Sarcosine and Decreased Risk for Prostate Cancer in Schizophrenia

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Schizophrenia is a disabling major mental illness that affects approximately 1% of the world population, characterized by positive symptoms (e.g., unusual thoughts or perceptions, including hallucinations, delusions, thought disorder, and disorders of movement) and negative symptoms (e.g., loss or a decrease in the ability to initiate plans, speak, express emotion, or find pleasure in everyday life), and cognitive deficits (e.g., problems with attention, certain types of memory, and the executive functions). For almost 100 years, there has been speculation that patients with schizophrenia have lower cancer risks than the general population. In recent years, population-based studies have become available, allowing an analysis of the data by specific types of cancer and schizophrenia. Mortensen [1] reported that the incidence of prostate cancer in the male patients with schizophrenia was significantly lower than that of the general Danish population. A recent population-based, nested, case-controlled study demonstrated a 40.7% lower risk of prostate cancer in male patients with schizophrenia [2], consistent with that of previous studies [1,3], which have shown an approximately 50% lower risk. In contrast, patients with bipolar disorder had similar cancer risks as people without either mental health condition after adjustment for the potential confounding factors (e.g., socioeconomic status, smoking, obesity, comorbidity, and concurrent use of other medications) [2], indicating the specificity for schizophrenia. It has been suggested that genetic factors, antipsychotic medications, and lifestyle differences may be associated with the lower risk of prostate cancer [4,5] although the precise etiology underlying the lower risk of prostate cancer in schizophrenia were unclear.

In the 2009 February issue of *Nature*, Sreekumar *et al.* [6] reported that sarcosine (*N*-methylglycine) was identified as a biomarker that was highly increased during prostate cancer progression to metastasis and can be detected non-invasively in urine. Sarcosine is generated by the enzymatic transfer of a methyl group from *S*-adenosylmethionine to glycine (Fig. **1**), and this reaction is catalyzed by the enzyme glycine *N*-methyltransferase (GNMT) (Fig. **1**), which is expressed in prostate at high levels

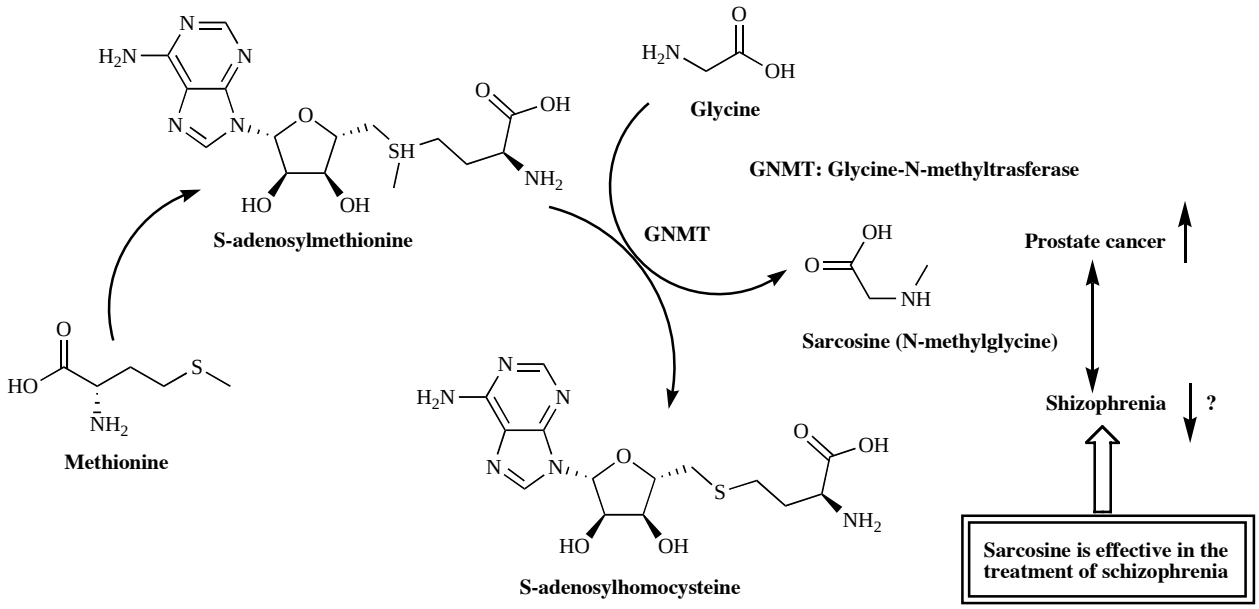

Fig. (1). A role of sarcosine in the pathophysiology of schizophrenia.

Sarcosine (*N*-methylglycine) is generated by the enzymatic transfer of a methyl group from *S*-adenosylmethionine to glycine. This reaction is catalyzed by the enzyme glycine *N*-methyltransferase (GNMT). Patients with prostate cancer exhibited higher levels of sarcosine [6], and sarcosine was effective in the treatment of schizophrenia [15,16]. The author propose a hypothesis that sarcosine may be involved in the lower risk of prostate cancer in male patients with schizophrenia.

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[7,8]. Furthermore, they suggested a transcriptional link between cancer progression and the GNMT activity, through the binding of both the androgen receptor and the oncogene ERG, the ETS related gene, to the promotor sequence of the *GNMT* gene in tumor cells [7,8].

A number of evidences suggest that N-methyl-D-aspartate (NMDA) receptors play a role in the pathophysiology of schizophrenia, and glycine-modulatory site on the NMDA receptors is a therapeutic target for this disease [9-13]. Sarcosine is an inhibitor of glycine transporter-1, and is one of the most attractive therapeutic drugs for schizophrenia [14]. Interestingly, a randomized, double-blind, placebo-controlled study demonstrated that sarcosine (2 g/day for 6-weeks) can benefit not only patients with long-term stable disease but also acutely ill persons with schizophrenia [15]. A recent randomized, double-blind study showed that sarcosine (2 g/day for 6-weeks) was also effective in acutely symptomatic drug-free patients with schizophrenia [16]. It is, therefore, of interest to study whether blood levels of sarcosine are altered in male subjects of schizophrenia since alteration in the levels of sarcosine may be involved in the pathophysiology of this disease.

Taken together, I propose that sarcosine pathway may play a role in the lower risk for prostate cancer in male subjects with schizophrenia although further detailed studies should be necessary to confirm this hypothesis.

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ABBREVIATIONS

ERG = ETS related gene

GNMT = Glycine *N*-methyltransferase

NMDA = *N*-methyl-D-aspartate

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