Short Communication

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Brain Disorders 2020: Alterations on the kynurenine pathway as potential mechanisms underpinning obesity-induced cognitive impairment

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In addition to be a primary risk factor for type 2 diabetes and cardiovascular disease, obesity is associated with learning disabilities. However, the mechanisms underlying the cognitive impairment induced by obesity are poorly understood. Here we examined whether a dysregulation of the brain kynurenine pathway (KP) might underlie the learning deficits exhibited by obese individuals. The KP pathway is the major route of tryptophan (Trp) metabolism. It is initiated by the enzymatic conversion of Trp into kynurenine (KYN) by indoleamine 2,3-dioxygenase (IDO). KYN is further converted to several signalling molecules including Kynurenic acid (KA) and Quinolinic acid (QA) which have a negative impact on learning. Wistar rats were exposed either to standard chow or to a free choice high-fat high-sugar (fcHFHS) diet from weaning to 120 days of age. Their learning capacities were then evaluated using a combination of the novel object recognition and the novel object location tasks, and the concentrations of tryptophan and kynurenine-derived metabolites in several brain regions determined by ultra-performance liquid chromatography-tandem mass spectrometry. Obese rats exhibited reduced learning capacity characterized by impaired encoding and consolidation of memory along with increased concentrations of Trp, QA and Xanthurenic acid (XA) in the hippocampus, but not in the frontal cortex and brain stem. Conversely, obesity enhanced the expression of IDO in the former regions but not in the hippocampus. QA and XA stimulate the glutamatergic system and their increased production leads to cognitive impairment. These results therefore suggest, that altered kynurenine pathway metabolism contributes to obesity-associated learning disabilities.

Introduction:

The main physiological roles of tryptophan metabolism are to generate the serotonin and melatonin and the essential co-factor nicotinamide adenine dinucleotide through kynurenine pathway. In neuroinflammatory conditions, the KP is strongly up regulated leading to the production of several neuroactive metabolites that can be either neuroprotective, neurotoxic or immuno-modulatory. It was previously been demonstrated that the kynurenine pathway is activated in several neurodegenerative and neuropsychiatric disorders including Alzheimer's disease.

Interestingly, this central dysregulation of the KP homeostasis also manifests in the blood in AD patients. Higher ratios of KP metabolites, kynurenine (KYN) to tryptophan (K:T) in serum and plasma have been reported in patients with AD and mild cognitive impairment (MCI) and this ratio (K:T) also inversely correlated with cognitive performance. Further, a decline in plasma and erythrocyte concentrations of the KP metabolite kynurenic acid (KYNA), which is produced via a secondary branch of the KP and precludes NAD+ production from KYN, has been reported in patients with AD and MCI11. Furthermore, elevated plasma levels of the excitotoxin quinolinic acid, have been reported in AD. Additionally, a relatively recent study reported that an association between dementia risk and elevated plasma levels of the kynurenine pathway metabolite, anthranilic acid (AA).

However, KP metabolite alterations have never been investigated in the preclinical stage of AD that is characterised by high neocortical amyloid-β load (NAL) measured via positron emission tomography (PET), prior to the cognitive decline given that the deposition of NAL begins to occur two to three decades prior to the clinical manifestation of the disease. Therefore, the current pilot study investigated whether the dysregulation of the KP occurs within the preclinical stage of the AD pathogenesis trajectory, in cognitively normal individuals. Serum tryptophan and KP metabolites, primarily comprising, KYN, KYNA, 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), AA, picolinic acid and quinolinic acid, were hence measured in, and compared between, cognitively normal individuals with preclinical AD characterised by high NAL (NAL+; standard uptake value ratio (SUVR) ≥1.35) and individuals with no apparent risk to AD, characterised by low NAL (NAL−, SUVR <1.35).

Results:

QA and XA stimulate the glutamatergic system and their increased production leads to cognitive impairment. These results therefore suggest, that altered kynurenine pathway metabolism contributes to obesity-associated learning disabilities.

Discussion:

In mammals, the KP has been reported to account for over 90% of peripheral tryptophan catabolism. Our findings exhibit aberrant peripheral tryptophan metabolism, via the KP, in preclinical AD wherein, significantly elevated KYN, AA and 3-HK serum concentrations were present in NAL+ versus NAL− females. Additionally, within female study participants, a significant positive correlation was observed between NAL and the aforementioned serum KP metabolite concentrations. Similar to findings in the current preclinical AD study, elevated

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serum KYN concentrations and K:T ratios have been reported previously in clinical AD and in individuals with MCI. The foremost step in the KP i.e. the generation of KYN from tryptophan, via N-formyl-KYN, is catalysed by enzymes indoleamine 2, 3-dioxygenase or tryptophan 2, 3-dioxygenase (TDO; predominantly expressed in hepatocytes). Significantly higher IDO1 and TDO immunoreactivity has been reported in AD patient hippocampi. Further, IDO1 and TDO, have been reported to be regulated by immune system signalling molecules, growth factors and steroids1, 22, 27,28, all of which have been shown to be associated with AD pathogenesis. Our findings of elevated serum KYN concentrations along with higher K:T ratios in NAL+ versus NAL− participants together with the afore cited literature are therefore indicative of increased tryptophan degradation via the KP, from the preclinical stages of the AD pathogenesis trajectory, prior to cognitive impairment.