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Alcohol Use Disorder and Inflammatory Cytokines in a Population Sample of Young Adults

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Abstract

Background: Alcohol abuse is followed by neuroadaptive brain changes, in addition to inducing changes in the immune system. The objective of this study was to investigate the peripheral levels of proinflammatory (IL-6, and TNF-α) and anti-inflammatory (IL-10) cytokines, as well the inflammatory balance in relation to alcohol use in subjects from a young population-based sample.

Methods: This is a cross-sectional study nested in a population-based study of people aged 18–35 years, involving 629 participants. The CAGE questionnaire was used to evaluate Alcohol Use Disorder, and CAGE scores ≥ 2 were considered a positive screen for alcohol use disorder. Serum levels of IL-6, IL-10 and TNF-α were measured by ELISA using a commercial kit.

Results: There was as a statistically significant increase in IL-6 ($p \leq 0.001$) and statistically significant decrease in IL-10 ($p=0.017$) serum levels in the Alcohol Use Disorder group when compared with subjects that did not abuse alcohol and that a CAGE score <2. TNF-α levels were not significantly different. There was a statistically significant difference in IL-6/IL-10 ($p \leq 0.001$). The median ratios were 0.28 (0.20 to 0.36) in the CAGE group with scores <2 and 0.70 (0.52 to 0.93) in the group with alcohol use disorder for the IL-6/IL-10.

Conclusion: Our results suggest that cytokines, especially IL-6 and IL-10, are involved in the pathophysiology of abuse and dependence of alcohol, and could be candidate markers of alcohol use disorder.

Keywords: Alcohol use disorder; Cytokines; IL-6; TNF-α; IL-10

Introduction

Alcohol consumption is widespread throughout the world and it results in numerous negative consequences for health and quality of life, especially in the young population [1-4]. Alcohol abuse is responsible for 3.2% of all deaths, placing it next to tobacco as a major preventable cause of death and disability [5]. Alcohol intake is followed by neuroadaptive changes; in addition, it induces changes in the immune system, increasing the risk of infections [6]. Nowadays, the diagnosis of alcoholism is based on clinical signs and peripheral injury markers, which, unfortunately, are not specific or sensitive enough to determine the effects of alcohol abuse on central nervous system (CNS) [7,8].

Alcohol abuse has been described to increase immune activity in the CNS, contributing to the process of neurodegeneration and impaired neurological function [9]. The immune system plays an important role in the CNS related to survival and neuronal death [10,11]. In recent years, many studies have suggested the involvement of inflammatory cytokines in the pathophysiology of several neurological and psychiatric disorders such as alcoholism [12]. Abuse of alcohol induces microglia to release proinflammatory cytokines, such as IL-6 and TNF-α, increasing inflammation and neuronal damage [13,14]. To reduce the release of proinflammatory cytokines, the immune system releases immunosuppressive cytokines, such as IL-10. However, imbalance in cytokine levels can lead to insufficient mediation or inhibition of normal immune reaction to disease manifestation [15]. This has been recently documented in animal models of chronic alcohol consumption showing an increase in proinflammatory cytokines and a decrease in anti-inflammatory cytokines (IL-10) [9,16]. Therefore, these studies indicate that changes in inflammatory balance may be involved in alcoholism. Alcohol use disorders are usually underdiagnosed and present major difficulties regarding monitoring and treatment. The combination of multiple biomarkers may

significantly increase the sensitivity and specificity of the biochemical tests, putatively helping in early detection and, consequently, therapeutic success. Given the role of cytokines in chronic alcohol exposure, the objective of this study was to investigate the peripheral levels of proinflammatory (IL-6 and TNF-α) and anti-inflammatory (IL-10) cytokines, as well the inflammatory balance in relation to alcohol abuse in subjects from a young population-based sample compared to subjects that did not abuse alcohol

Materials and Method

This is a cross-sectional study nested in a population-based study of people aged 18-35 years, involving 629 participants living in the city of Pelotas, Brazil. The study was approved by the Catholic University of Pelotas's Ethics Committee (2010/15). After the subjects were identified and invited, volunteers signed an informed consent and answered to a questionnaire, which collected sociodemographic data, drug misuse and The National Economic Indicator–IEN [17]. To evaluate alcohol use disorder, the participants also responded to the CAGE questionnaire, which asks about four consequences of drinking. CAGE is a validated screening test for alcohol abuse and dependence [18]. Briefly, patients score 1 point for each "yes" on the CAGE and "0" points if all questions are answered "no". A score of 2 or more (CAGE ≥ 2) is usually considered a positive screen for alcohol use disorder. A score below 2 points (CAGE<2) constituted the subjects did not abuse alcohol [19].

For the biochemical analyses, 10 millilitres of blood were withdrawn from each subject by venepuncture into an anticoagulant-free vacuum tube after the interview. The blood was immediately centrifuged at 4,000 rpm for 10 min, and the serum was kept frozen at -80°C until analyses. Serum levels of IL-6, IL-10, TNF-α were measured using a commercial immunoassay kit (Duo Set ELISA Development, R&D Systems, Inc., USA). IL-6, IL-10, TNF-α serum levels were expressed in pg/mL. The ratio of pro- and anti-inflammatory cytokines (IL-6/IL-10 ratio) provided an index for the balance between pro and anti-inflammatory status, and the ratio was considered as an index of proinflammatory activity. Statistical analyses were performed with the Statistical Program for Social Sciences (SPSS) 21.0 and Graph Pad Prism 6 software's. IL-6, IL-10, TNF-α serum levels had non-Gaussian distributions. For nonparametric data, we utilized the Mann-Whitney and Kruskal-Wallis tests and Spearman correlation. Serum levels of cytokines were presented as median and interquartile range. A linear regression analysis was applied to control for possible confounding factors with a p value ≤ 0.2 in the bivariate analyses. Results with p values ≤ 0.05 were considered statistically significant.

Results

Among the 629 analyzed subjects, 70 (11.1%) were identified with alcohol use disorder. Table 1 shows the sociodemographic characteristics and serum levels of cytokines (IL-6, IL-10 and TNF-α).

Characteristics	Sample Distribution	IL-6 level (pg/mL)	IL-10 level (pg/mL)	TNF-α level (pg/mL)
Gender[a]		p=0.354	p=0.143	p=0.07
Female	360 (57.2)	15.90 (11.38-21.60)	56.75 (47.38-69.35)	18.02 (12.03-31.43)
Male	269 (42.8)	16.81 (11.58-25.84)	54.57 (39.90-70.36)	19.75 (13.89-39.63)
Age (years)[b]	26.05 ± 5.06	p=0.850 r=0.008	p=0.910 r=0.005	p=0.001 r=-0.138
Brazilian Economic index[c]		p=0.108	p=0.906	p=0.276
1 (minor)	208 (33.1)	17.04 (12.08-22.75)	55.21 (45.23-72.24)	18.51 (12.18-33.68)
2 (middle)	210 (33.4)	16.95 (12.01-22.17)	55.80 (44.03-70.12)	18.06 (12.90-32.96)
3 (highest)	209 (33.2)	14.40 (10.58-22.19)	55.90 (45.57-68.88)	19.82(13.53-36.59)
Age of scholar[b]	11.10 ± 3.41	p=0.050 r=-0.78	p=0.699 r=0.015	p=0.468 r=-0.029
Tobacco use[a]		p=0.001	p=0.789	p=0.030
No	465 (73.9)	15.73 (10.80-21.59)	55.84 (45.37-69.05)	18.71 (13.37-37.02)
Yes	158 (25.1)	17.59 (12.86-31.45)	55.86 (40.39-73.66)	17.62 (11.89-30.99)
Alcohol abuse[a]		p ≤ 0.001	P=0.017	p=0.788
CAGE<2	555 (88.2)	15.40 (10.78-21.27)	56.42 (47.51-69.24)	18.54 (12.87-34.13)
CAGE ≥ 2	70 (11.1)	22.07 (16.62-43.66)	33.81 (21.28-80.40)	19.45 (12.45- 33.94)
Total	**629**	**16.40 (11.52-22.43)**	**55.84 (44.72-69.87)**	**18.58 (12.76-34.19)**

[a]Mann-Whitney test, [b]Spearman correlation test, [c]Kruskal-Wallis. CAGE<2: low alcohol-drinking group; CAGE ≥ 2: high alcohol-drinking group, alcohol use disorder.

Table 1: Distribution of sample, median of IL-6, IL-10 and TNF-α levels with interquartile according to demographic and socioeconomic characteristics, tobacco use and alcohol dependence.

There was a statistically significant difference between groups in IL-6 ($p \leq 0.001$) and IL-10 ($p=0.017$) serum levels. IL-6 levels were higher in the alcohol use disorder group, with a median of 22.07 (16.62 to 43.66) pg/mL, in relation to the group with CAGE scores <2, which had a median of 15.40 (10.78 to 21.27) pg/mL. In addition, levels of IL-10 were lower in the alcohol use disorder group, with a median of 33.81 (21.28 to 80.40) pg/mL, compared to subjects that did not abuse alcohol, which had a median of 56.42 (47.51 to 69.24) pg/mL. For TNF-α levels, there was no significant difference ($p=0.788$) (Table 1).

In the alcohol abuse disorder group, 34.3% (n=24) of individuals presented depression and 30% (n=21) were anxious. We did not find a significant association between alcohol abuse disorder and depression ($p=0.112$), however, there was a trend for anxiety ($p=0.082$). Furthermore, there were no significant differences between socioeconomic terciles ($p=0.748$) and alcohol abuse disorder.

In order to evaluate the influence of possible confounding factors interfering in the results, we performed an adjusted analysis according to gender (IL-10 and TNF-α), age (TNF-α), socioeconomic index (IL-6), years of schooling (IL-6), and tobacco use (IL-6 and TNF-α), and the results remained significant (IL-6: $p=0.030$; IL-10: $p=0.027$). To verify the relationship between proinflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-10), a ratio between these cytokines in each individual was calculated. There was a statistically significant difference in IL-6/IL-10 ($p \leq 0.001$). The median ratios were 0.28 (0.20 to 0.36) in the group CAGE scores <2 group and 0.70 (0.52 to 0.93) in the alcohol use disorder group for IL-6/IL-10. After adjustment for potential confounders, both ratios remained statistically significant (IL-6/IL-10: $p \leq 0.001$) (Figure 1).

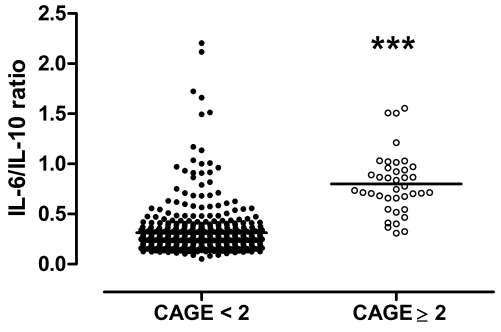

Figure 1: Relationship between proinflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-10). The IL-6/IL-10 ratio was increased in the alcohol use disorder group when compared with subjects CAGE<2 (median: 0.70 (0.52 to 0.93); 0.28; median: (0.20 to 0.36); respectively, $p \leq 0.001$). *** $p \leq 0.001$ versus CAGE<2 alcohol use group using Mann-Whitney test.

Discussion

In this study, we evaluated cytokine levels related to alcohol use disorder in young subjects. Subjects with alcohol use disorder showed higher IL-6 serum levels and lower IL-10 serum levels, with no change in TNF-α serum levels when compared with subjects that did not abuse alcohol. Moreover, the IL-6/IL-10 ratio was significant.

Cytokines have been increasingly recognized as a signal molecule regulating the homeostatic responses of several tissues, and the deleterious effects of alcohol abuse on the immune system are widely recognized [16]. Furthermore, several studies have suggested that imbalance in the immune system can reflect negatively in the brain function and behavior, suggesting that these effects may be implicated in neuropsychiatric disorders in alcoholic individuals [20]. In this sense, several studies have shown an increase in proinflammatory cytokines in alcohol-dependent patients [21-23], suggesting a possible involvement of these molecules in alcohol abuse disorder [21]. In this study, we suggest that the increase of proinflammatory cytokines may be indicative of alcohol abuse disorder, as we found similar results to those in the literature that supports our hypothesis. Likewise, Gonzalez-Quintela [24] observed increased serum concentrations of cytokines (IL-6 and IL-10) in alcoholic patients. After a few days of withdrawal, there was a significant decrease. However, levels remained elevated when compared with healthy subjects [24].

Imbalance of the inflammatory state induced by alcohol abuse leads to several physiological and behavioral changes [9]. Several studies have shown that the inflammatory system is closely related to the emergence of various mood disorders [25-28]. Immune system activation affects several neural pathways, particularly the neurotransmission and expression of trophic factors [29]. Excessive alcohol consumption leads to increased levels of inflammatory cytokines in the central and peripheral nervous systems [9]. Because peripheral system cytokines may cross the blood-brain barrier, the increase of cytokines in the CNS leads to detrimental effects on the brain, contributing to alterations in neurological function and neurodegeneration [30]. Given the fundamental role of neurotrophins in neurogenesis and synaptic plasticity, the inflammatory process may affect brain function, potentially altering Brain-derived neurotrophic factor (BDNF) modulation [31,32]. Several studies have shown that inflammatory response in the brain can change BDNF expression, which may compromise the process of neuroplasticity [33,34]. In a previous study, we found that individuals who abused alcohol had increased levels of neurotrophic factors (BDNF, NGF and GDNF) [35].

Alcohol abuse is closely related to increased morbidity and mortality, and has been specially associated with psychiatric disorders [36]. Moreover, alcohol is often used as "self-medication" in patients with psychiatric disorders, as it is reported to temporarily alleviate feelings of anxiety and depression [37]. In our study, no differences were observed in the prevalence of mood disorders among individuals who abused and did not abuse alcohol.

In alcohol abuse disorder subjects, cytokines have been suggested to link inflammatory processes in the periphery with neuroinflammatory

changes in the brain [38]. Alcohol-induced liver damage generates inflammatory cytokines, which may influence brain cells [39], and thus alter brain functions [38]. The neuroinflammation process is accompanied by an increase of reactive oxygen species and inflammatory proteases, causing cellular damage and microglia activation [38,40]. It is theorized that high concentrations of cytokines in the CNS that are associated with heavy alcohol consumption can remain active for an extended period of time, thereby altering neurotransmission, neurogenesis, neurite outgrowth, myelination, and may promote neurodegeneration [38,41,42]. Thus, alcohol-induced immune system changes can be relevant in the development of neuropathological and behavioral changes [12,38]. In addition, alcoholic patients without cirrhosis have presented increase in IL-6 levels [22]. In fact, reliable markers may be useful to confirm the diagnosis and the current stage of the disease, especially with the uncertain information provided by patients [43,44]. Therefore, abusive alcohol consumption increases proinflammatory release, promoting, supposedly, the appearance of mental disorders. In this study, we cannot evaluate the frequency and amount of intake in individuals who abused alcohol and also the period of abstinence. Also, we were unable to assess the stage of the disorder. However, our study differs from other literature because it involves young individuals from a population-based study; they were not making use of medication and they were not admitted into clinics for treatment of alcohol abuse or other disorders. In order to find new biomarkers to aid diagnosis in clinical assessment, treatment and monitoring alcohol use disorders, our results suggest that inflammatory parameters, such as IL-10 and IL-6 may be involved in the pathophysiology of this disorder. However, more studies are needed to assess inflammatory status in the different stages of this disorder.

The search for biological and clinical markers for psychiatric disorders is highly relevant for diagnosis, treatment, and monitoring of these disorders, thus enabling higher precision and agility in the diagnosis. Current markers (liver enzymes and hematological changes) of alcoholism are only useful when the patient has already been in heavy alcohol usage for quite a while, so it is necessary to find new biological parameters for the early diagnosis of alcohol use disorder [45]. Our results suggest that cytokines, especially IL-6 and IL-10, are involved in the pathophysiology of alcohol abuse/dependence. Moreover, they may be candidate markers of neuronal damage. However, these actions are complex and the mechanisms responsible for ethanol's effect on immune responses remain elusive. More studies are needed to better assess the profile of cytokines in alcohol use disorder.

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References

1. Meier MH, Caspi A, Houts R, Slutske WS, Harrington H, et al. (2013) Prospective developmental subtypes of alcohol dependence from age 18 to 32 years: implications for nosology, etiology, and intervention. Dev Psychopathol 25: 785-800.
2. Hicks BM, Iacono WG, McGue M (2010) Consequences of an adolescent onset and persistent course of alcohol dependence in men: adolescent risk factors and adult outcomes. Alcohol Clin Exp Res 34: 819-833.
3. Wang ZY, Miki T, Lee KY, Yokoyama T, Kusaka T, et al. (2010) Short-term exposure to ethanol causes a differential response between nerve growth factor and brain-derived neurotrophic factor ligand/receptor systems in the mouse cerebellum. Neuroscience 165: 485-491.
4. Fergusson DM, Boden JM, Horwood LJ (2013) Alcohol misuse and psychosocial outcomes in young adulthood: results from a longitudinal birth cohort studied to age 30. Drug and alcohol dependence 133: 513-519.
5. Guilbert JJ (2006) The World Health Report 2006: working together for health. Education for health. Educ Health (Abingdon) 19: 385-387.
6. Goral J, Karavitis J, Kovacs EJ (2008) Exposure-dependent effects of ethanol on the innate immune system. Alcohol 42: 237-247.
7. Achur RN, Freeman WM, Vrana KE (2010) Circulating cytokines as biomarkers of alcohol abuse and alcoholism. J Neuroimmune Pharmacol 5: 83-91.
8. Hashimoto E, Riederer PF, Hesselbrock VM, Hesselbrock MN, Mann K, et al. (2013) Consensus paper of the WFSBP task force on biological markers: biological markers for alcoholism. World J Biol Psychiatry 14: 549-564.
9. Kane CJ, Phelan KD, Douglas JC, Wagoner G, Johnson JW, et al. (2014) Effects of ethanol on immune response in the brain: region-specific changes in adolescent versus adult mice. Alcohol Clin Exp Res 38: 384-391.
10. Webster JI, Tonelli L, Sternberg EM (2002) Neuroendocrine regulation of immunity. Annual review of immunology 20: 125-163.
11. Alfonso-Loeches S, Pascual M, Guerri C (2013) Gender differences in alcohol-induced neurotoxicity and brain damage. Toxicology 311:27-34.
12. Crews FT, Bechara R, Brown LA, Guidot DM, Mandrekar P, et al. (2006) Cytokines and alcohol. Alcohol Clin Exp Res 30: 720-730.
13. Rajayer SR, Jacob A, Yang WL, Zhou M, Chaung W, et al. (2013) Cold-inducible RNA-binding protein is an important mediator of alcohol-induced brain inflammation. PloS one 8: e79430.
14. Chaturvedi LS, Zhang P, Basson MD (2012) Effects of extracellular pressure and alcohol on the microglial response to inflammatory stimulation. American journal of surgery 204: 602-606.
15. Rubio-Perez JM, Morillas-Ruiz JM (2012) A review: inflammatory process in Alzheimer's disease, role of cytokines. TheScientificWorldJournal 2012: 756357.
16. Kane CJ, Phelan KD, Douglas JC, Wagoner G, Johnson JW, et al. (2013) Effects of ethanol on immune response in the brain: region-specific changes in aged mice. J Neuroinflammation 10: 66.
17. Barros A, Victora C (2005) A nationwide wealth score based on the 2000 Brazilian demographic census. Rev Saúde Pública 39: 523-529.
18. Buchsbaum DG, Buchanan RG, Welsh J, Centor RM, Schnoll SH (1992) Screening for drinking disorders in the elderly using the CAGE questionnaire. J Am Geriatr Soc 40: 662-665.
19. Bradley KA, Bush KR, McDonell MB, Malone T, Fihn SD (1998) Screening for problem drinking: comparison of CAGE and AUDIT. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. J Gen Intern Med 13: 379-388.
20. Buhler M, Mann K (2011) Alcohol and the human brain: a systematic review of different neuroimaging methods. Alcohol Clin Exp Res 35:1771-1793.
21. Heberlein A, Kaser M, Lichtinghagen R, Rhein M, Lenz B, et al. (2014) TNF-alpha and IL-6 serum levels: neurobiological markers of alcohol consumption in alcohol-dependent patients? Alcohol 48: 671-676.
22. Gonzalez-Reimers E, Santolaria-Fernandez F, Martin-Gonzalez MC, Fernandez-Rodriguez CM, Quintero-Platt G (2014) Alcoholism: a systemic proinflammatory condition. World J Gastroenterol 20: 14660-14671.
23. Leclercq S, Cani PD, Neyrinck AM, Starkel P, Jamar F, et al. (2012) Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects. Brain Behav Immun 26: 911-918.

24. Gonzalez-Quintela A, Dominguez-Santalla MJ, Perez LF, Vidal C, Lojo S, et al. (2000) Influence of acute alcohol intake and alcohol withdrawal on circulating levels of IL-6, IL-8, IL-10 and IL-12. Cytokine 12: 1437-1440.
25. Bergink V, Gibney SM, Drexhage HA (2014) Autoimmunity, inflammation, and psychosis: a search for peripheral markers. Biol Psychiatry 75: 324-331.
26. Altamura AC, Buoli M, Pozzoli S (2014) Role of immunological factors in the pathophysiology and diagnosis of bipolar disorder: comparison with schizophrenia. Psychiatry and clinical neurosciences 68: 21-36.
27. Felger JC, Lotrich FE (2013) Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 246: 199-229.
28. Horvath S, Mirnics K (2014) Immune system disturbances in schizophrenia. Biol Psychiatry 75: 316-323.
29. Lason W, Budziszewska B, Basta-Kaim A, Kubera M, Maes M (2013) New trends in the neurobiology and pharmacology of affective disorders. Pharmacol Rep 65: 1441-1450.
30. Stoll G, Jander S, Schroeter M (2002) Detrimental and beneficial effects of injury-induced inflammation and cytokine expression in the nervous system. Adv Exp Med Biol 513: 87-113.
31. Calabrese F, van der Doelen RH, Guidotti G, Racagni G, Kozicz T, et al. (2015) Exposure to early life stress regulates Bdnf expression in SERT mutant rats in an anatomically selective fashion. J Neurochem 132: 146-154.
32. Stepanichev M, Dygalo NN, Grigoryan G, Shishkina GT, Gulyaeva N (2014) Rodent models of depression: neurotrophic and neuroinflammatory biomarkers. BioMed Res Int 2014: 932757.
33. Schnydrig S, Korner L, Landweer S, Ernst B, Walker G, et al. (2007) Peripheral lipopolysaccharide administration transiently affects expression of brain-derived neurotrophic factor, corticotropin and proopiomelanocortin in mouse brain. Neurosci lett 429: 69-73.
34. Guan Z, Fang J (2006) Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. Brain Behav Immun 20: 64-71.
35. Lhullier AC, Moreira FP, da Silva RA, Marques MB, Bittencourt G, et al. (2015) Increased serum neurotrophin levels related to alcohol use disorder in a young population sample. Alcohol Clin Exp Res 39: 30-35.
36. Cummings SM, Bride B, Cassie KM, Rawlins-Shaw A (2008) Substance abuse. Journal of Gerontological Social Work 50: 215-241.
37. Mangerud WL, Bjerkeset O, Holmen TL, Lydersen S, Indredavik MS (2014) Smoking, alcohol consumption, and drug use among adolescents with psychiatric disorders compared with a population based sample. J Adolesc 37: 1189-1199.
38. Umhau JC, Schwandt M, Solomon MG, Yuan P, Nugent A, et al. (2014) Cerebrospinal fluid monocyte chemoattractant protein-1 in alcoholics: support for a neuroinflammatory model of chronic alcoholism. Alcohol Clin Exp Res 38: 1301-1306.
39. Blednov YA, Benavidez JM, Geil C, Perra S, Morikawa H, et al. (2011) Activation of inflammatory signaling by lipopolysaccharide produces a prolonged increase of voluntary alcohol intake in mice. Brain Behav Immun 25: S92-S105.
40. Yang G, Meng Y, Li W, Yong Y, Fan Z, et al. (2011) Neuronal MCP-1 mediates microglia recruitment and neurodegeneration induced by the mild impairment of oxidative metabolism. Brain Pathol 21: 279-297.
41. Crews FT, Zou J, Qin L (2011) Induction of innate immune genes in brain create the neurobiology of addiction. Brain Behav Immun 25: S4-S12.
42. Lull ME, Block M (2010) Microglial activation and chronic neurodegeneration. Neurotherapeutics 7: 354-365.
43. Davies DL, Bortolato M, Finn DA, Ramaker MJ, Barak S, et al. (2013) Recent advances in the discovery and preclinical testing of novel compounds for the prevention and/or treatment of alcohol use disorders. Alcohol Clin Exp Res 37: 8-15.
44. Moonat S, Sakharkar AJ, Zhang H, Pandey SC (2011) The role of amygdaloid brain-derived neurotrophic factor, activity-regulated cytoskeleton-associated protein and dendritic spines in anxiety and alcoholism. Addict Biol 16: 238-250.
45. Topic A, Djukic M (2013) Diagnostic characteristics and application of alcohol biomarkers. Clin lab 59: 233-245.