Resequencing of Spermidine/Spermine N1-acetyltransferase (SAT1) promoter region in bipolar suicide completers and healthy controls.

P. Niola[1], J. Gross[2], C. Chillotti[3], V. Deiana[3], C. Pisanu[1], G. Severino[1], G. Turecki[2], M. Alda[4],M. Del Zompo[1,3], A. Squassina[1]

[1]Section of Neuroscience and Clinical Pharmacology, Dept. of Biomedical Sciences, University of Cagliari, Cagliari, Italy
[2]McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada
[3]Unit of Clinical Pharmacology, Teaching Hospital, Cagliari, Italy
[4]Dept. of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada

Spermidine/Spermine N1-acetyltransferase (SAT1) is a rate-limiting enzyme in the catabolic pathway of polyamines (PAs). PAs are small and ubiquitous molecules implicated in many aspects of cell function in different tissues. In the brain, PAs plays an important role in acute and chronic stress and are responsible for the polyamine-mediated stress response (PSR). Findings from animal and human studies suggest that this stress response mechanism could be at the base of the development of psychiatric disorders (Fiori and Turecki 2008). This evidence is supported by recent findings showing a decreased expression of SAT1 gene in the brain of subjects who committed suicide compared to controls (Sequeira et al., 2006; Guipponi et al., 2008). Moreover, polymorphisms in the promoter region of SAT1 were associated with suicide completion (Fiori et al., 2009) and rs6526342 was shown to correlate with SAT1 expression levels (Sequeira et al., 2006). Interestingly, lithium therapy blocks the brain PSR of rats chronically treated (Gilad et al., 1998). A recent study by our group showed that lithium in vitro increased the expression of SAT1 gene in B lymphoblastoid cell lines derived from bipolar subjects (BD) with high and low genetic risk of suicide as well as in healthy controls, but not in bipolar patients who committed suicide (Squassina et al., 2013).

In order to explore whether the difference in lithium-induced SAT1 expression is determined by genetic variants located in the gene promoter, we resequenced a 6 Kbs fragment before the transcription start site in the same samples of suicide completers (Sardinian, n=6; Canadian, n=4) and healthy controls (Sardinian, n=12; Canadian, n=9). We found 8 polymorphic SNPs that showed no differences in allele and genotype frequency between the two groups. Moreover, we tested the correlation between the 8 SNPs and SAT1 expression and explored whether this effect was different in completers and controls by means of two-way repeated measures analysis of variance (ANOVA). Findings showed that genotypes did not correlate with SAT1 expression and that there was no interaction between genotypes and phenotype in predicting lithium effect on mRNA levels.

These data indicate that the altered regulation of SAT1 expression observed in suicide completers in our previous study is not determined by polymorphisms within the promoter region of the gene. More studies are warranted in order to further explore the mechanisms underlying lithium effect on SAT1 expression.

Fiori and Turecki (2008). *J Psychiatry Neurosci*. 33, 102-10.
Sequeira et al. (2006). *Arch Gen Psychiatry*. 63, 35-48.
Guipponi et al. (2008). *Am J Med Genet*. Part B, 150B, 799–807.
Sequeira et al. (2006) Arch Gen Psychiatry. 1, 35-48.
Fiori et al. (2009). *Biol Psychiatry*. 66, 460–467.
Gilad et al. (1998). *Int J Devl Neuroscience*. 05, 160-167.
Squassina et al. (2013). *Int J Neuropsychoph. In press.*