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COMMENT

"Blockade of Nitric Oxide Overproduction and Oxidative Stress by Nigella Sativa Oil Attenuates Morphine-Induced Tolerance" by Abdel-Zaher et al.

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Sirs,

We have read and appreciated the article entitled "Blockade of Nitric Oxide Overproduction and Oxidative Stress by Nigella sativa Oil Attenuates Morphine-Induced Tolerance" by Abdel-Zaher et al. [1] published on this journal.

In the cited article, authors have investigated and demonstrated the capability of Nigella sativa oil (NSO) to blunt the morphine dependence and tolerance in mice and, among other things, the enhancing of this inhibition by the concurrent administration of N-acetylcysteine (NAC).

In particular, they focused the attention on antioxidant properties of NAC such as its activity against: increasing in malondialdehyde level (MDA), an end product of lipid peroxidation; nitric oxide overproduction; and as well against the decreasing in intracellular reduced glutathione (GSH) levels. Events reported by Abdel-Zaher et al. as consequence of repeated morphine administration or naloxone injections, in morphine dependent mice. Instead no significantly difference were supplied in glutamate brain concentration by NSO administration, nor alone nor with NAC.

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Nevertheless we would like to underline, now, that NAC is, even, a cysteine prodrug, and cysteine, converted in cystine as mentioned in the above-cited article, shares an antiporter (Xc) with glutamate that conducts cystine inside glial cells and glutamate in the extracellular space, supplying the major part of extrasynaptic glutamate [2].

The Xc derived extrasynaptic glutamate seems to be the principal agonist for class II metabotropic glutamate receptor, in particular for the mGluR2/3 [2]. During morphine syndrome withdrawal in mice experimental mGluR2/3 agonists are able to decrease the severity of symptoms: e.g. it almost completely have eliminated teeth chattering, writhing and significantly and have attenuated the severity of diarrhea [3, 4] furthermore Popik et al. [5] reported that mGluRII agonist may inhibit the development of tolerance to analgesic effect of morphine. On similar basis, and on the growing body of evidence that supports the involving of glutamatergic system in development and maintenance of drug addiction, Xc and consequently mGluR, trough NAC administration, is becoming a target for the therapy of addiction and compulsive behavior in preclinical and/or clinical studies, e.g. are: cocaine [6–8], heroin [9], cannabis [10] addictions and even pathologic gambling [11], trichotillomania [12] and nail biting [13].

We trust that this NAC activity could play, at least in part, a significantly role in morphine dependence and tolerance inhibition observed during the concurrent administration of morphine, NSO and NAC and thereby should be considered in data interpretation. Abdel-Zaher et al. reported the absence of difference in glutamate concentration between samples from mice that received morphine, NSO plus NAC and sample from mice treated with morphine, NSO, and other compounds. We suggest that it could be justified simply by a change in glutamate localization, from the synaptic space to the extrasynaptic one. This shift

should be caused in part by the reduction of vesicular glutamate release through a presynaptic inhibition, that involves mGluR2/3, inducted by the increased extrasynaptic glutamate due to NAC administration [14].

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