Author’s response to reviews

Title: Hypocholesterolemia is an independent risk factor for depression disorder and suicide attempt in Northern Mexican population

Authors:
Marcela Segoviano (marcela_segoviano@hotmail.com)
Manuel Cárdenas (long_xue_@hotmail.com)
José Salas (jsalas_pacheco@hotmail.com)
Osmel La Llave (ollave56@yahoo.es)
Marcelo Barraza (sbmaj30@hotmail.com)
Francisco Castellanos (xavier_castellanos@hotmail.com)
Fernando Vázquez (feralaniz1@hotmail.com)
Jazmin Méndez (jazminedmeh@gmail.com)
Ernesto Miranda (ernesto.miranda@mail.com)
Oscar Arias (arias@ciencias.unam.mx)
Edna Méndez (edna_madai@hotmail.com)

Version: 4 Date: 06 Jan 2018

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Dear Editors at BMC Psychiatry,

As a follow-up to your current observation(s), we have now modified the text previously found in the Discussion section (lines 178-213, pages 10-12). All paragraphs have been selectively rephrased and restructured in order to minimize overlap as much as possible. This modified text is now found in the Discussion section (lines 178-218, pages 10-12) of the current manuscript. All words and phrases now found in capital letters were modified from the original text as follows:

“It HAS BEEN ESTABLISHED that NEARLY all brain CHOLESTEROL is PRODUCED in situ THROUGH de novo synthesis and that ADEQUATE PREVENTION OF ITS uptake from the BLOOD STREAM IS PROVIDED BY SELECTIVITY OF the blood-brain barrier [38-40]. NONETHELESS, it is VIABLE that DECREASED peripheral cholesterol in THOSE individuals
with psychiatric disorders OCCURS CONCURRENTLY WITH cholesterol MODIFICATIONS that take PLACE in DISTINCT synaptic lipid rafts in neurons (by a com¬mon regulatory mechanism). This could PRODUCE the MINIMIZED ACTIVITY of serotonergic communication and, CONSEQUENTLY, GIVE RISE TO INSTINCTIVE RESPONSES and violent suicidal behavior [2,41].

Cholesterol is the PARAMOUNT CONSTITUENT of CELLULAR MEMBRANES IN HIGHER EUKARYOTES and is ESSENTIAL in membrane FUNCTION AND ORGANIZATION AS WELL AS DYNAMICS AND SORTING. It is COMMONLY found DISPERSED IN A NON-RANDOM FORM in SPECIFIC AREAS (domains) in BOTH biological and model membranes [42-44]. These AREAS, OFTEN DENOMINATED as ‘lipid rafts’ [44,45], are THOUGHT to be FUNDAMENTAL IN the PRESERVATION of the structure and function of the membrane. HOWEVER, DESCRIBING the spatiotemporal resolution of these domains has TURNED OUT to be A DIFFICULT TASK [44,46]. It has been SUGGESTED that these FORMATIONS be membrane domains in which SIGNALING FROM A NEUROTRANSMITTER MAY ARISE VIA a GROUP of receptors, such as serotonin1A (5-HT1A) receptor [47].

Previous STUDIES DEMONSTRATED the IMPERATIVE NECESSITY of membrane cholesterol in the FUNCTION AND ORGANIZATION of the 5-HT1A receptor [46,48-53]. RESULTS FROM ADDITIONAL STUDIES SHOWED that the FLUIDITY OF LIPIDS CONSIDERABLY REGULATES the binding of serotonin (5-HT) in MURINE brain membranes. IT IS THEREFORE EXPECTED THAT DECREASED LEVELS OF CHOLESTEROL would increase the FLUIDITY OF THE cellular membrane. While, AT THE SAME TIME, MINIMAL EXPOSURE OF THE 5-HT receptors WOULD BE FOUND in the synaptic cleft [2,54].

REPORTEDLY, DISTURBANCE of rafts by cholesterol DEFICIENCY NOTABLY LOWERS agonist binding and COUPLING OF G PROTEIN to 5-hydroxytryptamine 1A (5-HT1A) serotonin receptors in bovine hippocampal membranes [47,48]. Serotonin1A receptors TYPIFY one of the MOST FORMIDABLE, evolutionarily PRIMITIVE, yet LARGELY conserved families of seven transmembrane G protein-coupled receptors (GPCRs) THAT SPAN THE MEMBRANE [46,55]. ALSO, serotonergic signaling CONSTITUTES AN IMPORTANT PART in the FORMATION and REGULATION of A MULTITUDE OF FUNCTIONS SUCH AS behavioral, cognitive, and developmental [46]. MOREOVER, STUDIES HAVE DEMONSTRATED THAT THERE IS an association between DECREASED 5-HT activ¬ity and suicide [2,56].

IT IS NOTEWORTHY TO MENTION THAT recent STUDIES DEScribed crystal structures of GPCRs, including serotonin1A receptor, THAT DEMONSTRATED structural proof of cholesterol binding sites [46,58,59]. CURRENTLY, two CONCEIVABLE PATHWAYS have been PROPOSEd by which membrane cholesterol could AFFECT the structure and function of GPCRs: (i) BY WAY OF a direct/specific interaction with GPCRs, or (ii) VIA an indirect pathway by MODIFYING THE physical properties OF THE membrane in which the receptor is INSERTED, OR AS A RESULT OF AN INTEGRATION of both [46,60].
About cholesterol levels and their relation to gender, our study showed that the decrease in total cholesterol levels occurred in both men and women. Other authors have reported a relationship between REDUCED cholesterol and suicidal TENDENCIES only in males [13,61-64]. However, IT IS WORTH NOTING THAT ADDITIONAL studies on the association between gender and serum cholesterol have been UNCONVINCING.”

We sincerely hope that these modifications will suffice in preventing overlap with previously published information. Thank you for your consideration and we look forward to hearing from you.

Best regards,

Our research group