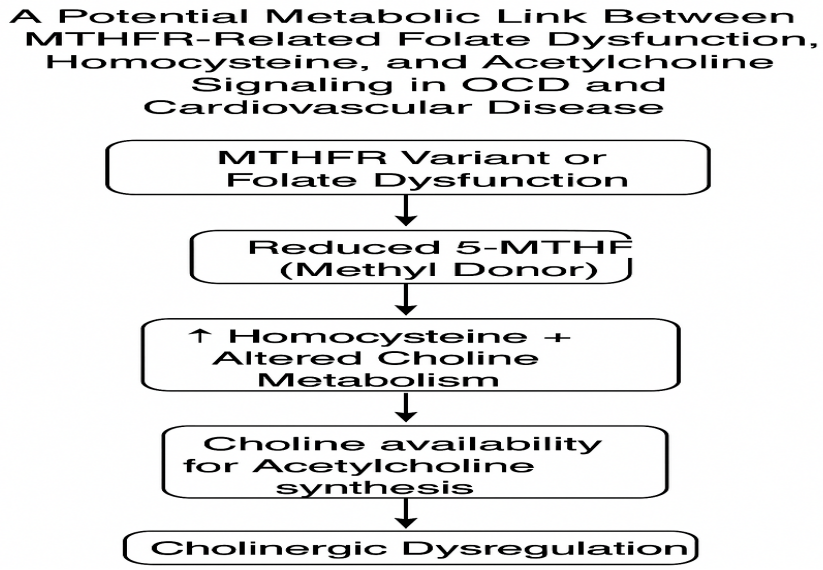
Possible link between MTHFR-related folate metabolism, homocysteine, and acetylcholine function in OCD and cardiovascular disease

Abstract

This hypothesis explores a possible biochemical link between methylenetetrahydrofolate reductase (MTHFR) polymorphisms, folate metabolism, and the regulation of choline and acetylcholine synthesis. It proposes that MTHFR dysfunction may elevate homocysteine and reduce methylation capacity, leading to altered choline metabolism and decreased acetylcholine availability. This biochemical cascade could connect cardiovascular risk with neuropsychiatric manifestations such as Obsessive-Compulsive Disorder (OCD).

Figure 1. Proposed pathway linking MTHFR dysfunction to homocysteine elevation, choline/acetylcholine imbalance, and resulting clinical effects.



Hypothesis

MTHFR or related folate-pathway variants may reduce 5-MTHF availability, leading to elevated homocysteine and altered choline metabolism. This would reduce choline supply for acetylcholine synthesis, potentially causing both vascular and neuropsychiatric manifestations such as OCD.

Supporting Evidence

Several animal and human studies support parts of this mechanism. MTHFR deficiency alters brain methylation and lipid metabolism, including choline and phosphatidylcholine pools (Chew et al., 2011). High folate intake in MTHFR-deficient mice produces pseudo-deficiency states affecting acetylcholine levels (Bahous et al., 2017). Mild MTHFR deficiency induces early brain aging features, including neurotransmitter imbalance (Chan et al., 2018). Elevated homocysteine further impairs vascular and endothelial function (Devlin et al., 2004).

Proposed Experiments

1. Examine choline and acetylcholine levels in MTHFR-deficient mice and human carriers with high homocysteine.
2. Assess whether folate or choline supplementation normalizes acetylcholine levels and OCD-like behavior in model systems.
3. Conduct clinical metabolomic profiling of OCD patients with and without MTHFR variants.

Conclusion

This hypothesis proposes a unified biochemical mechanism linking MTHFR dysfunction, altered one-carbon and choline metabolism, and acetylcholine-related neuropsychiatric and cardiovascular manifestations. It provides a framework for metabolic subtyping in OCD and encourages integrative biochemical research bridging psychiatry and cardiovascular science.

References

1. Chew TW et al. (2011). Folate intake, MTHFR genotype, and sex modulate choline metabolism in mice. *J Nutr* 141(8):1477–1483.
2. Bahous RH et al. (2017). High dietary folate in pregnant mice leads to pseudo-MTHFR deficiency and altered acetylcholine availability. *Hum Mol Genet* 26(6):1016–1030.
3. Chan A et al. (2018). Early manifestations of brain aging in mice due to mild MTHFR deficiency. *Neurobiol Aging* 62:1–10.
4. Devlin AM et al. (2004). Effect of Mthfr genotype on diet-induced hyperhomocysteinemia and vascular function. *Blood* 103(6):2624–2629.