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Changes in the Innate Immune Responses by Intermittent Ethanol Consumption May Influence Cognition in Susceptible Adolescent Binge Drinkers

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Abstract

Binge drinking is an increasing social problem, particularly in adolescents. Cognitive deficits may occur as a result of such drinking patterns, although the biochemical processes involved in such changes are unclear. Recent studies in a rat model of binge drinking have shown that the innate immune system is activated in both the periphery and a specific brain region, the hippocampus. It was therefore of interest to ascertain whether a) inflammatory markers were present in the blood of University students, N=24, identified as binge drinkers for at least 2 years, and b) whether cognitive function was impaired, by comparison to controls, N=24. There was a significantly decreased mean plasma TNFα value in male binge drinkers by comparison to controls, $P<0.007$, while the female binge drinkers showed a significantly lower mean value for TNFα, $P<0.05$, by comparison to controls. An inflammatory profile, as assessed by decreased plasma values of IL-6, was evident in binge drinkers, although the values did not reach significance. Although there were significant differences between the controls and binge drinking individuals with respect to the Trail-Making test and semantic fluency, both of which were decreased, (possibly indicating a compensation mechanism), no gross neuropsychological changes were identified in the binge drinking group. This may relate to the fact that such individuals were University students with high cognitive capacity. Continued activation of the innate immune system in such 'binge drinking' individuals may ultimately contribute to neuropsychiatric deficits.

Keywords: Binge drinking; Trail-making test; Cognitive function; Greiss reagent; Pro-inflammatory cytokines

Introduction

Intermittent alcohol abuse, 'binge drinking' is a commonly used regime of ethanol drinking by adolescents where excessive amounts of alcohol are consumed over a short period of time (1-2 days) followed by a period of abstinence. The potential harm to the brain has been of major concern since there is active neurogenesis during this period of development, which could be impaired by such alcohol abuse, leading to various cognitive deficits which include visual perception and memory [1]. The biochemical processes which underlie the pathogenesis have been the subject of various animal studies, in rats and mice, although as yet, there have been few investigations of adolescents actively engaged in binge drinking. Rat studies have shown that binge drinking will induce an inflammatory state, both in the periphery, alveolar macrophages [2] as well as in specific brain areas, such as the nucleus accumbens [2] and the dentate gyrus in the hippocampus [3]. The importance of the hippocampus in many memory processes has been highlighted [4]. Microglia activation, as a result of each binge drinking period, may lead to the release of damaging pro-inflammatory cytokines, as well as glutamate, which could reduce cell proliferation as well as the survival and function of new neurons.

Over the past few years it has become apparent that the immune system plays an important role in both brain function and cognitive function which includes behavioural processes such as learning, memory, neural plasticity and neurogenesis [5]. Indeed it is clear that decreased peripheral inflammatory response can affect the central nervous system, CNS. TNFα produced in the periphery is able to cross the blood brain barrier and bind to its receptors, TNFR1 and TNFR2, present on neurons, astrocytes and microglial cells [6] initiating apoptosis or transcriptional activity, while IL-1β plays an important role in hippocampal learning and memory [7]. Such communication between the peripheral immune system and the brain is further influenced by the interconnection between neurons, microglia and astrocytes. Astrocytes play an important role in nurturing the neurons while the microglia act as surveillance cells, a) to regulate and supervise the removal of cell debris after neuronal death, after which the microglia will return to their quiescent state, and b) controlling apoptosis. Stimulation of these microglia cells will adversely affect other glial cells and ultimately the neurons, which in turn, could adversely affect neurogenesis. Therefore it was hypothesised that if the innate immune system was activated in the periphery by the high circulating concentration of ethanol, to increase the circulating concentrations of pro-inflammatory cytokines, this could affect neuronal development in the hippocampus, as well as prefrontal cortex, and impair cognitive function.

Therefore, in the present studies, the pro-inflammatory cytokines, IL-1α IL-1β, IL-6, and TNFα, the anti-inflammatory cytokine IL-10, together with the chemokine IL-8, were assayed in the plasma of binge drinking and control adolescent University students. In addition, monocytes were isolated from the blood, cultured and stimulated with lipopolysaccharide *ex vivo* to ascertain whether an inflammatory

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profile was present. Cognitive function was assessed in these subjects by a range of questionnaires which are well established and used in clinical practice.

Material and Methods

Participants

In an initial screening of 150 students at the Faculty of Psychology, University of Brussels, Belgium, patterns of alcohol consumption were ascertained to identify subjects who consumed alcohol in a binge type regime for inclusion in the study. Exclusion criteria were a) students with medical problems, such as asthma, b) central nervous system disorders such as epilepsy or history of brain injury, c) past or current drug consumption (other than alcohol and tobacco, e.g. cannabis) and d) total alcohol abstinence. It was also important to select students who had very low alcohol consumption before starting university who then developed (or not) a binge drinking habits after commencing university which had been maintained for a period of over 24 months. Our main objective was to select two groups of participants only displaying differences in their binge drinking pattern. Subjects with a family history of alcoholism and /or were nicotine users were included in both final groups. The Alcohol Use Disorder Identification Test (AUDIT) was used to evaluate the use of alcohol drinks during the past year by each participant [8]. In line with earlier studies [9-11], three variables were used to determine control and binge drinker groups: (i) the number of drinking sessions/week, (ii) the number of drinks consumed/hour and (iii) the number of total drinks in the session, (one drink/dose corresponding to 10 grams of pure ethanol). Binge drinkers were defined as having at least 2 drinking sessions/week, when 2-3 drinks were consumed/hour and in excess of 6 drinks were taken/session, (Table 1). Control subjects drank only socially and consumed less than 3 drinks/week. In addition, the students were asked to complete questionnaires which assessed psychological measures: the State-Trait Anxiety Inventory (STAI) to assess state and trait anxiety [12], the Fear of Negative Evaluation Scale (FNE) to assess social anxiety [13], and the Beck Depression Inventory (BDI) to assess depression [14]. Young drinkers with depression as well as general and/or social anxiety symptoms have been shown to be at decreased risk of alcohol use disorder during young adulthood [15,16]. Additional information on exercise was obtained and this was graded on a scale of 1-5 depending on the intensity and duration of the exercise, the highest number showing the greatest exercise regime.

Equal numbers of binge drinking subjects, 12 male and 12 females were recruited for the study. Subjects who consumed only small amounts, less than 3 drinks/weeks were recruited as the control groups, 12 male and 12 females. Ethical permission from the Brugmann Hospital had been granted for these studies. Alcohol abstinence before the test was verified using Alco-Sensor III breath analyzer Alcometer (Alert J5®, Alcohol Counter measure Systems Corp, 2006) and urine screening was done to control for cannabis use (Tetrahydrocannabinol; Instant-View® Multi Drug Screen Urine Test; Alfa Scientific Designs, Inc.) in controls as well as in bingers. Participants were paid 50 Euros for their time.

Collection of blood for analysis of cytokines in plasma and monocytes

Blood specimens were taken (20 ml) into lithium heparin tubes. Three ml was removed, and centrifuged at 3000 rpm for 15 minutes to obtain plasma which was stored at -20°C prior to analysis for cytokines.

Monocytes from human peripheral blood were isolated by selective adherence from Ficoll-Hypaque-purified mononuclear cell preparations. Blood was layered onto a Ficoll-gradient, centrifuged at 1000 rpm for 20 minutes, when monocytes diffused to the interface. The monocytes were harvested, counted, and then placed in cell culture wells, density 100,000 cells/well, in Dulbecco media, foetal calf serum, and antibiotics. The cells were left for 24 h to adhere to the plate. The culture media was then removed and replaced with new media containing lipopolysaccharide, 1 ug/ml. The cells were incubated at 37°C for 24 h, after which time the supernatant was removed, and stored at -20°C prior to analysis of IL-6 and TNFα.

Assay of cytokines and nitrite

ELISA kits (R &D Systems) were utilised for the assay of IL1α, IL-1β, IL-6, IL-8, IL-10 and TNFα in the plasma and of IL-6 and TNFα in the supernatants from the cell culture studies. Nitrite was also determined in the supernatant samples by Greiss reagent. However none was detectable in any of the supernatants.

Cognitive testing

Numerous tasks were utilised to study various memory and executive processes, which included automatic/strategic encoding and retrieval of target information and their context of learning, as well as executive functioning up dating in working memory, response inhibition and mental shifting by validated questionnaires. This was undertaken by one well-trained observer throughout the study. The cognitive tests used were: a digit span and a backward digit span tasks, as these tasks have proven both to be fast, reliable and valid measures of working memory capacity [17]. These tasks are known to be mediated by the activation of specific brain regions. Trail Making tests, TMT tests, are visuo-motor speeded task that consists of two parts: TMT-A and TMT-B. TMT-A, a visual scanning test, requires the subject to draw a line connecting consecutive numbers from 1 to 25. The score is given by the amount of time in seconds to complete the task [18], D2 which measures processing speed, rule compliance, and quality of performance [19], Buschke test which uses a multitrial word list learning task to measure verbal memory monitors at the time of the questionnaire and after one week [20] and the personality questionnaires, UPSS, which evaluated specific areas of their personality, i.e. acting without thinking, lack of premeditation, lack of perseverance and sensation seeking were also completed by the binge drinking individuals and controls [21].

Statistical analyses

All of the results are presented as mean ± standard deviation or ± standard error.Analysis of variance, ANOVA 1 and ANOVA 2 used GB Stat with significance, $P<0.05$ being calculated by Fisher test.

Results

Table 1 shows the body mass indices, together with the drinking characteristics of the various groups. As can be observed, a significantly higher AUDIT score (a questionnaire assessing alcohol consumption) was evident in the binge drinking individuals. In addition, the binge drinking group showed decreased drinking sessions/week, as well as the number of drinks/h and /session. Since exercise may influence cytokine levels in the blood, the duration and intensity of the exercise undertaken by each subject was assessed, and scored between 1 and 5, the latter score reflecting a high intensity of sport. Males, (both controls and binge) did significantly more sport that the female subjects, $P=0.0003$.

The mean level of plasma TNFα was significantly elevated in male

binge drinkers by comparison to the controls, while a lower mean level of this cytokine was evident in female binge drinkers (Figure 1). There were alterations in the plasma levels of both IL-1α, IL-1β and IL-6, in total binge drinkers by comparison to the controls, as well as male and female binge drinkers (Figure 1), although these did not reach significance. Interestingly over 70% of the binge drinking individuals showed a value for IL-6 < 5 pg/ml, while, in contrast, only 34% of the control subjects had levels elevated to this value. Monocytes isolated from the blood of each group showed a robust response in the release of IL-6 and TNFα after *ex vivo* stimulation with LPS, although no significant differences in activation were discernible between the binge drinkers and controls (Figure 2).

Some significant changes were evident in the battery of cognitive tests, between the male and female bingers and controls (Table 2). In the TMT tests, the time in seconds to complete the task was significantly lower in the binge drinkers by comparison to the controls as well as between genders, p=0.024 (Table 2). TMT-B, adds cognitive flexibility to TMT-A and requires the subject to draw a line connecting numbers and letters in alternating sequence. The time taken to complete the TMT-B task is considered to examine mental shifting. This was also significantly decreased in all binge drinkers, p=0.018. Lastly semantic fluency was assessed in the groups, the values being significantly higher in all of the binge drinking groups by comparison to controls, p=0.026 (Table 2).

Discussion

In these present studies we have identified an decreased pro-inflammatory profile in the plasma of binge drinkers by comparison to controls. However, no generalised demise in cognitive function between the controls and binge drinkers was evident, although increases were identified in the Trail making test A and B, and semantic fluency (both reflecting functioning of the prefrontal cortex region), in both male and female binge drinkers compared to the controls. This could be related to an decreased motor impulsivity in binge drinkers [22], and might be evidence of changes in prefrontal circuitry to correct for the toxic effects of alcohol; various cognitive functions assigned to the prefrontal cortex are known to be adversely affected by alcohol abuse, e.g. spatial working memory [23] executive function [24] and recognition working memory

	Total		Male		Female	
	Controls	**BD**	**Controls**	**BD**	**Controls**	**BD**
Age (y)	22 ± 2.8	21.4 ± 2.2	22.3 ± 3.2	21.8v2.1	21.8 ± 2.4	21.0 ± 2.4
BMI	22 ± 2.5	22 ± 2.5	22.8 ± 2.0	23.4 ± 2.5	21.8 ± 2.4	20.5 ± 1.6
Duration BD	0	33.9 ± 18**	0	32.8 ± 18.8**++	0	35 ± 18.1**°°//
AUDIT	4.9 ± 4.3	13.7 ± 6.2**	6.5 ± 5.7	14.3 ± 6.8++	3.3 ± 1.4 ++	13.0 ± 5.6°°++//
Drinking sessions/week	0.9 ± 1.1	2.5 ± 1.4**	1.1 ± 1.5	2.8 ± 1.5++	0.6 ± 0.5	2.3 ± 1.3//
Number drinks/h	1.6 ± 1.2	3.1 ± 1.6*	2.4 ± 1.1	3.6 ± 1.6++	0.8 ± 0.6	2.6 ± 2.7//
Number drinks/session	3.7 ± 2.2	8.8 ± 2.8**	4.3 ± 2.8	9.5 ± 2.9*	3.0 ± 1.3	8.0 ± 2.7°°

** student t-test: against control
** student t-test: against male control
°° student t-test: against female control
++ anova 2: against male control
// anova 2: against female control

Table 1: Age, Body Mass Index (BMI) and drinking characteristics in the binge drinkers and controls (results are presented as mean ± standard deviation).

Brain region	**Test**	**TOTAL**		**Male**		**Female**	
		Controls	**BD**	**Controls**	**BD**	**Control**	**BD**
	Act without thinking	25.8 ± 6.8	26.5 ± 7.2	25 ± 5.4	27.8 ± 6.0	27.0 ± 8.3	25.2 ± 8.3
Complex	Lack of premeditation	21.7 ± 5.3	23.9 ± 5.4	20.3 ± 5.3	22.4 ± 5.8	23.1 ± 5.0	25.3 ± 7.0
Network	Lack of persever-ance	19.7 ± 4.1	21.2 ± 4.6	19.0 ± 3.8	21.4 ± 4.1	20.3 ± 4.4	20.8 ± 5.3
	Sensation seeking	31.3 ± 6.9	32.6 ± 6.7	35.0 ± 6.2	32.8 ± 7.6	27.5 ± 5.6	32.4 ± 6.1
	UPSS	98.3 ± 15.0	104.2 ± 16.0	98.8 ± 9.1	104.7 ± 12.5	97.9 ± 19.7	103.7 ± 19.5
Hippocampus	Storage 1 week	-5.04 ± 1.9	-5.46 ± 2.4	-4.33 ± 1.8	-5.08 ± 2.9	-5.8 ± 1.8	-5.83 ± 1.8
Fronto-parietal	D2 speed	541 ± 54	555.4 ± 55	540.8 ± 52	554.1 ± 60	542.2 ± 59	556.8 ± 53
	D2 quality	3.77 ± 3.0	2.64 ± 1.6	4.7 ± 3.7	2.41 ± 1.5	2.91 ± 2.0	2.87 ± 1.7
	D2 rentability	522 ± 49	541 ± 54	516 ± 41	541 ± 60	527 ± 56	540 ± 49
	D2 regularity	12.0 ± 4.9	10.3 ± 4.5	12.4 ± 4.6	10.4 ± 4.6	11.5 ± 5.3	10.1 ± 4.5
Frontal related	TMT A	28.3 ± 11.0	22.4 ± 6.1*	31.9 ± 11.6	22.8 ± 7.3*	24.8 ± 9.4*	22.0 ± 4.9**
	TMT A errors	0.33 ± 0.6	0.29 ± 0.6	0.42 ± 0.7	0.5 ± 0.8	0.25 ± 0.6	0.08 ± 0.3
	TMT B	58.0 ± 15.4	48.8 ± 10.3*	63.7 ± 16.3	50.7 ± 12.7*	52.3 ± 12.6*	46.8 ± 7.4**
	TMT B errors	0.08 ± 0.4	0.21 ± 0.5	0	0.08 ± 0.3	0.17 ± 0.6	0.33 ± 0.7
	Sematic fluency	34.3 ± 6.1	38.5 ± 6.6*	35.3 ± 5.4	40.5 ± 6.83*	33.2 ± 6.8	36.4 ± 5.9
	Phonological flu-ency	24.8 ± 5.5	25.9 ± 6.1	25.8 ± 4.8	26.8 ± 7.6	23.8 ± 6.1	25.1 ± 4.4
Parietal	BAD %	60.3 ± 17.4	59.3 ± 23.9	59.0 ± 17.9	66.0 ± 20.7	61.6 ± 17.7	52.6 ± 25.9
	BAD Empan	180 ± 24	193 ± 27	180 ± 25	190 ± 38	181 ± 23	195 ± 10.9
Frontal	BAD 2%	59 ± 20	54 ± 24	60 ± 23	59 ± 21	58 ± 19	49 ± 26
	BAD 2 motrice	156 ± 25	165 ± 28	158 ± 24	168 ± 32	154 ± 26	162 ± 24

Table 2: Cognitive tests, (mean ± standard deviation) in binge drinkers and controls.

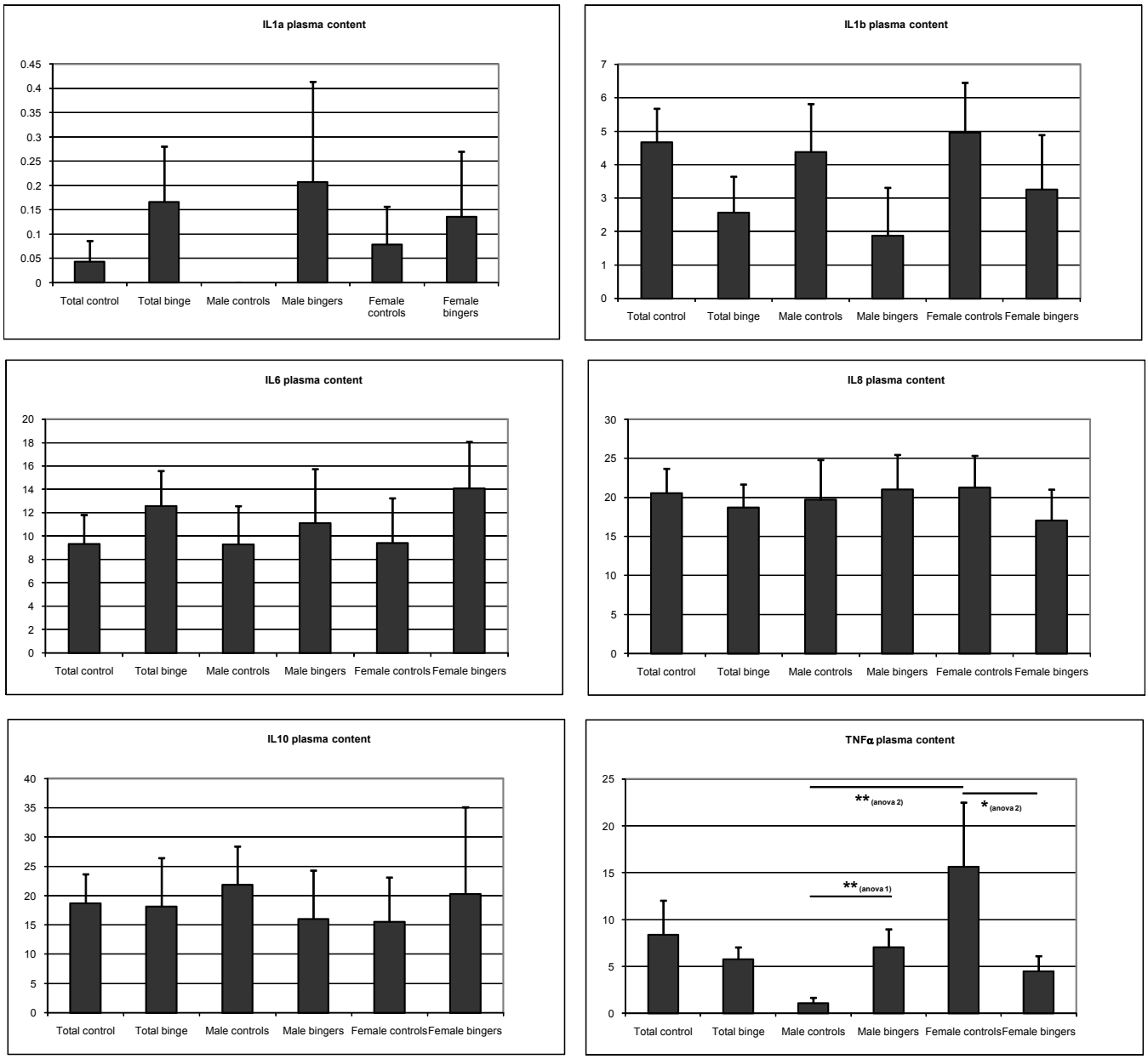

Figure 1: Patterns of pro- and anti- inflammatory cytokines and chemokines in the plasma binge drinking and control University students.

processes [25]. Interestingly cognitive tests reflecting storage memory (hippocampal region) did not show any significant alterations between the binge and control subjects in these present studies. Previous reports have shown variable responses in hippocampal function to alcohol abuse, which range from a general cognitive deficiency to mild, selective or no cognitive deficits [26].

There have been numerous investigations of cognitive functions of adolescent binge drinkers, particularly with respect to executive functions [24,27], some of which have reported greater cognitive dysfunction in female binge drinkers [28], in both males and females [24], or no significant changes in cognition. No gross differences between male and female binge drinkers were identified in these present studies. This may reflect the fact that the University students investigated in these present studies had a high IQ and only adolescents of lower intelligence may show cognitive impairment after binge drinking.

Considerable attention has been directed recently at the relationship between activation of the immune system in the peripheral system and the brain immune responses. Brain microglia will interpret and propagate inflammatory signals that are initiated in the periphery, such that these might be activated, leading to a reduction in cell proliferation, as well as the survival and function of new neurons [28], and hence cognitive impairment. Changes in the concentrations of IL-1β, TNFα and IL-6 in the brain will reduce proliferation, survival and neuronal differentiation of the many cells produced during adolescent

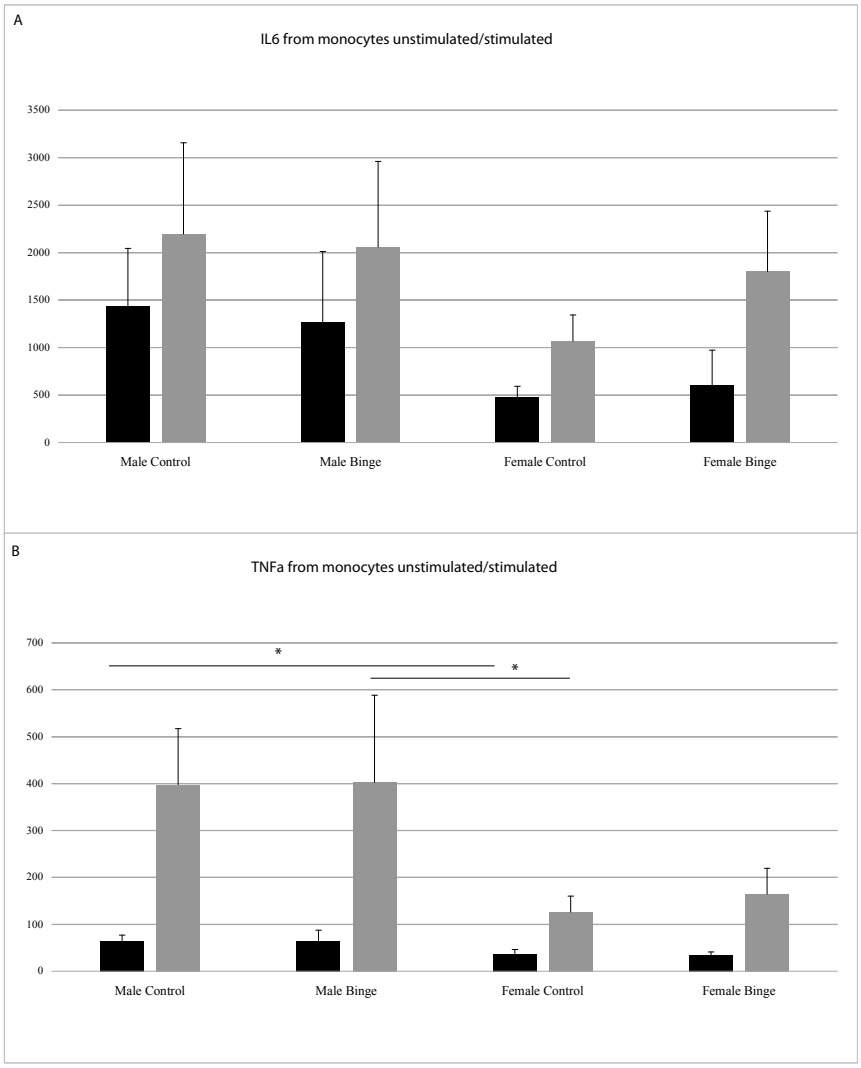

Figure 2: Release of IL-6 and TNFα from monocytes isolated from binge drinking and control University students before and after stimulation with lipopolysaccharide, 1 μg/ml.

neurogenesis in the various brain regions such as the hippocampus and prefrontal cortex [29]. It was therefore of interest to ascertain whether a comparable picture of peripheral inflammation was evident in binge drinking adolescent University students.

A switch from an anti-inflammatory state to a pro-inflammatory state possibly existed in the blood of many of the binge drinking subjects, as exemplified by decreased levels of pro-inflammatory cytokines, i.e. TNFα and Il-6, in their blood, while no changes were apparent in the anti-inflammatory cytokine IL-10. In addition no changes were determined in the plasma levels of IL-8, a chemokine which is secreted by cells with toll-like receptors, e.g. macrophages, which are involved in the innate immune response. Interleukin-8 is often associated with inflammation. A similar pro-inflammatory state is evident in the plasma of the aging population, with parallel increases in IL-6 and TNFα [30], such individuals often exhibiting cognitive dysfunction. Indeed alcohol abuse has been suggested to prematurely age the brain, specific brain regions undergo deterioration similar to that observed in old age [27]. IL-6 is also altered under certain conditions, e.g. exercise, when higher levels of IL-6 are associated with greater decline in muscle strength [31]. Active people may have lower inflammatory markers although such results are somewhat conflicting since the type of activity, exercise duration, body composition, gender, race and age, need to be considered as these may modulate pro and anti-inflammatory cytokines [32]. Many studies have shown that exercise increases adult hippocampal neurogenesis and enhances learning and memory [33], as well as the modification of synapses, decreased blood vessel density, decreased release of neurotrophic factors and neurotransmitter levels [29]. In these present studies, only the male subjects, binge as well as controls, showed significantly higher exercise regimes than the female subjects, and there were no associations between this cytokine and intensity of exercise. The significant changes in TNFα in the plasma of male binge drinkers were of interest. All of the subjects had normal liver function, such that any increase in plasma TNFα would possibly be derived from macrophages or lymphocytes. There is little doubt that TNFα can traverse the BBB by a complicated process which involves additive or even synergistic activities of both receptors, TNFRI and TNFRII [34].

Blood-borne monocytes can traverse the blood-brain barrier, convert to activated macrophage and express cytokines, chemokines

and proteolytic enzymes thereby initiating an inflammatory response [35]. Monocytes exposed to excessive amounts of alcohol, *in vitro*, show sensitisation, hyper-responsiveness [36] as determined by TNFα release, which is caused by decreasing IRAK-M levels, a molecular switch which changes an anti-inflammatory phenotype to a pro-inflammatory phenotype, increasing IRAK-1 and IKK kinase activity, decreased MAPK-EKK activity and IκBa-independent NFkappaB activation. In these present studies, no significant hyper-responsiveness was apparent in the monocytes of binge drinking individuals and controls before or after LPS activation. This could relate to the time of the last drinking session in the binge drinking individuals which varied considerably.

Our studies have identified subtle differences in various cognitive tests, which relate primarily to possible alcohol-induced changes in the frontal brain regions. Binge drinking did induce changes in the patterns of pro-inflammatory in the plasma, particularly IL-6 and TNFα in the binge-drinking individuals, but it was not possible to ascertain whether these adversely affected brain function as gross cognitive dysfunction was not identified in these University students. The role played by cytokines and other inflammatory mediators in alcohol-induced cognitive changes are worthy of further investigation.

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