BACKGROUND

Tryptophan (TRP) catabolism pathway (Fig.1) has been emerging as possible candidate contributing to depression. Bipolar patients showed higher TRP breakdown index (Kyn/TRP) and KMO activity, confirmed by increased 3-HK levels, and reduced KynA compared to controls [1]. Neuroimaging studies in bipolar disorder (BD) highlighted the influence of TRP and Kyn catabolites on the widespread disruption of white matter tracts involved in both cognitive and emotional aspects of behavior [2]. Cognitive distortions are a core symptom of BD and lead to mood-congruent biases: bipolar depressed patients demonstrate facilitation in processing negative emotional stimuli paralleled by abnormal functional response in corticolimbic network [3, 4]. No previous studies explored the effect of Tryptophan catabolites on this circuitry.

AIM

We evaluated the effect of serum levels of Kyn, KynA, and 3-HK as well as the approximated activity of the IDO/TPO (measured by Trp Breakdown, Kyn/TRP), KMO (measured by 3-HK/KYN ratio), KAT II (measured by KYNA/KYN ratio), and the 3-HK/KYN ratio on the functional neural correlates of mood-congruent information processing bias in bipolar depression.

METHOD

• fMRI in 15 BD patients
• Regressions were performed in order to explore the effect of TRP catabolites and enzymatic ratios on brain regions specifically involved in inhibiting response to negative stimuli during an affective (morally tuned adjectives, eg. brave or vile) go-no-go task.
• Antidepressant medication load was entered as nuisance covariate.
• Whole brain analyses were thresholded at cluster-size pFDR<0.05 (p<0.001 uncorrected at peak).

RESULTS

Trp Breakdown (Kyn/TRP) was associated to an increase of BOLD signal in right dorsolateral prefrontal cortex (PFC), KynA in bilateral supragenual anterior cingulate cortex, 3-HK in ventromedial PFC, and Kyn in right precuneus, cerebellum and bilateral premotor areas. No significant associations were found with other ratios.

CONCLUSIONS

Our results showed that TRP breakdown, Kyn, 3-HK, and KynA are associated to an higher neural response in dorsolateral and ventromedial PFC, in anterior cingulate cortex, in precuneus and premotor cortex during the inhibition of response to negative morally tuned adjectives. These areas are involved in monitoring processes, in inhibitory control, in directing emotional response. An higher response in these areas has been associated to mood-congruent information processing in BD [3, 4] and TRP catabolites could exert a detrimental effect on them. Considering the enzymatic activity, TDO is mainly induced by TRP itself and by steroids, whereas IDO, KMO and KATII have been primarily associated to proinflammatory stimuli and cytokines. The absence of significant effects related to these last enzymes on corticolimbic network could suggest that the detected effect of TRP breakdown could be related to TDO. Thus, it underlies to a glucotoxic overproduction and chronic HPA hyperactivation, previously hypothesized as biological underpinning of the disorder [5]. This is in line with the absence of 3-HK/KYNA effect on this circuitry, ratio usually associated to a neurotoxicity of inflammatory related end-products.

REFERENCES


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