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CONFERENCE REPORT

Proceeding of the 9th Alcohol Hangover Research Group Meeting

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Abstract: ***Background*:** Alcohol hangover is a common occurrence among individuals who have experienced an episode of heavy alcohol consumption the previous night. Until now defined as the general feeling of misery that develops once the Blood Alcohol Concentration approaches zero. Despite its prevalence and several related adverse consequences, insufficient research has been conducted with regards to this matter and further understanding of the pathology of alcohol hangover is necessary. During the 9th Alcohol Hangover Research Group meeting, held on April 29th 2017, Utrecht, The Netherlands, numerous aspects of alcohol hangover were presented and many advances with regards to determinants, biological and cognitive consequences and potential treatment have been presented.

***Conclusion*:** Precisely, a definition of alcohol hangover has been established and wider understandings of biological and cognitive effects, alcohol metabolism, immune functioning and potential treatment of alcohol hangover were presented and discussed. Further research and development are necessary to attain a wider understanding of the pathology of alcohol hangover.

Keywords: Alcohol, ethanol, hangover, treatment, definition, metabolism, resistance.

1. INTRODUCTION

Alcohol hangovers are extremely prevalent and generally experienced among human population as a consequence of alcohol consumption [1]. Although alcohol hangover has been associated with several detrimental symptoms, such as general misery, nausea and fatigue [2], until recently a clear and absolute definition had yet to be asserted. Recent studies have reported the detrimental consequences of hangover on health, economy and society. The cost of paucity of productivity at work, car accidents and criminal-justice occurrences, all related to alcohol consumption, is equivalent to several billions of dollars [3A]. Physical and mental impairment have been investigated and observed by researchers in relation to cognition, physical performance, work absenteeism and risk of injury [3B-11]. A wider understanding of the pathology and the implications of alcohol hangover are necessary to expand our knowledge of this area and subsequently identify a potential prevention or treatment of hangover. To support alcohol hangover related research, the Alcohol Hangover Research Group (AHRG) was established to promote international research and collaboration, review and enhance methodological procedures and general knowledge of alcohol hangover. The present proceedings provide a synopsis of the 9th AHRG meeting, held on April 29th 2017, Utrecht, The Netherlands.

2. DEFINITION OF ALCOHOL HANGOVER

Alcohol hangover has been described by researchers by means of several definitions, most of which referred to the adverse effects experienced the day after a night of alcohol ingestion. A general consensus about the hangover state was implemented upon recommendation of the AHRG [12]. It was suggested that alcohol hangover is experienced once the Blood Alcohol Concentration (BAC) has reached the value of zero, however a definite and absolute definition was yet to be asserted.

Marith van Schrojenstein Lantman (Utrecht University, The Netherlands), discussed the development of an adequate and common definition of alcohol hangover for scientific purposes. An online survey was utilized among social drinkers who recently had experienced alcohol hangover, in which a definition of hangover was asked to be provided for analysis. Three main definitions arose from the content analysis and text mining which were presented to all members of the AHRG for revision. Upon consideration of their observations and recommendations, a final definition of alcohol hangover was established: 'The alcohol hangover refers to the combination of mental and physical symptoms, experienced the

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day after a single episode of heavy drinking, starting when blood alcohol concentration approaches zero. Specific symptoms, causes and consequences of alcohol hangover can be presented and discussed, however it is important to understand that these topics are not constituents of the definition.

Sally Adams (University of Bath, UK) discussed qualitative data from a study exploring how student drinkers conceptualize and experience alcohol hangover. Whilst, hangover symptoms have been examined in cognitive psychology, drinkers' own experiences of hangover have been largely ignored and under-researched. Adams and colleagues conducted semi-structured interviews with 23 student drinkers, aged between 18-30 years, who had experienced a hangover in the past 6 months. The interview schedule included questions related to; (1) definition of alcohol hangover, (2) perceived cause and consequences of hangover and (3) effects of hangover. Several themes were identified in participants' accounts of alcohol hangover. Firstly, participants acknowledged that hangovers were primarily caused by heavy drinking, but also expressed confusion regarding the contribution of different factors to the experience of hangover. Secondly, participants reported a range of physical and psychological effects of hangover and discussed the relationship between alcohol consumption and hangover. Participants indicated that hangover was a consequence of excessive drinking and a "punishment" for having a good time. Finally, participants acknowledged that reducing drinking was only a temporary option as a means of reducing hangover. These findings have the potential to inform further lines of study in quantitative and experimental research. Additionally, these findings could help frame the development of alcohol education interventions aimed at student drinkers.

3. BIOLOGICAL EFFECTS OF ALCOHOL HANGOVER

Several factors influence the severity of hangovers, for instance, amount and type of alcohol ingested, sleep quality and duration, food intake and individual differences, such as personality and family history. However, the biological underpinnings of hangovers are still enigmatic and further research is needed to reveal them [13-14].

Joris Verster (Utrecht University, The Netherlands) presented his research with regards to the pattern which hangover severity follows during the day. Results from a previous survey [15] among drinkers who experienced hangover were examined. On the grounds of pre-defined temporal idiosyncrasies, each individual hangover was assigned to one of six categories of hangover pattern. Findings showed three main types of hangover patterns: Severity Type 1, characterized by a continuous decline, Severity Type 2 identified by a steady pattern and Severity Type 3, represented by hyperbolic curve. The highest scores of severity of hangover symptoms were found in relation to Type 1 severity, which, in addition is more common among men than women. Type 2 was associated to the lowest ingestion of alcohol and severity scores. This type of severity was predominant among women compared to men. Lastly, Type 3 are equally experienced by women and men and are identified by greater gastrointestinal complaints. Three main hangover severity patterns were identified by this study, all of which are dependent to the amount of alcohol consumed by the individual and their subjective evaluation of symptom severity. For future research, it is important to relate the observed patterns to the presence and severity of individual hangover symptoms. This will enhance the knowledge on the pathology of the alcohol hangover, and perhaps explains why certain hangover treatments are effective in one drinker but not the other (as they have different severity Types).

Sean Johnson (University of the West of England, UK) discussed the prevalence and correlates of the alcohol hangover. Johnson utilized an on-premise study to investigate the prevalence and severity of the alcohol hangover. Potential participants were approached as they exited popular night-time venues in Bristol City Centre in the UK. Participants were breathalyzed and asked to report on their subjective intoxication and alcohol consumption practices during that evening. The following day participants were contacted via email and asked to report on their hangover severity using the Alcohol Hangover Severity Scale. The mean hangover severity score was used to split participants (N = 347) into mild (N = 99, 29%), moderate (N = 229, 66%) and severe (N = 19, 5%) hangover severity groups based on 33% percentile split. It was found that those reporting severe hangovers were more likely to be male, consumed more alcoholic drinks, had a higher Breath Alcohol Concentration (BrAC) and higher subjective intoxication than those reporting moderate and mild hangovers. There were no significant differences in age, whether respondents were students/non-students, AUDIT-C scores or time spent drinking. Regression analyses showed that "the total number of drinks consumed on premise", "total number of alcoholic drinks" and "BrAC" together explained 26% of the variance in alcohol hangover severity scores. The symptoms that were significantly more prominent in the severe hangover group included stomach pain, nausea, dizziness and heart pounding.

4. COGNITIVE EFFECTS OF ALCOHOL HANGOVER

Research conducted with regards to the workplace has reported that 24% of employees had experienced alcohol hangover during working hours and that adverse consequences, such as poor productivity and absenteeism, were reported more often in relation to alcohol abuse than other substances [11]. Alcohol hangover is also associated with impaired psychomotor skills [6] in relation to driving a car and piloting an aircraft [7, 8]. Hangovers have been shown to increase the risk of injury among athletes, such as skiers [9], and to have adverse effects on physical performance of rugby players [10]. Lastly, cognitive impairment has been observed in relation to alcohol hangover, such as memory retrieval [3], subjective evaluations of feelings and mood [4] and attention [5].

Craig Gunn (University of Bath, UK) presented a systematic review and meta-analysis examining the effects of alcohol hangover on cognitive performance. Using terms derived from the words 'alcohol' and 'hangover', Gunn and colleagues searched the databases PubMed, PsycNET and Embase. The search returned 770 articles, of which 34 full text articles were screened. 18 articles met the criteria for inclusion in the systematic review, and 11 had sufficient data to be analyzed in a meta-analysis. Findings from the systematic review suggest that sustained attention and psychomotor

skills are impaired during hangover. However, there was no evidence of impairment in divided attention during hangover, and there were mixed findings for impairment Of Short-Term Memory (STM) and Long-Term Memory (LTM) during hangover. Gunn and colleagues also examined the effect that alcohol hangover had on 'real-life' simulations (*e.g.* driving). Meta-analysis findings suggest that STM, LTM, sustained attention, and psychomotor speed are impaired during hangover. Results from the meta-analysis on divided attention did not reveal significant impairment during hangover. This is in contrast with studies investigating the effects of alcohol hangover on driving and flying simulations [7, 8]. The systematic review and meta-analysis revealed significant impairment for 'real-life' simulations of driving and flying during alcohol hangover. Overall, the authors concluded that the systematic review and meta-analysis indicate support for hangover-related impairment of cognition and psychomotor functioning.

Ann-Kathrin Stock (TU Dresden, Germany) presented the results of a binge drinking study investigating the effects of acute alcohol intoxication (BAC 0.10%) and the subsequent hangover on response selection processes in a within-subjects design using healthy young male participants [16]. The study combined behavioral data obtained by means of a moving dots paradigm with neurophysiological (electroencephalogram) data. Given that acute intoxication is mainly driven by ethanol (which enhances both dopaminergic and gamma-aminobutyric acid mediated (GABAergic) signaling, while the hangover state is characterized by the presence of acetaldehyde (which enhances dopaminergic signaling but decreases GABAergic signaling) [17-19], similarities were expected for aspects modulated by dopamine while differential effects were expected for aspects modulated by changes in GABA. While responses were faster during both intoxication and hangover, the speed of information accumulation was decreased/compromised during intoxication and increased/improved during the subsequent hangover state (as compared to the sober state). The speeding of responses was reflected by larger amplitudes of the N2 event-related potential and larger activation of the anterior cingulate cortex, which likely indicates more cognitive conflict and/or greater (compensatory) cognitive effort during the intoxicated and hangover states [20]. The differential modulation of the speed of information accumulation was reflected by the latency of the N2 peak as well as the amplitude of the visual P1 component and underlying changes in the activation of occipital networks. Taken together, this suggests that the increased speed of information accumulation during hangover states might be due to decreases in GABAergic signaling while increases in response times, conflict processing and cognitive effort might potentially be due to an increase in dopaminergic signaling. Yet, the latter could also partly be an effect of over-compensation in case subjects anticipate impaired cognitive functioning [21].

Agnese Merlo, (University of the West of Scotland, UK) presented her data on the effects of alcohol hangover on attention. Specifically, it was examined whether social drinkers who are experiencing alcohol hangover at the time of testing would exhibit an attentional bias towards hangover-related stimuli. Previous research has consistently demonstrated the presence of an Alcohol-Related Attentional Bias (AAB) among social drinkers [22, 23], but this is the first study to examine attentional bias in relation to alcohol hangover. The current research employed a naturalistic hangover study, in which participants consumed alcohol at time and location of their choosing *i.e.* there was no control over their consumption. An automated alcohol hangover Stroop test was utilized to measure alcohol and Hangover-related Attentional Bias (HAB) and three categories of words were presented: alcohol, hangover and neutral. Participants were breathalyzed, to ensure their Breath Alcohol Concentration was close to zero, then they were asked to complete the automated alcohol hangover Stroop test and five questionnaires to measure hangover severity, sleep quality, mood, drinking desire and typical alcohol consumption. The Stroop test illustrated that both alcohol and hangover related attentional bias were found to be present among participants. Specifically, longer reaction times for the alcohol and hangover words were recorded in comparison to the reaction times for the neutral category of words. For the first time, the occurrence of hangover related attentional bias was examined and observed within social drinkers experiencing alcohol hangover. Moreover, correlations between HAB scores and the others questionnaires all resulted not statistically significant. This negative correlation is however favorable to the study, as it demonstrates that the HAB, and AAB, are related to alcohol hangover and alcohol consumption. Sleep quality and duration, mood and drinking desire have not affected participants' performance. Additionally, it was predicted that higher scores of hangover severity would be associated with a greater hangover attentional bias interference, however this was not found. Findings suggest that hangover related attentional bias is present, alongside AAB, within social drinkers experiencing alcohol hangover. This preliminary study reports evidence of the delaying effects of alcohol hangover on selective attention and it should be further investigated as it causes individuals to react slower to alcohol and hangover stimuli whilst experiencing alcohol hangover. This can adversely affect our economy and society, as AAB and HAB can lead to decreased productivity among the work and academic environment and increase risk of incidents and injuries due to distraction and delayed reaction time.

Lydia Devenney (University of Ulster, Northern Ireland) discussed the effects of alcohol hangover on spatial working memory and attentional set-shifting. Alcohol related studies tend to utilize student samples, which are easily accessible and notorious for their drinking habits. However, according to the Higher Education Statistics Agency [24] 80% of undergraduates are 20 years or younger, which indicates that this population, by law, has only been consuming alcohol for two years or less. In Northern Ireland, people aged 30 to 44 years are twice as likely as those aged 18 to 29 years to drink daily [25]. Therefore, unlike previous studies, Devenney examined the next day effects of a night's drinking on a non-student sample. The impact of alcohol consumption on the next day's cognitive performance and methodological shortcomings that may contaminate results were investigated and addressed. A mixed measures design was adopted to compare hangover and no hangover states with order as a between measures variable. Specifically, 45 participants with a mean age of 31.7 year took part in the study. All participants were breathalyzed before testing and participants with a BAC level above 0% were excluded from the study. A series of cognitive tasks were administered along with question-

naires on demographic information, mood, sleep, previous night's alcohol consumption and usual alcohol consumption. In addition, a Task Related Motivation scale was administered before and after each task and ambulatory blood pressure was taken. The analysis revealed that in the hangover state, reaction times were significantly slower on the Stroop interference task and the Eriksen's Flanker Task. Also, in the hangover state significantly less words were recalled on the Free Recall test. These findings suggest that attention and memory are impaired the morning after alcohol consumption. Whereas the number of errors does not differ between the hangover and the control day, the overall response times are slowed in the hangover state, irrespective of task load/item difficulty.

Sarah Benson (Melbourne, Australia) discussed the effects of alcohol hangover on mood and cognitive multi-tasking. Previous research demonstrated deficits in cognitive performance during a hangover state, most notably found in delayed recall in memory tasks and tasks requiring sustained attention. The vast majority of research assessing cognitive performance during a hangover has been laboratory studies using controlled doses. While this methodology offers many benefits, it does not mimic naturalistic settings and may not capture the changes and impairments seen in 'real-life'. With this in mind, Benson *et al.* presented preliminary data (N=16) from a naturalistic study design to determine the effects of hangover on cognitive impairment and mood. In this study, each participant completed testing procedures during a screening visit and two conditions: i) with a hangover and ii) without a hangover (counterbalanced). The hangover visit followed a night out of typical drinking resulting in a hangover. During each testing visit, participants complete the PURPLE Multi-Tasking Framework, Bond-Lader Visual Analogue Scale, Profile of Mood States (POMS) and NASA Task Loading Index (NASA-TLX). Regarding mood, analyses revealed that participants were significantly less alert and content, and significantly more anxious and mentally fatigued during the hangover visit. Additionally, participants' accuracy and reaction time in the Stroop task was significantly impaired during the hangover compared to non-hangover condition. Lastly, participants reported the PURPLE Multi-Tasking Framework to be significantly more physical and temporal demanding and require more effort during the hangover condition. In conclusion, significant impairments on mood and cognitive multi-tasking were observed during alcohol hangover.

5. ALCOHOL HANGOVER TREATMENT

Joris Verster (Utrecht University, The Netherlands) discussed the need of an effective cure for alcohol hangover. Despite the notorious and commonly reported negative consequences of alcohol consumption [1], no effective treatment has been made available yet [26, 27]. Contrarily, treatments for most diseases are constantly investigated and have significantly improved over the years. Several are the adverse consequences of alcohol hangover, which affect daily performance and functioning, and have negative socioeconomic consequences. Hangovers may result in absenteeism and reduced productivity at work, increase the risk of injury, and cause people to fail to fulfil their social obligations [1, 28, 29]. Hence, from a financial and social perspective it would be wise to develop an effective hangover treatment, however, alcohol hangover has been largely neglected by scientists and pharmaceutical companies. The development of an effective treatment has been considered unethical, as it could encourage and lead individuals to increase their amount of alcohol consumption. Although, alcohol hangovers can be interpreted as a natural punishment for excessive alcohol ingestion and therefore, lead to a prevention of such behaviour in the future, there is no scientific evidence to corroborate this conjecture. People experiencing alcohol hangover have stated they will "never drink again (...that much)", reality has shown us that individuals have not respected their statement or adapted their drinking behaviour accordingly [30]. Interestingly, it was observed that students categorized as heavier drinkers overestimated the amount of alcohol they could consume without experiencing a next-day hangover [30]. Alcohol hangover has triggered a wide commercial interest given the large number of treatments available on the internet. Products found on the internet claim to be effective in reducing the presence and severity of hangover symptoms, however, this is usually not supported by (convincing) scientific evidence. For instance, placebo-controlled clinical trials that investigated the effectiveness of such products have shown little or no efficacy [26, 27].

Jacqueline Iversen, (Sen-Jam Pharmaceutical, USA) discussed why antihistamines may be effective in the treatment of alcohol hangover. Histamines are contained in alcoholic beverages to varying amounts [31]. Dietary histamines can cross the gastrointestinal lumen [31, 32]. In addition, the metabolism of alcohol's by-product, acetaldehyde, by the enzyme aldehyde dehydrogenase is the same enzyme that regulates the metabolism of histamine into its inactive forms [31, 32]. It is suggested that the increased intake of histamine derived from alcoholic beverages in addition to the dysregulation of histamine's metabolism results in a higher concentration of systemic histamine. High concentrations of systemic histamine cause effects similar to alcohol hangover symptoms: stomach ache, malaise, nausea, headache, dizziness, vasodilation, flushing, palpitations and sleep disturbances [31]. Interestingly, a number of disorders have a histamine and/or alcohol connection. Alcohol consumption can cause gastritis [33]. Histamine intolerant patients are advised to avoid alcohol [31-33]. Individuals with "Asian flush", a genetic reduction in the enzyme aldehyde dehydrogenase, have shown some relief with the administration of H-1 receptor antagonists [33]. Individuals with Japanese alcohol induced asthma, exhibit high concentrations of acetaldehyde, with the asthma symptoms responding to H-1 antihistamines [34, 35]. A high abundance of mast cells and high concentrations of systemic histamine have been identified in some gastrointestinal disorders including irritable bowel syndrome, irritable bowel disease and ulcerative colitis [32, 34, 35]. The administration of H-1receptor antagonists has been shown to provide some relief to these gastrointestinal disorders. In addition, animal studies have shown that H-1 receptor antagonists with mast-cell stabilizing capabilities, like fexofenadine can provide a protective effect to the gastrointestinal mucosal in the murine ulcerative colitis model [34]. H-1 receptor antagonists with mast cell stabilizing capabilities may reduce the release of pro-inflammatory cytokines, specifically IL-12 and INF-gamma [36]. These cytokines may be increased following alcohol consumption [37]. An exploratory study was performed of 12 subjects who were

administered a fixed dose combination of naproxen plus fexofenadine prior to consuming alcohol for 2.45 hrs. BrAC was measured at t=2hrs, 3hrs and again at t=11hrs after subjects were allowed to sleep for 8 hours. BrAC did not differ significantly with the administration of the fixed dose concentration versus placebo suggesting that the fixed dose combination does not affect alcohol absorption or elimination. Further studies need to be conducted to evaluate the value of antihistamines and their use in alcohol hangover.

6. BIOLOGICAL MARKERS OF ALCOHOL HANGOVER

Alcohol hangover begins once the blood alcohol concentration approached zero and the human body has metabolized the present alcohol [38]. Several biological changes have been observed during the hangover state, such as altered endocrine, metabolic and immune system parameters [39, 40].

Marlou Mackus (Utrecht University, The Netherlands) discussed the metabolism of alcohol during hangover and the case of hangover resistant social drinkers. Mackus reported that despite the consumption of large amounts of alcohol, a minority of social drinkers report to be resistant to developing a hangover. Investigating these drinkers may provide a better insight in the pathology of the alcohol hangover. Previous research demonstrated that urinary ethanol concentrations were significantly lower in hangover resistant individuals compared to hangover sensitive drinkers [41]. This finding suggests that the rate of ethanol metabolism is faster in drinkers who do not experience an alcohol hangover. Alcohol metabolism was directly compared after administering a low dose of ethanol to hangover resistant drinkers and drinkers who experience hangovers. For the presented study, social drinkers who previously participated in hangover trials at Utrecht University were invited to participate. It was aimed to include 12 hangover resistant drinkers and 12 drinkers who experience hangovers after a heavy drinking session. Participants consumed alcohol to reach a Breath Alcohol Concentration (BrAC) of 0.05%. Every 5 minutes BrAC was determined, until BrAC reached zero. Every 15 minutes, the Karolinska Sleeping Scale (KSS) was administered to assess subjective sleepiness, and subjective intoxication was measured. Findings for 23 participants, with a mean age of 22.4 years old, showed that no significant difference in BrAC over time was found between the hangover resistant group and the hangover sensitive group. In line, sleepiness scores and subjective intoxication ratings did not significantly differ between the groups at any point in time after alcohol consumption. Therefore, hangover resistant and hangover sensitive drinkers did not significantly differ on BrAC, subjective sleepiness, and subjective intoxication. These findings suggest that drinkers who usually experience hangovers after a heavy drinking occasion do not experience alcohol intoxication differently than hangover resistant drinkers.

Aurora van de Loo (Utrecht University, The Netherlands) discussed the variation of cytokines concentration during alcohol, hangover. The immune system responds to toxic substances such as alcohol and cytokines are important mediators of this immune response. It has been shown that blood cytokine concentrations are elevated the day after heavy alcohol consumption. Two naturalistic studies were presented, the first aimed at comparing hangover sensitive drinkers with drinkers claiming hangover resistance by looking at saliva cytokine concentrations and hangover symptoms the morning after an evening of drinking alcohol (9 AM). The second study focused on the examination of possible temporal variability in this immune response to alcohol throughout the hangover day (9 AM – 4 PM). The concentration of multiple cytokines (GM-CSF, IFN-γ, TNF-α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8 and IL-10) in saliva were determined by multiplex immunoassays. Furthermore, participants rated the severity of multiple hangover symptoms. Hangover severity on the hangover day was compared between hangover sensitive drinkers (the hangover group) and the hangover resistant drinkers (the hangover resistant group). Significant increases in IL-4, IL-5, IL-6, IL-10, IFN-γ and TNF-α concentration were found in the hangover condition compared to the cytokine concentrations on the control day. Interestingly, no significant differences were demonstrated between hangover sensitive and hangover resistant drinkers. Most common and severe symptoms in the hangover sensitive group were sleepiness, being tired, thirst, headache, concentration problems, nausea, clumsiness, dizziness and stomach pain. In contrast, the hangover resistant group reported only a modest increase in sleepiness, being tired, concentration problems and thirst, without any relevant effects on the more disabling symptoms such as nausea (for a full description of hangover symptoms, and comparison between the hangover resistant and hangover sensitive group, see Hogewoning *et al.* 2016) [42]. In the second study, the overall pro- and anti-inflammatory immune response was tested for significance for several timepoints during the day, using paired sample T-tests. Significant increases in pro-inflammatory cytokine concentrations were observed 6 to 12 hours after stopping drinking. The biggest effect was seen 6 to 9 hours after drinking. No significant increases in cytokine concentrations were seen for anti-inflammatory cytokines. No significant differences in saliva cytokine concentrations were found between subjects with a hangover and hangover resistant subjects.

Livia Wilod Versprille (Utrecht University, The Netherlands), discussed the effect of ethanol on gut permeability and cytokine production. Studies have shown an increased inflammatory mediator response after alcohol consumption in blood and saliva of humans and *in vitro* in caco-2 cells. *In vitro* studies also showed an alcohol induced increased cytokine response of several epithelial cell lines. Previous studies showed a dose dependent increase in TNF-α and IL-6 in gut epithelial cells after ethanol stimulation [41, 43]. In addition, it has been shown an increased permeability of Caco-2 cells after alcohol exposure indicative for a disrupted epithelial integrity [44, 45]. Some studies investigated the possible role of eicosanoids, especially prostaglandins and leukotrienes in ethanol associated symptoms and diseases, and possibly in the alcohol mediated hangover symptoms. Moreover, the interaction between ethanol and eicosanoid biosynthesis interaction results in the modulation of various cellular processes [46]. This interaction could contribute to hangover symptoms by locally modulating cellular processes. Considering previous research, a study proposal was discussed to examine the direct effects of alcohol on immune reactivity and permeability of intestinal epithelial cells in an *in vitro* setting. A pilot study investigating two different human

epithelial cell lines showed increased permeability of Caco-2 cells after a 90-min stimulation with 2% ethanol. Furthermore, a concentration-dependent release of TNF-α and IFN-γ was found in HT-29 after a 90-min stimulation with ethanol. The production of TNF-α and IFN-γ by epithelial cells was still evident 3 hours after the 90 minutes' stimulation with ethanol. These preliminary findings suggest that in the proposed study it is likely that an immune response to alcohol can be provoked. In addition, the effects of Non-Steroidal Anti-Inflammatory Drugs (NSAID) and H1-receptor antagonists on the alcohol-induced immune response can be studied as a potential treatment of the alcohol hangover.

DISCUSSION AND CONCLUSION

Several aspects of alcohol hangover were discussed during the 9th Alcohol Hangover Research Group meeting, specifically, advances in relation to determinants, consequences and treatment of alcohol hangover were presented. One major progression was the development and formulation of a precise definition of alcohol hangover, which distinguishes alcohol hangover from hangover symptoms or severity, which are subject to individual experience. Hangover symptoms are usually assessed only once or twice at fixed time points. New research demonstrated the temporal variability of alcohol hangover severity, suggesting that there are different types of hangovers, depending on their temporal variability of the presence and severity of specific individual hangover symptoms. More research into this area is warranted.

Using different research methodologies, several researchers reported on the cognitive and mood effects of the alcohol hangover. Given the small sample size, and great variability in methodologies of past hangover studies, a great progress in this area is the conductance of meta-analysis to aggregate and summarize the available data. Neurophysiological data on brain activity during alcohol hangover is scarce. In the 1970s, two studies with small samples sizes were conducted. Jarvilehto *et al.* [47] revealed that auditory evoked responses are suppressed during hangover, and Sainio *et al.* [48] demonstrated decreased alpha activity and increase of theta activity when measuring EEG in the hangover state. Fox *et al.* [49] did not find a significant effect on stimulus evaluation (P3 amplitude and latency), but a dose-related increase in N2 amplitude (maybe related to sleepiness during hangover) was evident in their assessments of brain activity. At the current meeting, new data confirmed cognitive slowing and increased mental demands during the hangover state, which could be linked to specific brain areas and electroencephalographic activity (*i.e.* specific components of event-related potentials). Future research in this area is needed, preferably combined with other brain imaging techniques such as MRI.

Data was presented showing that hangover resistant drinkers do not differ from hangover sensitive drinkers in the temporal changes in BrAC after an alcohol challenge. As no significant differences were observed in peak BrAC and time to return to a BrAC of zero, these assessments suggest that the groups do not differ in alcohol metabolism. Also, other research presented at the AHRG meeting revealed that hangover resistant and hangover sensitive drinkers both show a similar immune response to heavy alcohol. As this immune response, *i.e.*, the increased presence of cytokines, has been suggested to provoke a hangover, it is unclear why this is also seen in drinkers who claim to be hangover resistant. Future research is needed to understand to what extent hangover sensitive drinkers differ from hangover resistant drinkers.

The negative health, social and economic consequences due to hangover were highlighted and utilized to emphasize the need of a cure. In this context, the immune response to alcohol intoxication was discussed, as well as the possible role of Non-Steroid Anti-Inflammatory Drugs (NSAIDs) and H1-receptor antagonists in the prevention or treatment of the alcohol hangover. An *in vitro* model to provoke gut cell cytokine production by alcohol, developed at Utrecht University, will be used in future research to determine whether NSAIDs and antihistamine drugs are capable of counteracting the immune response to alcohol. Once successful, a logic next step would be to test these drugs as possible hangover treatment in humans.

Taken together, at the 9th Alcohol Hangover Research Group Meeting a variety of important new research topics were discussed. Over the past year significant progress has been made to enhance the research field. New international collaborations were set-up to further strengthen research in the field of alcohol hangover.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Sarah Benson has received funding from Red Bull GmbH. Jacqueline Iversen is the Head of Clinical Development of Sen-Jam Pharmaceutical. Sean Johnson has undertaken sponsored research for Pfizer, AstraZeneca, Merck, Gilead, Novartis, Roche, Red Bull GmbH, The Department for Transport, and Road Safety Trust. Andrew Scholey has held research grants from Abbott Nutriton, Arla Foods, Bayer Healthcare, Cognis, Cyvex, GlaxoSmithKline, Naturex, Nestlé, Martek, Masterfoods, Wrigley, and has acted as a consultant/expert advisor to Abbott Nutrition, Barilla, Bayer Healthcare, Danone, Flordis, GlaxoSmithKline Healthcare, Masterfoods, Martek, Novartis, Unilever, and Wrigley. Joris Verster has received grants/research support from the Dutch Ministry of Infrastructure and the Environment, Janssen Research and Development, Nutricia, Red Bull, Sequential, and Takeda, and has acted as a consultant for the Canadian Beverage Association, Centraal Bureau Drogisterijbedrijven, Coleman Frost, Danone, Deenox, Eisai, Janssen, Jazz, Purdue, Red Bull, Sanofi-Aventis, Sen-Jam Pharmaceutical, Sepracor, Takeda, Transcept, Trimbos Institute, and Vital Beverages. The other authors have no potential conflicts of interest to disclose.

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