



ELSEVIER

Letter to the Editor

Answer to Letter sent to the Editor by Drs. E. Abegaz and R. Bursey (Ajinomoto Corporate Services LLC, Washington, USA) related to Simintzi et al. report published in *Pharmacol Res* 2007;56:155–9

We are obliged to answer to Dr. E. Abegaz and Dr. R. Bursey as follows:

1. Aspartame and neurological symptoms: In the USA, the aspartame ADI is 50 mg/kg/day and 40 mg/kg/day for the rest of the world (Butchko et al., 2002, Ref. 24 in the letter [1]). With regards to the presence of neurological symptoms in individuals consuming abuse or toxic doses of the sweetener (200 mg/kg), there are several reports by Stegink et al. (1987, 1988; see our last report published in *Pharmacol. Res.* [2]. Moreover, Rico et al. (2006) have reported that methanol (aspartame metabolite) alters ecto-nucleotidases and acetylcholinesterase in zebrafish brain suggesting its implication in neurodegenerative events.
2. Phenylalanine and neurotransmitters: There is much debate on phenylalanine vs. neurotransmitters. In the case of maternal-fetus amino acids' transportation, no one may exclude that the rise of phenylalanine and aspartate levels is 2-fold for phenylalanine and 6-fold for aspartate, respectively. So, it is obvious that the transported amino acid concentration is high especially in PKU-carriers consuming large amounts of the sweetener (see, also Stegink et al. 1987, 1988). Similarly, we may not exclude methanol transplacental action and its possible role in the fetus (we found no references in PubMed about transplacental action of methanol). Methanol is known to produce side-effects on human eyes.
3. The components of aspartame in many common foods: In Greece, there is no milk containing the artificial sweetener, because milk must remain a pure natural product. We cannot accept that 18 mg methanol in beverages is better than tomato-juice with 107 mg methanol [1]. Both of them may be harmful on cell membranes of sensitive populations.

Our results (as presented in Ref. [2]):

1. The experiments took place in vitro and not in vivo. So, it is expectable the findings to be related to the direct effect of

each or the sum of aspartame metabolites on the suckling rat brain tissue, not in humans.

2. Suckling rat brain tissue is an immature tissue and sensitive to wide alterations (including acetylcholinesterase activity) caused by chemical compounds.
3. The above in vitro study shows the acute and immediate (direct) action of aspartame compounds.

With regards to previous in vitro study in rat hippocampus using the same aspartame concentrations, Na^+, K^+ -ATPase activity was modulated as well [3]. In addition, incubation of the erythrocyte membranes from healthy individuals with toxic or abuse concentrations of each or the sum of aspartame degradation products resulted in a remarkable modulation of AChE and Na^+, K^+ -ATPase activities. The latter showed, in vitro, that the studied human erythrocyte membrane enzyme activities were sensitive in alterations by the sweetener [4,5].

The actions and especially the side-effects of aspartame consumption are still under debate among researchers. With regards to the references mentioned in the letter by Drs. Abegaz and Bursey, we should note that Ref. 10 is not indexed in the Pub Med (is Ref. 10 published in *Biosci. Biotech. Biochem.* 1993;57(4):689–690 by Z.U. Haque and Z. Mozaffar correctly written?). Additionally, we should have carefully in mind the references about the harmful effects of aspartame collected by Dr. Rich Murray, which support our findings.

References

- [1] Butchko HH, Stargel WW, Comer CP, Mayhew DA, Benninger C, Blackburn GL, et al. Aspartame review of safety. *Regul Toxicol Pharmacol* 2002;35:S1–93.
- [2] Simintzi I, Schulpis KH, Angelogianni P, Liapi C, Tsakiris S. The effect of aspartame on acetylcholinesterase activity in hippocampal homogenates of suckling rats. *Pharmacol Res* 2007;56:155–9.
- [3] Simintzi I, Schulpis KH, Angelogianni P, Liapi C, Tsakiris S. L-Cysteine and glutathione restore the reduction of rat hippocampal Na^+, K^+ -ATPase activity induced by aspartame metabolites. *Toxicology* 2007;237:177–83.
- [4] Tsakiris S, Giannoulia-Karantana A, Simintzi I, Schulpis KH. The effect of aspartame metabolites on human erythrocyte membrane acetylcholinesterase activity. *Pharmacol Res* 2006;53:1–5.
- [5] Schulpis KH, Papassotiriou I, Parthimos T, Tsakiris T, Tsakiris S. The effect of L-cysteine and glutathione on inhibition of Na^+, K^+ -ATPase activity by aspartame metabolites in human erythrocyte membrane. *Eur J Clin Nutr* 2006;60:593–7.

Stylios Tsakiris ^{a,*}
Kleopatra H. Schulpis ^b

^a Department of Experimental Physiology, Medical School,
Athens University, P.O. Box 65257, GR-15401 Athens, Greece

^b Inborn Errors of Metabolism Department, Institute of Child
Health, Research Center, Greece

* Corresponding author:

E-mail addresses: stsakir@cc.uoa.gr
(S. Tsakiris),
inchildh@otenet.gr
(K.H. Schulpis)