Blood urea levels associated to antidepressant drug treatment: Role of nitrogen and nitric oxide

Sir,

Nitric oxide (NO) plays a significant role in the pathophysiology of depression, modulating the level of several neurotransmitters in the central nervous system, such as serotonin, dopamine (DA), γ-aminobutyric acid (GABA), and glutamic acid (Glu). Moreover, distinct classes of antidepressants (e.g., escitalopram) have been found to modulate NO levels and regulate the conversion of arginine (Arg) into citrulline/NO by NO synthetase (NOS).[1]

Some neuropharmacological studies on nitrogen narcosis have also revealed that exposure to hiperbaric nitrogen (N_2) decreases the synthesis of citrulline/NO and the release of Glu and DA from the Striatum and enhances GABA-A receptor activities in Substantia nigra.[2,3]

Therefore, we aimed to analyze levels of blood urea to determine the influence of antidepressant (SCIT) drug treatment on NOS activity or NO concentration in brain tissue. All procedures were followed in accordance with the standards set by the ethics committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Updating data from previous work (presented at the "XIV National Congress of Psychiatry" in Barcelona, 2010) using a larger sample, we herein analyze the concentration of blood urea (a metabolite of the conversion of Arg to ornithine within the urea cycle) among a group of escitalopram-treated (SCIT) patients diagnosed for depression or anxiety disorder (n = 87; female 69%; age 60 ± 17 years; weight 65 ± 14 kg) compared to a group of risperidone-treated (RIS) patients diagnosed for schizophrenia or schizoaffective disorder (n = 59; female 63%; age 44 ± 16 years; weight 70 ± 23 kg), with the latter group acting as a control.

The average values obtained were 37.6 ± 17.1 and 25.5 ± 10.2 mg urea/dL for the SCIT- and RIS-treated groups, respectively. The intergroup differences were 12.1 mg/dL (Student's t-test $P < 0.001$) or 8.5 mg/dL (Student's t-test $P < 0.001$), with the latter result obtained when adjusting these values by age (a difference of 3.6 mg/dL was attributed to distinct intergroup mean age).[4]

According to these results and consulted literature, we suggest that NO produced by the action of NOS on Arg alternatively could react with the nitrogen in the carbamoyl group of glutamine (Gln) to generate Glu (an excitatory neurotransmitter) and N_2 gas. Glu would undergo further decarboxylation to yield GABA (an inhibitory neurotransmitter), as favored by the gas laws since two volumes of NO gas are transformed into one volume of N_2. Thus, the production of Glu plus N_2 or the production of urea would be altered by antidepressant treatment, which would promote urea production by means of inhibiting citrulline/NO synthesis from Arg.

This interpretation of results is by analogy with the known reaction of ammonia combustion to yield N_2, with NO as an intermediate product.[5] Such a reaction, in eukaryotic cells, would consist in the oxidation, by enzymatic catalysis, of the amino and amido groups contained in organic compounds (e.g., Glu) to produce NO (as an intermediate product) and finally N_2.

In brief, and following the previous scheme, treatment with antidepressants would modulate the urea cycle, coupled to Gln–Glu interconversion and decarboxylation of Glu to GABA, to yield urea instead of citrulline/NO plus N_2.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Roberto Lozano, Reyes Marín[1], María-Jesús Santacruz[1], Alberto-José Frutos[2]
Departments of Pharmacy and [1]Psychiatry, Hospital of Our Lady of Grace, [2]Department of Pharmacy, Hospital Clinico Universitario "Lozano Blesa", Zaragoza, Spain.
E-mail: rlozano@salud.aragon.es

REFERENCES

1. Oliveira JP, Zuardi AW, Hallak JE. Role of nitric oxide in patients with schizophrenia – A systematic review of the literature. Curr Psychiatry Rev 2008;4:219-27.
2. Vallée N, Rissoe JJ, Blatteau JE. Effect of an hyperbaric nitrogen narcotic ambience on arginine and citrulline levels, the precursor and co-product

of nitric oxide, in rat striatum. Med Gas Res 2011;1:16.
3. Rostain JC, Lavoute C. Neurochemistry of pressure-induced nitrogen and metabolically inert gas narcosis in the central nervous system. Compr Physiol 2016;6:1579-90.
4. Musch W, Verfaillie L, Decaux G. Age-related increase in plasma urea level and decrease in fractional urea excretion: Clinical application in the syndrome of inappropriate secretion of antidiuretic hormone. Clin J Am Soc Nephrol 2006;1:909-14.
5. Tudela D. Ammonia-air mixtures can be explosive. J Chem Educ 1999;76:468.

Access this article online

Website: www.indianjpsychiatry.org

Quick Response Code

DOI: 10.4103/psychiatry.IndianJPsychiatry_141_10

How to cite this article: Lozano R, Marín R, Santacruz MJ, Frutos AJ. Blood urea levels associated to antidepressant drug treatment: Role of nitrogen and nitric oxide. Indian J Psychiatry 2019;61:314-5.