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ARTIGO DE REVISÃO/REVIEW ARTICLE

Does Fat Bingeing Increase Ethanol Consumption in Adolescents?
O Consumo Alcoólico Estará Aumentado em Adolescentes com Fat Bingeing?

JOÃO MARQUES*[1], ISABEL BRANDÃO[2]
1. Master's degree in medicine, at Faculty of Medicine of Porto University, Porto, Portugal
2. PhD, Member of the Clinical Neurosciences and Mental Health Department, at Faculty of Medicine of Porto University, Porto, Portugal

Abstract
Evidence has been suggesting that neurochemical and behavioral adaptations emerging during one addictive behavior may enable a subsequent, different, addiction, even when the first one has ended. Such association seems remarkably accurate to fat bingeing and ethanol consumption, which constitute a relevant example of addictive patterns sequential association, particularly in adolescence.
Therefore, the main purpose of the following review is to comprehend if adolescents who have engaged on fat bingeing escalated their ethanol consumption, after fat bingeing terminus, and secondly, in a positive scenario, to highlight why such association may happen.
After searching databases such as MEDLINE (PubMed) and Clarivate Analytics Web of Science, all articles focused on adolescent humans or adolescent rats or adolescent mice, that included topics on fat bingeing and consequent ethanol consumption, were considered.
Gathered results strengthened the referred hypothesis. Reports stating that adolescent fat bingers engage on escalated ethanol consumption were fundamentally supported by a prevalent fast food and ethanol cultures, bingers 'shared personality traits, adolescence 'susceptibilities for addictive behaviors and neurochemical and behavioral craving installment after fat bingeing cessation.
Given that adolescence is a key structural and functional phase of human development, and that fat and ethanol consumption are linked to harmful physiological and social effects, priority must be given to multidisciplinary interventions aiming to challenge addictions, both pharmacologically and psychotherapeutically.

Resumo
A evidência tem sugerido que existem alterações, de índole neuroquímica e comportamental, que ocorrem durante uma perturbação aditiva e que propiciam uma perturbação aditiva subsequente, inclusive após a primeira ter terminado. Esta associação, entre dependências de substâncias, parece ser bastante representativa para *fat bingeing* e consumo alcoólico, que constituem, então, um exemplo representativo de associação sequencial entre perturbações aditivas, particularmente na adolescência.
Assim, o objetivo principal da seguinte revisão é verificar se adolescentes com *fat bingeing*, tiveram aumento do consumo alcoólico, após término do *fat bingeing*, e num cenário positivo, compreender porque é que tal associação acontece.
Depois de uma pesquisa em bases de dados, como a MEDLINE (PubMed) e a Clarivate Analytics Web of Science, foram considerados os artigos que incluíram *fat bingeing* e consumo alcoólico em adolescentes, quer humanos quer ratos.
Os resultados reunidos defendem fortemente a hipótese questionada. Os diferentes estudos, que afirmaram que adolescentes com fat bingeing têm consumo alcoólico aumentado, baseiam-se, fundamentalmente: na vigente cultura de *fat food* e consumo alcoólico, nos traços de personalidade transversais a doentes com dependência de substâncias, nas

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* Autor Correspondente/Corresponding Author: João Filipe Saraiva Marques | Joaofsm1995gmail.com | Avenida Dr. Artur Melo e Castro, Bloco C, nº 67, 4º andar, esquerdo/traseiras, 4630-204, Marco de Canaveses | ORCID: 0000-0002-9057-5590
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suscetibilidades inerentes à própria adolescência para dependência, e na instalação neuroquímica e comportamental de *craving*, após a cessação de *fat bingeing*.
Tendo em conta que a adolescência é uma fase chave no desenvolvimento estrutural e funcional do ser humano, e conhecendo os efeitos pejorativos, fisiológicos e sociais, do fat bingeing e do consumo alcoólico, é recomendado que seja dada prioridade a intervenções multidisciplinares, de nível psicoterapêutico e farmacológico, que possam combater as perturbações consideradas.

Keywords: Adolescent; Alcohol Drinking; Binge-Eating Disorder; Dietary Fats

Palavras-chave: Adolescente; Consumo de Bebidas Alcoólicas; Gorduras na Dieta; Transtorno da Compulsão Alimentar

INTRODUCTION

Over the past years, evidence specified numerous behavioral and neurochemical adaptations simultaneously occurring among different addictive patterns. Such adaptations increase the probability of one addictive behavior leading to another, even after the original has ended.[1] Fat bingeing has been an addictive pattern increasingly studied that leads to other addictions. Particularly, fat bingeing and escalated ethanol consumption constitute a pivotal example of addictive patterns co-dependence. [2,3]

The main purpose of this review is to understand if adolescents who have engaged on fat bingeing escalated their ethanol consumption, after fat bingeing terminus and, secondly, in a positive scenario, to highlight why such association may happen. Binge eating can be addressed as episodes or a disorder. Episodes are defined by people eating amounts of food larger than normal, within a short period of time, while experiencing loss of control. On the other hand, binge eating can be faced as a disorder, defined by DSM-5 criteria. Binge eating disorder (BED) criteria is well-suited to represent both the episodes and the disorder itself. Likewise, ethanol consumption may be differently addressed. DSM-5 addresses it as "ethanol use disorder", including dependence and abuse, whereas ethanol consumption can be interpreted as episode drinking (binge drinking).[4] Although definitions concerning how many drinks constitute binge vary, the most used specify five or more consecutive drinks, per episode, for men, and four or more drinks, for women, in a 2-hour period. Adolescence is the period when most binge behaviors begin (peaking between 14 and 19 years), shared among the same peer network, and when binge behaviors' correlation is maximized.[5,6] Therefore, it is fundamental to tackle bingeing during adolescence. Prevalence and incidence of eating disorders are globally increasing. Statistics differ between binge eating episodes and BED. Binge episodes affect are more common in women.[7] Whereas BED, unlike others eating disorders, is documented equally among both males and females.[8] According to the World Mental Health (WHO) Surveys, prevalence of BED is 0.8%–1.9%. Although the prevalence of ethanol consumption is at historic lows, it continues to be adolescents' first choice of substances of abuse. Approximately 20% to 50% of American and European adolescents engage in binge drinking episodes, and approximately 33% of them evolve to an ethanol use disorder.[9]

Of note, evidence already gathered is prominently based on adult population and focus on binge for a display of substances, instead of ethanol exclusively, and in general binge eating, or sugar bingeing, instead of fat bingeing exclusively. Consequently, reviewing literature to collect information about fat bingeing and ethanol consumption in adolescents is essential.

METHODOLOGY

Research was initiated in database MEDLINE (PubMed), using the PubMed search builder: ("Binge-Eating Disorder"[Mesh]) AND ("Diet, High-Fat"[Mesh]) AND ("Ethanol"[Mesh])). Part of the considered studies were also enlisted in other databases, such as Clarivate Analytics Web of Science.

English, Spanish and Portuguese written articles, focused on adolescent humans or adolescent rats or adolescent mice (both groups will be addressed as rats), published from 1988 to 2018, were considered. All considered studies were filtrated according to exclusion criteria. Studies that did not include human adolescents (10-19 years of age) or did not include adolescent rats (living between days 35 to 55 post-born) were excluded. Studies that did not include fat bingeing, but only other types of binge eating, and did not include ethanol, but only other substances, were excluded. Articles focused on escalated fat consumption in previous ethanol consumers (reverse relation) were excluded. Also, articles that included ethanol and fat bingeing occurring at the same time were excluded: fat bingeing had to be concluded, by the time of escalated ethanol consumption (Fig. 1). After application of exclusion criteria, 3 articles were eliminated after title reading, 7 articles were eliminated after abstract reading and 2 were eliminated after methodology reading. Three articles were not found available. This search narrowing lead to the final inclusion of 63 articles.

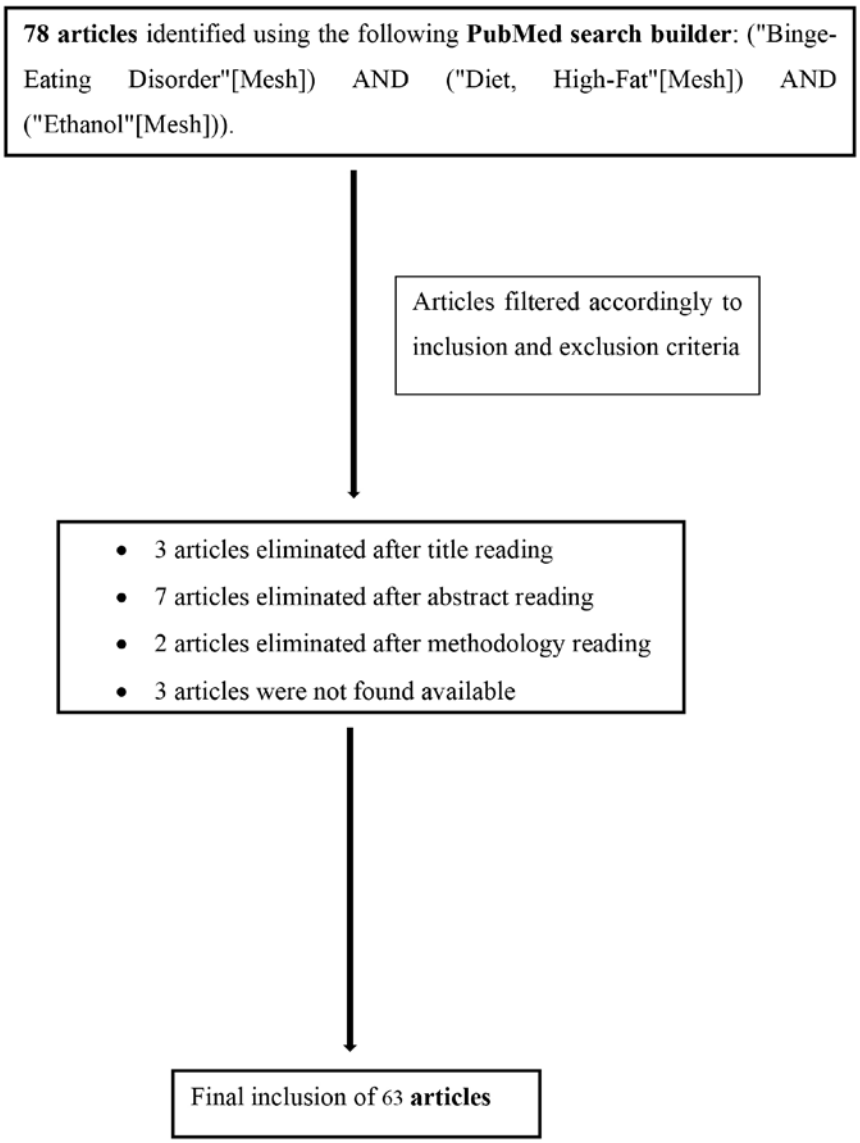

Figure 1. Methodology

RESULTS

a. Evidence highlighting the association

Evidence strengthened the hypothesis that fat bingeing increases adolescents' ethanol consumption. In 1994, a temporal-association between addictive patterns was documented in 51 samples (each one containing dozens of patients with eat and drink bingeing), from 51 analytic observational studies. It pinpointed that more than one additive pattern tends to appear in susceptible people.[10] In 1997, researchers found that engaging in various addictive substances elicits a future addiction, even when the first has ceased, and that earlier beginners are more prone to future addictions.[11] Evidence narrowed in subsequent years. In 2015, an epidemiologic study conducted on russian adolescents supported a bidirectional relation between fat ingestion and ethanol consumption. Such intakes are common amongst Russian adolescents.[12] To ascertain if these two behaviors were correlated, a 2003 school-based survey to 6th to 10th grade students was carried out in Arkhangelsk, Russia. A total of 2488 adolescents, with ages from 12 to 17 years old, were asked about drinking and eating, timely-separated, patterns. Information was collected regarding various eating problems, particularly fat bingeing, and binge drinking (5 or more drinks in a row), and a bidirectional correlation was found based on a logistic regression model. The prevalence of binge drinking was almost the same among females (42.8%) and males (40.4%) Regarding eat bingeing episodes, gender differences were found, with female overrepresentation. Results also determined that binge drinking and eating prevalence increase with age. A similarity between Russian and American adolescents' dietary habits had been previously confirmed.[13] Recently, investigation focused on experimental studies, on adolescent rats. Of note, a 2004 experimental study[14] has already proved that animals

addiction resembles human addiction, behaviorally and neurochemically. Drug self-administration (SA) protocol was used to study 17 rats' addictions. SA was observed for 3 months, in 40-minutes daily sessions (usually, SA protocols last 10-30 days). During this period, three hallmarks of addiction were verified. Firstly, rats had difficult stopping the drug. Secondly, rats were motivated in drug taking, augmenting activities aiming its consumption. Thirdly, despite harmful consequences (electric shocks) substance use was continued. To approach all the dimensions of addiction, propensity for relapses was also analyzed. After a 30-day withdrawal period, rats were exposed to a stimuli that induces relapse in humans - a smaller quantity of the consumed substance- which induced consumption reinstatement. Like humans, rats developed the three key aspects of addiction and relapse propensity. Subsequent experimental studies on rats have been mostly conducted in 2016, 2017 and 2018. The 2016 experiment induced adolescent rats into fat bingeing and ascertained what neurochemical changes have appeared.[15] Methodologically, rats were divided into four groups (10 rats each group): control and experimental males and control and experimental females. For 12 weeks, experimental groups were exposed to a daily dose-controlled fat diet, while control groups were given a dose-controlled standard diet (chow). After the 12-week period, for 8 days, besides the initial diets, experimental and control rats begin to have access to either limitless amounts of palatable fat or control diet, 1-hour per day. After the 8-days period, no male developed a binge pattern, whereas the female experimental group had greater consumption, compared to controls, becoming fat bingers. Weight, calories ingested, and abdominal fat pads' growth were documented to define a bingeing pattern. Dopamine genes expression was PCR-analyzed 4 weeks after the first evaluation. Gene studies were only conducted on female bingers that had their dopamine transporter (DAT) expression increased, while their tyrosine hydroxylase (TH) expression decreased. Both alterations did not normalize after a 4 week- limitless-fat removal period. In the nucleus accumbens, dopamine receptor D1 (DRD1) expression decreased, but increased after the 4-week fat removal period, while dopamine receptor D2 (DRD2) expression decreased but did not normalize. In pre-frontal cortex, dopamine levels have increased. A 2017 and a 2018 experimental studies expanded the 2016 results, adding that fat bingeing stimulates ethanol rewarding effects, mimicked by standard behavioral tests.[16, 17] Corwin's model was both used in 2016, 2017 and 2018 studies.[18] Such model uses time-limited access to limitless amounts of fat food to induce bingeing in non-deprived animals (bingeing is derived from hedonic, rather than metabolic needs). Since human binge eating is not driven by metabolic needs, exposure of satiated rats to palatable stimuli has been used as a bingeing model. Humans typically binge on foods to which they have access for a limited period. So, time-limited access to unrestrained of food access has shown to increase subsequent consumption, in controlled laboratory settings.[19] Like in 2016, experimental and control rats had time-limited food access, (fat and chow, respectively) before evaluation by behavioral tests. Thus, as expected, experimental rats were already fat bingers when behavioral tests were performed: exactly two weeks after fat bingeing pattern has been defined. Tests included ethanol self-administration (SA) paradigm, conditioned place preference (CPP) and locomotor sensitization. In SA paradigm rats learn to press a lever when they want a reinforcer (ethanol). CPP ascertains if environmental cues enhance motivation for ethanol consumption. Locomotor sensitization evaluates the existence of drug-induced locomotor activity. Rats from the 2017 study exposed to the Corwin's model protocol (experimental group) developed a binge pattern.[16] Of a total of 115 rats, 36 were allocated to SA protocol, and 79 were allocated to the CPP and Locomotor Sensitization protocols (for each test, the subsamples were divided in experimental and control groups). Fat bingers who underwent ethanol SA presented greater ethanol consumption. Bingers also presented preference for the "fat-food compartment", in the CPP, with subthreshold ethanol doses. Ethanol-induced locomotor sensitization was also found. In the 2018 study, 116 rats were, again, divided in experimental and control groups and were allocated to all the three behavioral tests.[17] Results were statistically significant: rats increased ethanol consumption and showed increased locomotor response. However, in this study, no effects were observed in CCP. Besides the referred experiments, a human's brain imaging study (a [^{11}C] *raclopride* scintigraphy) has been conducted, showing that food-evoked dopamine levels are increased in BED.[20] Such study compared 10 individuals with BED against 8 control individuals. The evaluation occurred after an oral methylphenidate (MPH) intake. MPH blocks dopamine reuptake transporter, amplifying dopamine signal. When MPH was given, food stimuli increased dopamine in dorsal striatum (caudate and putamen), only in binge eaters. This happened after olfactory and visual food presentation. Binge eaters also showed greater responses in medial orbitofrontal cortex, while viewing food.

Reviewed evidence is synthetized in Table 1.

Table 1: Evidence highlighting the association: synthesis

Holderness, Brooks-Gunn, Warren, 1994	Aggregation of 51 observational studies describe an association between consumption of substances (ethanol included) and eat bingeing (fat bingeing included).
Grant, Dawson, 1997	Observational studies describe that engaging in an addictive substance elicit future addictions, even after the first has ceased.
Deroche-Gamonet, Belin, Piazza, 2004	Rats develop behavioral and neurochemical addictive, human-like, behaviors.
Wang *et al*, 2011	Human brains 'imaging studies verify that food stimuli increased dopamine release in dorsal striatum, in patients with binge eating disorder.
Stickley *et al*, 2015	A bidirectional association between fat ingestion and ethanol consumption, in 2488 Russian adolescents, using a logistic regression analysis, is ascertained.
Carlin *et al*, 2016	Female rats, fat-diet-familiarized, develop fat bingeing, after access to time-limited, unrestrained amounts of fat food. Fat bingers increase dopamine transporter (DAT) gene expression, have a persistent decrease of *DRD2* and tyrosine hydroxylase (TH) gene expression and have a sporadic decrease of *DRD1* gene expression.
Blanco-Gandia *et al*, 2017	Female rats, fat-diet-familiarized, develop fat bingeing, after access to time-limited, unrestrained amounts of fat food. Fat bingers are submitted to behavioral tests that describe escalated ethanol consumption. Ethanol self-administration: escalated consumption. Ethanol-induced locomotor sensitization: ascertained. Conditioned place preference: preference for the fat-paired compartment
Blanco-Gandia *et al*, 2018	Female rats, fat-diet-familiarized, develop fat bingeing, after access to time-limited, unrestrained amounts of fat food. Fat bingers are submitted to behavioral tests that describe escalated ethanol consumption. Ethanol self-administration: escalated consumption. Ethanol-induced locomotor sensitization: ascertained. Conditioned place preference: not verified.

b. Reasons why the association occurs

iii. Topic A: Common personality traits

Binge behaviors are associated to specific personality traits. Neuroticism, depression and anxiety are consistently identified in addicted adolescents.[21] Impulsivity, which comprehends personality "sub-traits" like urgency, lack of planning and lack of persistence, is also reported.[22] Subsequently, if an individual is prone to feel negative affect and tends to act impulsively, his bingeing risk is exponentiated. Adolescents also engage in bingeing to cope with levels of negative affect, a singularity labeled as "emotion or affect regulation".[23] Additionally, since bingers 'self-awareness is characterized by unflattering views of self, bingeing allows an self-awareness escape.[24] Research has attempted to elect what can directly predict binge patterns. While coping motives appear to be directly correlated, self-reported motives do not seem reliable.[25] Expectations that drinking or eating will bring some positive outcome may also play a role, by influencing personal motives, but do not directly predict bingeing. Expectancies may modulate the correlation between personality traits and bingeing behaviors.[26] People's relationships have often failed to produce the expected findings. So, while personality traits, impulsivity and copying motives directly predict bingeing engagement, people's relationships, personal reasons and expectations cannot be directly considered. All these predictors are commonly found on adolescents.

iv. Topic B: Adolescence, a critical period

Fat ingestion and ethanol consumption's correlation differs between adult and adolescents: ethanol intake is more attenuated in adult fat bingers.[27] To establish a successful adult life, adolescents increase socialization time and engage in risk-taking behaviors, motivated by seeking out new, rewarding stimuli.[28] Moderate levels of risk-taking creates socially competent adolescents, in contrast with abstainers and frequent risk-takers, for who excessive levels of risk taking can be harmful, leading to abusive consumption.[29]

Adolescence is marked by a sexual hormonal increase, but such hormonal modifications do not associate to emerging behaviors. On the contrary, cerebral changes are main contributors to behavioral modulation, turning adolescents vulnerable to environmental threats.[30] Adolescence is mostly characterized by neuronal loss: gray matter declines in volume and thickness.[31] Anatomic modifications are accompanied by neurotransmitter modulation, as glutamate and GABA inputs to pre-frontal cortex diminish, while dopamine transmission increases,

in a general fashion. Reward pathway is a particular area undergoing remodeling: it initiates in the mesencephalic ventral tegmental area, where it projects to the ventral striatum, subdivided in nucleus accumbens and olfactory tubercle, to the dorsal striatum, subdivided in caudate and putamen, to the cerebral amygdala, to the hippocampus, and to the pre-frontal cortex. Nucleus accumbens works initially, as a limbic-motor interface, in which learned associations of motivational significance are converted into goal-directed behaviors.[32] In contrast, dorsal striatum acts after learning acquisition (when behavior becomes automatic).[33] Post-mortem studies showed that dopamine levels in projections from prefrontal cortex to subcortical regions (e.g., striatum) increase from adolescence to adulthood, and that activity of the dopamine degrading enzyme catechol-O-methyltransferase (COMT) only increases in mid-adulthood.[34] So, dopamine modulation may account considerable responsibility for adolescent behavior. Recent magnetic resonance imaging (MRI) evidence showed greater ventral and dorsal striatum activation, dopamine--dependent, in adolescents, compared to children and adults, when anticipating a reward.[35] Adolescence is also marked by a delayed maturation of pre-frontal cortex, comparatively to a rapid limbic cortex maturation, involved in emotional processing. So, many decisions are made based on emotion and short-timed benefits.

v. Topic C: Behavioral changes emerging after fat bingeing

As ethanol abuse may be regarded as a fat abuse equivalent, it may be interpreted as relapse occurring during a fat withdrawal period. So, it is crucial to comprehend relapses, for which craving and stress are two major determinants.[36] The inherent risk inputted by these determinants is enhanced by psychiatric comorbidities, socioeconomic conditions and perceived drug availability. According to WHO, craving is a strong desire for a psychoactive substance. Craving may be positive (euphoria after ethanol consumption) or negative (dysphoria, depression and anxiety).[37,38] After fat bingeing cessation, ethanol consumption is combusted prominently by negative craving. Craving begins during substance consumption, and exponentiates after its terminus. Its initiation relies on the ethanol itself and environmental-cues paired with ethanol, which augment its consumption, by allowing the development of environment-dependent tolerance. The setting in which ethanol is taken gives rise to an "opponent process", which allows ethanol tolerance. This tolerance creates a state of "conditioned pseudo-withdrawal". Opponent responses are rapidly installed. Craving has already been designed in a clinical setting[38]: rats were placed in a maze, where they were given daily injections of ethanol, which worked out as an anxiolytic, counterbalancing the stress maze-induced. At 10 days of consecutive ethanol injections, however, a saline water injection was given, exponentiating rats 'anxiety-like behavior, which mimicked negative craving. Brain-derived neurotrophic factor (BDNF), (known to induce neuronal survival and development), increased expression plays a role in craving, enhancing the need to stimulate the reward pathway.[39] Dopamine D4 receptor (*DRD4*) gene's long allele is also associated with craving.[40] Stress is another major relapse determiner: ethanol abstinent-rats that receive intermittent stress-inducible shocks were more susceptible to consume ethanol.[41]

vi. Topic D: Neurochemically changes emerging after fat bingeing

Cannabinoid, opioid and dopaminergic systems, as well as hormones like ghrelin and orexin, contribute to escalate ethanol consumption in previous fat bingers.[16] Dopamine (DA), a predominant catecholaminergic neurotransmitter, controls locomotor activity, food intake, emotion and reward processing. So, due to chief adaptations in dopaminergic pathways, adolescents are more susceptible to develop binge patterns "DA-dependent". Both ethanol and fat food increase dopamine release in reward pathway.[42] Moreover, dopaminergic circuits are sensitive to orexin (OX) – a neuropeptide produced in lateral hypothalamus which increases food intake- and hormone ghrelin – produced in gastrointestinal tract, with similar effects. Orexin release is activated by fat food and ethanol consumption, but a pharmacological blockage of orexin 1 receptor fails to interrupt an escalating consumption. However, the beginning of consumption may be reduced by an orexin 1 receptor antagonist. Initial consumption may require an orexin 1 receptor signaling, but not its escalation.[43] Fat and ethanol intake increase after hypothalamic orexin injection, and ethanol craving reduces after peripheral administration of an orexin 1 receptor antagonist, which suggests OX enhance a positive feedback of dopaminergic activation between ethanol and fat.[44]

Opioid and cannabinoid systems act as dopaminergic system modulators.[45-47] CB1 receptor (CB1r) - best known for its reward properties - is expressed on the ventral tegmental area and the nucleus accumbens' dopaminergic neurons (direct modulation), as well as on GABAergic and glutamatergic axon terminals, that synapses with dopaminergic neurons (indirect modulation, by inhibition). Opioid and dopaminergic systems are also interdependent. Binding of an opioid ligand to their receptors in ventral tegmental area inhibits GABAergic inhibitory interneurons, which synapse on dopamine cells projecting to the nucleus accumbens, thus increasing activity of dopaminergic neurons.[46] Opioid and cannabinoid systems are overactivated after fat ingestion acting together to enhance the mesolimbic dopaminergic circuit.[46] When fat ingestion stops, the dopaminergic, opioid and cannabinoid inputs drop, which is perceived as negative craving (thus inducing ethanol consumption). Subsequent ethanol consumption exponentiate the same neurochemical circuits, creating again a vicious circle of positive feedback. The knowledge can have a therapeutic impact. Stimulation of alcohol intake by CB1r agonists is blocked by administration of SR141716 – a CB1R antagonist- or naloxone, an opioid antagonist. Chronic administration of Δ9-THC– a cannabinoid agonist - increases the synthesis of hypothalamic proopiomelanocortin, which induces the release of endogenous opioids, like prodynorphin and proenkephalin, that are linked to dopamine release.[48] Furthermore, administration of the

CB1 antagonist SR141716 reduces the rewarding effects of morphine -opioid agonist- and its effects on dopaminergic release.[49] Mu-opioid receptor (MOr), and cannabinoid 1 receptor (CB1r) gene expression in rats' nucleus accumbens decreases after fat bingeing and before ethanol consumption.[16] CB1r and MOr mRNA down-regulation can be explained as a response to increased cannabinoid and opioid levels (compensatory responses).[50] Concluding, neurochemical alterations are intertwined with craving: individuals in withdrawal suffer from low dopaminergic, cannabinoid and opioid input, and all it takes are small cues to reinitiate that lost input, through ethanol consumption. Additionally, circulating triglycerides (TGs) play a role correlating fat and ethanol intake. TGs increase proportionally to consumed fat, producing a short term stimulus on ethanol consumption, due to decreased levels of fat oxidation.[51] Ethanol also exponentiates circulating TGs, thus creating a vicious circle.[52]

DISCUSSION

Literature from last decades supports that fat bingeing induces escalated ethanol consumption, in adolescents, after fat bingeing has ended. Nonetheless, conclusions must be critically analyzed. Whereas the russian study added relevant information,[12] some considering must be well-thought-out. Researchers relied on adolescent's self--reports, without being able to verify their accuracy. Once more, ethanol bingeing definitions vary, which can lead to misestimations. Data reports to 2003 and today's russian consumption levels are lower, since binge drinking decreased between 2003 and 2011.[9] No more russian studies have been produce. The 2016 study showed that adolescents with regular fat-diets are more prone to develop fat bingeing, (through access to time-limited, unrestrained amounts of food), and that an addictive pattern results in dopaminergic changes.[15] Understanding which changes persist after a fat-consumption removal is fundamental to understand relapses. In the referred article, only female bingers were studied. Gender differences are controversy in literature: understanding if sex interacts with dopamine--gene expression is pivotal to tackle binge behaviors co-occurrence. Estrogen expression may justify genre differences, as estrogen metabolite 2-hydroxyestradiol increases binge eating.[53] The 2016 study demonstrated a D2DR and TH diminution, and a DAT expression increase. Plasma membrane dopamine transporter (DAT) transports dopamine in-and-out of terminals, increasing dopamine extracellular concentration. Tyrosine hydroxylase (TH) is a rate-limiting enzyme which synthetizes dopamine and is diminished in fat bingers to compensate overstimulation of dopaminergic pathways. DRD2 decrease is also a neuroadaptive response to food overconsumption.[54] DRD1 expression demands further analyzes. The 2017 and 2018 studies described enhanced ethanol consumption, and its rewarding effects, on fat bingers, using the SA, CPP and locomotor sensitization paradigms.[16,17] To evaluate SA, food-deprived rats (abstainers) were trained to access a substance by pressing a lever. Saccharin was used during training sessions and then gradually substituted to ethanol. It remains unclear if saccharine influenced ethanol consumption. CPP assesses rats' vulnerability to environmental stimuli. CPP has three phases.[55] Firstly, a pre-conditioning phase: experimental and control rats are distributed in a pair of compartments. During a conditioning phase, after access to fat-food, one half is injected with salt (control) and the other with ethanol. On alternate days, contingences are inverted: rats that received salt the day before were injected with ethanol and vice-versa, after being introduced into another compartment. Preference test is the ultimate phase, which demonstrates that fat bingers, when injected with ethanol, prefer the fat-food compartment. Ethanol locomotor sensitization shows an emerging behavioral or psychomotor sensitization, induced by ventral striatum.[56] Behavioral sensitization is an augmented motor-stimulant response, due to repeated exposure to a specific substance.[57]To ascertain locomotor sensitization, rats´ movements were recorded and translated to a horizontal distance traveled in centimeters, for 10 minutes. Augmented locomotor activity is long-lasting and can be seen after a one-year drug-free period. Thus, the 2017 and 2018 results suggest that even upon binge-eating interruption, adolescents continue more susceptible to ethanol consumption, comparing to their non-bingeing peers. Nonetheless, gender differences were not acknowledged. Also, both control and experimental groups were subdivided into small sample-sets, one of for each behavioral test, only. Another criticism that must be drawn is the insufficient two-week period used to separate fat bingeing initiation and behavioral tests performance. Real-life hiatus, between fat bingeing and ethanol consumption, appear to be much longer. In regards to the human-brain imaging study, MPH had to be used to enhance detection of dopamine.[20] So, a pharmacological interaction between MPH and a food stimulation response cannot be ruled out. Analyzes of adolescent behavior need to be substantiated by experimental approaches, to properly understand adolescence vulnerabilities. Not all can be accurately modeled in laboratory animals. Advances in imaging techniques will make adolescent human brain more accessible.

So, if data shows a positive correlation, what efforts should be made, to end this cycle? A holistic approach must be used. Cognitive-behavioral therapy and family- interventions should be undertaken. Pharmacological interventions can also modulate fat and drink binge patterns. For instances, acamprosate, know to work on disrupted ethanol--deprived individuals, may also work in fat-deprived individuals, preventing ethanol consumption initiation. Acamprosate may also tackle anxiety - a known craving engager.[58] Manipulating TG levels also affect ethanol consumption. By using fibrates lipoprotein lipase synthesis is increased, thus increasing clearance of TGs. Gemfibrozil has already been used to cause a suppression of circulating TG levels and ethanol intake. Besides lowering TG levels, gemfibrozil reduces orexin mRNA expression in lateral hypothalamus.[59] Ethanol decreased intake, gemfibrozil--mediated, may be consequence to a decrease in OX expression. Orexinergic input can also be counterbalanced

with orexin receptor antagonists, such Almorexant or Suvorexant. CB1r and mu opioid receptor blockade – naloxone or SR141716- play a role in drug seeking suppression as well, regardless the type of the abused substance.[16]

CONCLUSION

Fat bingeing enhances ethanol consumption, in adolescents, as a result of bingers 'personality traits, adolescence 'susceptibilities for addictive behaviors and neurochemical and behavioral modifications (craving) arising during fat bingeing and persisting after its terminus. The referred correlation must be terminated or at least, if an adolescent engages in fat bingeing, the prevention of subsequent ethanol consumption must be made. Literature is explicitly about the need to extinguish addictive behaviors: I) the synergism between eating and drinking disorders are a significant mortality risk factor among individuals with eating disorders[60]; II) alcohol influences the developing brain, which is shown by diminutions in neurocognitive functioning, especially attention, visuospatial functioning, and learning of verbal and nonverbal information[61]; III) ex-fat bingers experiencing craving may have increased reaction time, dysfunctional cognitive resource allocation, impaired working memory, and overestimation of intensity of negative feelings[62]; IV) finally, there may be potential reversibility of brain structural changes with long-term abstinence.[63]

Adolescence is a key structural and functional phase of human development. Therefore, future must be faced with a necessity of more experimental studies, on human subjects, with larger samples and longer periods between fat bingeing definition and performance of behavioral tests (which mimic enhanced ethanol consumption). Sex differences must be investigated, as well. Genetic studies on fat bingers have already been conducted, but they are required on ethanol consumers. Such studies much be accompanied by psychotherapeutic and pharmacologic (including pharmacogenetics) strategies, on an early state (before dorsal striatum learns acquisition), to tackle an increasingly prevalence of addictive patterns.

Responsabilidades Éticas

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