Differences in the tryptophan System between Primary and Substance induced Depression

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Introduction

Major Depression Disorder, primary or substance-induced, is the most prevalent comorbid condition in subjects with substance use disorder (Pettinati et al., 2013). The differentiation between primary depressive episodes and those substance-induced could be crucial in improving treatment outcomes (Tirado-Muñoz et al., 2017). The modulation of the tryptophan (Trp)/serotonin system has been reported as playing a key role in the pathogenesis of depression (Oxenkrug, 2013).

Aims

To study the serotonin/kynurenine pathway in subjects diagnosed with: cocaine use disorder (CUD); alcohol use disorder (AUD), CUD primary major depression (CUD-primary-MDD), alcohol primary major depression (AUD-primary-MDD), cocaine-induced major depression (CUD-induced-MDD); alcohol-induced major depression (AUD-induced-MDD), major depression (MDD) and matched-healthy controls (HC).

Methods

A total of 73 subjects participated in the study; 9 AUD, 14 CUD, 9 AUD-primary-MDD, 14 CUD-primary-MDD, 9 AUD-induced-MDD, 8 CUD-induced-MDD, 5 MDD and 8 HC. Clinical diagnoses were obtained with the Psychiatric Research Interview for Substance use and Mental Disorders (PRISM). We studied the serotonin system through the acute tryptophan depletion test (ATD), and kynurenine pathway after ATD. The ATD was performed with a randomized, double-blind, crossover, and placebo-controlled design. Markers of enzymatic activity of IDO/TDO, KAT and Kynureninase were established by the calculation of the Kyn/Trp, KA/Kyn and AA/Kyn ratios, respectively.

Results

The groups did not differ significantly in main sociodemographic characteristics with the exception of employment status, the AUD and AUD-Primary-MDD groups being less employed (Table 1). A consistent decrease in the Tryp levels was observed in all groups, but mainly in the CUD group (from 54.94±13.02 to 6.79±1.42; p=0.017) and in the AUD group (from 77.71±38.05 to 7.89±3.09; p=0.002) (Figure 1).

In the cocaine groups, the comparison between CUD-induced-MDD and MDD revealed significant differences for 5HT (decreased in MDD, p=0.039) and Kyn/5HT (increased in MDD, p=0.012) whereas for Kyn and 5HIAA/5HT trends were observed (increased in MDD, p=0.090 and p=0.054 respectively) (Figure 2). In the alcohol groups, the comparison between AUD-induced - MDD and MDD revealed only a trend in the decrease of Kyn levels (p=0.069) in AUD-induced –MDD (Figure 3).

Table 1. Sociodemographic and clinical characteristics

	HC N=8	MDD N=5	CUD-Induced-MDD N=8	CUD-Primary-MDD N=14	CUD N=14	AUD-Induced-MDD N=9	AUD-Primary-MDD N=6	AUD N=9	p
Sex (Men %)	50	100	75	85.7	78.6	66.7	66.7	88.9	NS
Age (Mean±SD)	32.13±3.94	43.80±13.9	38±12.17	44.21±8.26	38.29±9.83	43.56±5.29	49±8	39.22±16.25	NS
Civil status (% Single)	62.5	40	62.5	35.7	64.3	22.2	16.7	55.6	NS
Work status (% Employed)	25	40	37.5	50	21.4	22	16.7	11.1	0.023
Depression									
Age of onset first MDD (Mean±SD)	NA	39.8±10.3	NA	39.64±9.6	NA	NA	47.17±7.05	NA	NS
Age of onset first IMD (Mean±SD)	NA	NA	29.5±6.36	NA	NA	35.56±8.32	NA	NA	NS
Number of episodes (Mean±SD)	NA	1.6±0.89	6.63±8.23	2.08±1.04	NA	2.83±2.04	1.17±1.42	NA	NS
Months since last episode (Mean±SD)	NA	34.4±40.9	22.75±31.23	36.29±55	NA	27.11±27.33	16.33±21	NA	NS
Family history of depression (%)	NA	80	37.5	71.4	35.7	22.2	50	22.2	0.01
Current antidepressant treatment (%)	NA	100	37.5	57.1	7.1	55.6	100	22.2	<0.001
Substance Use Disorders (Mean±SD)									
Age of onset AUD	NA	NA	NA	NA	NA	26.78±4.35	25.50±11.88	32.56±7.75	NS
Age of problematic alcohol use	NA	NA	NA	NA	NA	24.11±6.05	26.00±11.66	32.00±10.33	NS
Maximum alcohol abstinence period(Months)	NA	NA	NA	NA	NA	23.67±30.89	42.00±42.54	33.33±34.96	N
N° relatives with alcohol problems	-	0.2±0.45	0.63±1.06	0.79±0.97	0.29±0.61	0.67±0.50	0.83±1.17	0.67±0.87	NS
Age of onset CUD	NA	NA	26.75±10.29	31.43±7.39	26.85±6.59	NA	NA	NA	NS
Age of cocaine problematic use	NA	NA	26.38±9.61	31.21±7.43	25.64±7.20	NA	NA	NA	NS
Maximum cocaine abstinence period (Months)	NA	NA	19.50±18.42	37.77±54.17	18.36±19.75	NA	NA	NA	NS
N° relatives with cocaine problems	-	-	0	0.64±0.93	0	0.11±0.33	0	0.14±038	NS

HC: Healthy controls; MDD: major depression disorder; CUD: cocaine use disorder; AUD: alcohol use disorder; NS: non-significant; NA: not applicable

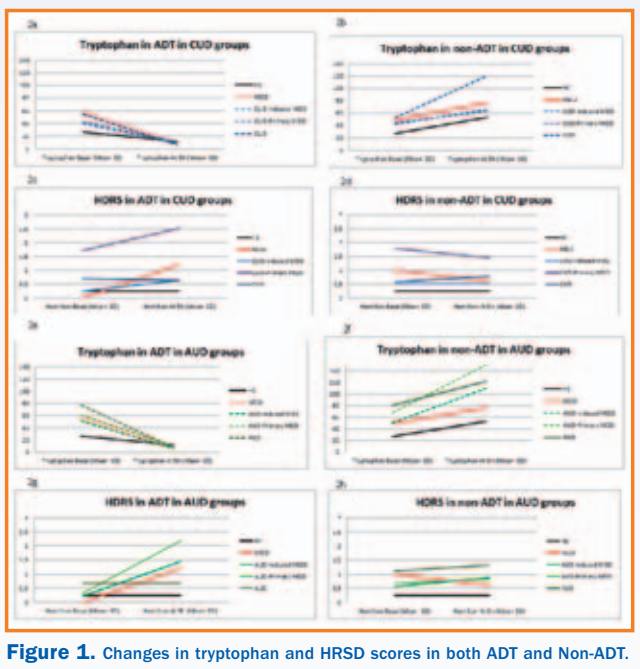

Figure 1. Changes in tryptophan and HRSD scores in both ADT and Non-ADT. Results are presented separately for CUD groups (2a,b,c,d) and AUD groups (2e,f,g,h) compared to HC and MDD. Dotted lines indicate changes between basal and 5h follow up. 2a) Tryptophan changes in CUD groups after ADT; significant differences between HC vs. CUD at basal (p=0.017). 2b) Tryptophan changes in CUD groups after non-ADT; significant differences between HC vs. CUD (p=0.043) at basal and CUD vs. CUD-Primary-MDD (p=0.024) HC vs. CUD (p=0.019) at 5h. 2c) HDRS score changes in CUD groups after ADT; significant differences between HC vs. CUD-Primary-MDD (p=0.003); CUD-Induced-MDD vs CUD-Primary-MDD (p=0.023) and CUD vs CUD-Primary-MDD (p=0.005) at 5h. 2d) HDRS score changes in CUD groups after non-ADT. 2e) Tryptophan changes in AUD groups after ADT; significant differences between HC vs. AUD at basal (p=0.002). 2f) Tryptophan changes in AUD groups after non-ADT; significant differences between HC vs. AUD (p=0.034) at basal and HC vs. AUD-Primary-MDD (p=0.027) at 5h. 2g) HDRS scores change in AUD groups after ADT. 2h) HDRS scores change in AUD groups after non-ADT.

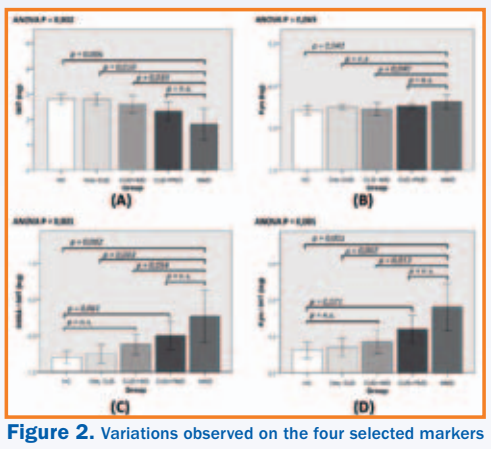

Figure 2. Variations observed on the four selected markers for the three CUD groups compared with HC and MDD. (A) 5HT, (B) Kyn, (C) 5HIAA/5HT, and (D) Kyn/5HT.

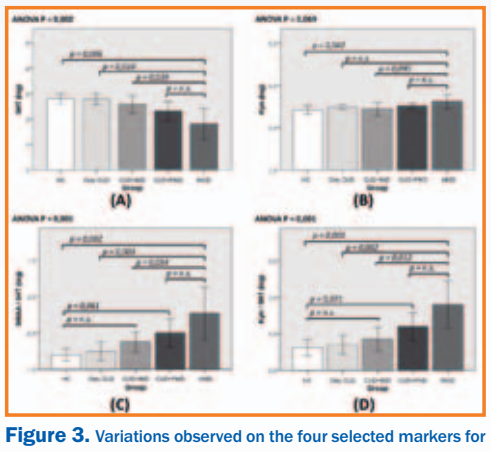

Figure 3. Variations observed on the four selected markers for the three AUD groups compared with HC and MDD. (A) 5HT, (B) Kyn, (C) 5HIAA/5HT, and (D) Kyn/5HT

Conclusions

This study supports the serotonin-kynurenine hypothesis of depression: there is a misbalance in the tryptophan catabolism with an increase of the kynurenine pathway. Regarding induced depressions, there is a different behavior of the serotonin/kynurenine system suggesting a different mechanism in the development of the cocaine-induced-MDD. The kynurenine pathway can be useful as a biomarker in dual depressed patients; nevertheless, other neurobiological systems should be explored, especially in CUD patients.

References

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