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Role of choline supplementation in pregnancy in preventing the development of schizophrenia

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Abstract
Schizophrenia is a debilitating neurodevelopmental illness which affects around 1% of the population. Dietary requirements for choline are high during pregnancy because of its several uses, including membrane biosynthesis, one-carbon metabolism, and cholinergic neurotransmission. The perinatal period may be a stage where even small interventions may alter the developmental course. By studying the role of choline dependent mechanisms in early brain development, and its relationship to schizophrenia-associated cognitive deficits, we may develop primary prevention strategies. Dietary choline supplementation during pregnancy for preventing the cognitive deficits of schizophrenia requires further exploration. Primary prevention strategies are seldom the goal of research. However, Schizophrenia is an illness where it's imperative to identify novel treatment strategies aimed at normalizing early brain development. This review article discusses one such avenue. Here, we review the available literature on the role of choline supplementation during pregnancy for the prevention of Schizophrenia.

Keywords: Choline, Schizophrenia, pregnancy, neurodevelopment

1. Introduction

Schizophrenia is a debilitating neurodevelopmental illness which affects around 1% of the population [2]. The pathogenesis begins long before the emergence of psychosis- as early as during fetal brain development, and is influenced by both genetic and environmental factors.

Cholinergic neurotransmission at nicotinic receptors, is one of the pathophysiological mechanisms involved [6, 13]. Choline activates these receptors in the fetal brain and facilitates normal development of cerebral inhibition, which is found to be reduced in Schizophrenia patients. This can be inferred from the fact that these adult patients report heightened sensory stimulation from subtle environmental cues. For eg. A Schizophrenic is unable to block out other people's conversations in his background and instead focusses on them so much that he has the delusion that he is the subject matter of their discussion (Delusion of Reference).

Both genetically diminished numbers of these receptors as well as dietary deficiencies in choline might contribute to abnormalities in the development of cerebral inhibition.

Dietary supplementation in the form of Phosphatidylcholine thus emerges as a possible intervention in pregnancy to alter the earliest developmental course of this illness.

Dietary requirements for choline are high during pregnancy because of its several uses, including membrane biosynthesis, one-carbon metabolism, and cholinergic neurotransmission. 30% pregnant women were found to have a deficiency. Choline is transported actively across the placenta, and sequesters in the fetal brain, reaching higher concentration than that in the maternal serum. It then activates the nicotinic receptors, chiefly in hippocampus.

Having a parent with schizophrenia increases the risk a child will later develop schizophrenia by approximately 10 times, so a parental history of schizophrenia is often used as a marker of risk. While majority of Schizophrenia patients have the onset of hallucinations and delusions between 15 and 35 years of age, difficulties in attention, concentration and social interaction can be seen from early childhood. Neonatal developmental delay in inhibition is associated with attentional deficit even during infancy, which has been established as an early expression of risk for the disorder.

Physiological tests of attention are based on the concept that selective attention toward one stimulus requires the automatic inhibition of attention towards other stimuli. For example, when a hippocampal pyramidal cell is tuned to specific stimulus characteristics, this also leads to increased activity in surrounding inhibitory interneurons. The inhibitory interneurons then inhibit activity in neighbouring pyramidal cells and also loop back to inhibit the initial pyramidal cell.

Role of Choline in Normal Neurophysiology

GABA, an inhibitory neurotransmitter of the mature brain, is excitatory in early fetal brain development. Expression of the membrane chloride transporter KCC2 that switches GABA from excitatory to inhibitory is stimulated by activation of postsynaptic α7-nicotinic acetylcholine receptors.

These receptors are expressed at 10-fold higher levels in fetal hippocampus than in adult hippocampus, perhaps reflecting this critical developmental function, but these receptors are diminished in the hippocampal tissue of persons with schizophrenia. Innervation of postsynaptic α7-nicotinic receptors by cholinergic axons does not occur until the end of the third trimester. Instead, they are activated by the millimolar concentrations of choline in the amniotic fluid.

Perinatal choline activates timely development of cerebral inhibition, even in the presence of gene mutations that otherwise delay it.

Additional risk factors and their influence on Choline

During maternal starvation, the high demand for Choline by the fetus is not met. If the mother is a smoker, nicotine reaches the fetus and deactivates its alpha-7 nicotinic receptors.

If the mother has any kind of stress during pregnancy, or an infection, the woman preferentially holds choline in her own liver, which lowers the levels observed in the serum available for the fetus.

The enzyme phosphatidylethanolamine-N-methyltransferase (PEMT) allows for human de novo synthesis of choline. In the healthy premenopausal adult female, this de novo synthesis is normally sufficient to meet daily needs. But not in the case of pregnant women. Polymorphisms in the gene PEMT are associated with diminished choline levels.

Testing Method for neuronal inhibition

One test of inhibition is to examine the decrement in response when two stimuli are presented in close succession.P50 sensory gating method was used. A decrease in the paired stimulus paradigm by at least 50% was the pre-determined criterion for normal development of cerebral inhibition. The ratio of the amplitude of the second P50 wave to the first P50 wave is the dependent measure. (A ratio of 0 represents complete suppression of the second response and is considered optimal inhibitory circuit performance; most adults have ratios below 0.4).These ratios are higher in Schizophrenia

Main findings from Human studies

The most notable research in this field was carried out under Dr. Robert Freedman in Colorado: In this recent, well-designed study, 100 women (93 infants) in their second trimester of pregnancy received either placebo or 900 mg phosphatidylcholine. There were no side effects for either mother or baby. Most of the 46 infants who were exposed to choline, as opposed to the 47 infants exposed to placebo, did not display an abnormality in their brain responses to specific stimuli similar to that seen in most adults with schizophrenia (6% displayed this response in the choline group, compared to 91% for the placebo group). This paper suggests that prenatal treatment with choline reduces the chance (by about 75%) the child will go on to develop schizophrenia.

The children in the study are now 4 years old, and are already showing fewer early signs of schizophrenia — such as certain attention and social problems — than expected. Half of the children in the study had an increased risk for schizophrenia because their mothers had depression, anxiety or psychosis.

Other Human studies

Attention dysfunction in young children (around age six) has been accepted as a reliable early marker of schizophrenia. Ross and colleagues, however, reviewed infants' responses to specific auditory stimuli and found that even this was consistent with a physiological response shared by adults with schizophrenia ("P50 sensory gating") [23]. This demonstrates that there is a specific attention dysfunction even in infants who are more likely to develop schizophrenia.

Théberge and colleagues examined brain scans of 19 people who had schizophrenia but were not taking antipsychotics (for up to 31 months). For both areas of interest in the brain, choline levels were increased with relationship to the duration of untreated psychosis. This rise in choline levels may reflect brain cell loss or damage. While this report is significant, other studies conflict with regards to levels of choline in the brains of people with schizophrenia. However, this is the first study to examine patients who had no current treatment with antipsychotics.

Findings from Animal Models

Genetic studies in rodent models identified CHRNA7, the gene that forms the alpha-7 nicotinic acetylcholine receptor subunits, as a candidate gene for the deficit in neuronal inhibition.

Single Nucleotide Polymorphisms in this gene's promoter unit result in formation of a truncated peptide, causing difficulty in assembly of the alpha 7 nicotinic receptors and thus their reduced activation. Also, rodent models were created with CHRNA 7 mutations such that the nicotinic receptor density was reduced by 50%. They were then supplemented with choline during pregnancy. The offspring of the mice who were supplemented performed better in cognitive and behavioral tests. Diminished neurodevelopment was seen in Choline deficient piglets as well [31].

Rodent models have shown that prenatal or postnatal choline supplementation reduces cognitive and behavioral deficits in Fetal alcohol spectrum disorders [29] and also ameliorates deficits in balance [30]. The mechanism of this can be explained by the fact that Choline aids in phospholipid production for axonal growth and myelination and acetylcholine enhancement. Alcohol is known to cause damage to the brain by formation of reactive oxygen species [8, 9]. Choline was also found to provide a beneficial effect on social behavior, anxiety, and repetitive behaviors in certain mouse models of autism [28].

Role of maternal choline supplementation on hippocampal cholinergic deficits in mice with Down's syndrome to prevent early onset of Alzheimer's was also outlined in some studies [7, 14].

Limitations

First of all, it is necessary to note that certain genes have increased expression in fetuses, and these switches to adult levels soon after birth. This suggests that the brief window of prenatal development may be biologically irreversible. The goal of preventive strategies is to affect the pathophysiology of an illness early in it's course. However, intervening during this prenatal window also means that the unintended effects of the preventive treatment will have an impact on the most delicate period of development in the human life cycle. Secondly, the evidence base supporting prenatal choline supplementation to prevent the subsequent schizophrenia development is very limited. This is because this field has just begun receiving attention. It is also due to the 20-year lag between the intervention (prenatal choline supplementation) and the outcome of interest (schizophrenia).

We can think of a retrospective study that examined the serum of women from 30 years ago, some of whom had births that resulted in an adult offspring with schizophrenia that would have been helpful. Unfortunately, such a study has not been conducted.

Implications

Several decades may pass before it could be definitively proven whether prenatal choline supplementation affects the number of persons who develop schizophrenia eventually [1]. Despite this, the short 6-month interval for choline

supplementation and the lack of any significant side effects for it suggest that intensive dietary intervention might be justifiable for pregnant women, to prevent mental illnesses that have a huge burden on society much later. In certain communities where supplementation isn't feasible, recommendations to increase consumption of choline rich products in diet during the last 6 months of pregnancy are pertinent. Some of these are meat, soyflour, liver, fish and eggs.

Conclusion

Neurodevelopmental illnesses are the result of a decades-long interaction between genetic and environmental factors. The perinatal period may be a stage where even small interventions may alter the developmental course. By studying the role of choline dependent mechanisms in early brain development, and its relationship to schizophrenia-associated cognitive deficits, we may develop primary prevention strategies. Dietary choline supplementation during pregnancy for preventing the cognitive deficits of schizophrenia requires further exploration.

Key Points

1. The perinatal period may be a stage where even small interventions may alter the developmental course.
2. By studying the role of choline dependent mechanisms in early brain development, and its relationship to schizophrenia-associated cognitive deficits, we may develop primary prevention strategies.
3. Dietary choline supplementation during pregnancy for preventing the cognitive deficits of schizophrenia requires further exploration.

References

1. Freedman R. Prenatal choline and the development of schizophrenia. Shanghai archives of psychiatry. 2015; 25-27(2):90.
2. Lin E, Desrochers S. Examination of Schizophrenia-like Symptoms in Rats with a Biallelic Deletion in the Disc1 Gene as a Function of Choline Supplementation.
3. Mellott T. Prenatal choline supplementation advances hippocampal development and enhances MAPK and CREB activation. The FASEB Journal. 2004.
4. Moran M. Choline May Protect Infants From Developing Schizophrenia. PN. 2013; 48(3):1-23.
5. Li Q. Dietary Prenatal Choline Supplementation Alters Postnatal Hippocampal Structure and Function. Journal of Neurophysiology. 2004; 91(4):1545-1555.
6. Schizophrenia and choline acetyltransferase. American Journal of Psychiatry. 1994; 151(4):627a-627.
7. Strupp B, Powers B, Velazquez R, Ash J, Kelley C, Alldred M, *et al.* Maternal Choline Supplementation: A Potential Prenatal Treatment for Down Syndrome and Alzheimer's Disease. CAR. 2015; 13(1):97-106.
8. Thomas J, Abou E, Dominguez H. Prenatal choline supplementation mitigates the adverse effects of prenatal alcohol exposure on development in rats. Neurotoxicology and Teratology. 2009; 31(5):303-311.
9. Hernández JA, López-Sánchez RC, Rendón-Ramírez A. Lipids and Oxidative Stress Associated with Ethanol-Induced Neurological Damage. Oxidative Medicine and Cellular Longevity. 2016, 5.
10. Sarter M, Lustig C, Taylor SF. Cholinergic contributions to the cognitive symptoms of schizophrenia and the viability of cholinergic treatments. Neuropharmacology. 2012; 62(3):1544-53.
11. Money TT, Scarr E, Udawela M, Gibbons AS, Jeon WJ, Seo MS, *et al.* Treating schizophrenia: novel targets for the cholinergic system. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2010; 1-9(2):241-56.
12. Gioiosa L, Iannitelli A, Aloe L. Stress, anxiety schizophrenia and neurotrophic factors: the pioneer studies with nerve growth factor. Rivista di psichiatria. 2009; 1-44(2):88-94.
13. Raedler TJ, Freedman R. Cholinergic Mechanisms in Schizophrenia. Handbook of Neurochemistry and Molecular Neurobiology. 2009,17-38.
14. Toyohara J, Hashimoto K. α7 nicotinic receptor agonists: potential therapeutic drugs for treatment of cognitive impairments in schizophrenia and Alzheimer's disease. The open medicinal chemistry journal. 2010; 27:4(1).
15. English BA, Hahn MK, Gizer IR, Mazei-Robison M, Steele A, Kurnik DM, *et al.* Choline transporter gene variation is associated with attention-deficit hyperactivity disorder. Journal of neurodevelopmental disorders. 2009; 28:1(4):252.
16. Ahmadi M, Hosseini Ravandi H, Aghabarari A. Role of Muscarinic Receptors in Schizophrenia. The Neuroscience Journal of Shefaye Khatam. 2014; 15-2(3):160-136.
17. Hajos M, Rogers BN. Targeting α7 nicotinic acetylcholine receptors in the treatment of schizophrenia. Current pharmaceutical design. 2010; 1-16(5):538-54.
18. Jones CK, Byun N, Bubser M. Muscarinic and nicotinic acetylcholine receptor agonists and allosteric modulators for the treatment of schizophrenia. Neuropsychopharmacology. 2012; 1-37(1):16-42.
19. Freedman R. α7-nicotinic acetylcholine receptor agonists for cognitive enhancement in schizophrenia. Annual review of medicine. 2014; 14(65):245-61.
20. Davis KL, editor. Brain acetylcholine and neuropsychiatric disease.
21. D'Souza MS, Markou A. Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits. Neuropharmacology. 2012; 31-62(3):1564-73.
22. Deutsch SI, Schwartz BL, Schooler NR, Brown CH, Rosse RB, Rosse SM. Targeting alpha-7 nicotinic neurotransmission in schizophrenia: A novel agonist strategy. Schizophrenia research. 2013; 148(1):138-44.
23. Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, *et al.* Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. American Journal of Psychiatry. 2013.
24. Bekdash RA, Zhang C, Sarkar DK. Gestational Choline Supplementation Normalized Fetal Alcohol-Induced Alterations in Histone Modifications, DNA Methylation, and Proopiomelanocortin (POMC) Gene Expression in β-Endorphin-Producing POMC Neurons of the Hypothalamus. Alcoholism: Clinical and Experimental Research. 2013; 37(7):1133-42.
25. Zeisel SH, Da Costa KA. Choline: an essential nutrient for public health. Nutrition reviews. 2009; 67(11):615-23.

26. Jiang X, West AA, Caudill MA. Maternal choline supplementation: a nutritional approach for improving offspring health? Trends in Endocrinology & Metabolism. 2014; 25(5):263-73.
27. Biswas S, Giri S. Importance of Choline as Essential Nutrient and Its Role in Prevention of Various Toxicities. Prague medical report. 2015; 116(1):5.
28. Langley EA, Krykbaeva M, Blusztajn JK, Mellott TJ. High maternal choline consumption during pregnancy and nursing alleviates deficits in social interaction and improves anxiety-like behaviors in the BTBR T+ Itpr3tf/J mouse model of autism. Behavioural brain research. 2015; 278:210-20.
29. Wozniak JR, Fuglestad AJ, Eckerle JK, Fink BA, Hoecker HL, Boys CJ, *et al.* Choline supplementation in children with fetal alcohol spectrum disorders: a randomized, double-blind, placebo-controlled trial. The American journal of clinical nutrition. 2015; 102(5):1113-25.
30. Bearer CF, Wellmann KA, Tang N, He M, Mooney SM. Choline Ameliorates Deficits in Balance Caused by Acute Neonatal Ethanol Exposure. The Cerebellum. 2015; 14(4):413-20.
31. Mudd AT, Getty CM, Sutton BP, Dilger RN. Perinatal choline deficiency delays brain development and alters metabolite concentrations in the young pig. Nutritional neuroscience, 2015.