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Review article

Personality driven alcohol and drug abuse: New mechanisms revealed

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ABSTRACT

While the majority of the regular consumers of alcohol controls their consumption well over life span and even takes instrumentalization benefits from it, a minority, but yet high total number of users develops an alcohol addiction. It has long been known that particular personality types are more addiction prone than others. Here we review recent progress in the understanding of neurobiological pathways that determine personality and facilitate drug abuse. Novel approaches to characterize personality traits leading to addiction proneness in social settings in mice are discussed. A common genetic and neurobiological base for the behavioural traits of sensation seeking or a depressed phenotype and escalating alcohol consumption are reviewed. Furthermore, recent progress on how social and cognitive factors, including impulsivity and decision making, act at brain level to make an individual more vulnerable to alcohol abuse, are discussed. Altogether, this review provides an update on brain mechanisms underlying a broad spectrum of personality traits that make an individual more prone to alcohol and drug abuse and addiction.

1. Introduction

Alcohol use is a widely displayed behaviour in many human societies, which can develop into an abuse behaviour and addiction. Alcohol addiction is a very common psychiatric disorder with severe health consequences for the individual and detrimental effects for social environment and society (Wittchen et al., 2011). Although symptoms of alcohol addiction are by definition of current diagnostic manuals very similar among different individuals, there are different developmental pathways that shape the transition from controlled alcohol consumption, which is an accepted part of Western society culture (Müller and Schumann, 2011a,b, Müller and Schumann, 2011a,b; Müller, 2017), to abuse and addiction. A major factor for how alcohol interacts with an individual and imposes the risk of addiction development is the personality of the individual human being. It has been shown that individuals with different personality traits display distinct risks of establishing alcohol consumption, of instrumentalizing alcohol effects, and of addiction development (Conrod et al., 2006; Castellanos-Ryan et al., 2013; Whelan et al., 2014). Underlying neurobiological mechanisms for these relationships may be found in genetic/epigenetic factors (G), environmental factors (E), and a G x E interaction (Goldman et al., 2005; Stacey et al., 2016; Ruggeri et al., 2015). It was shown that genetic factors, such as DNA single nucleotide polymorphisms (SNPs) determine the chance of whether and at what age an individual starts

Abbreviations: ASM, acid sphingomyelinase; AUD, alcohol use disorder; DA, dopamine; DH, dorsal hippocampus; DNA, deoxyribonucleic acid; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; E, environmental factor; EFhd2, EF hand domain containing 2 protein (also known as Swiprosin-1); 5-HT, 5-hydroxytryptamine (serotonin); G, genetic factor; GABA, gamma-aminobutyric acid; KO, knock out; METH, methamphetamine; MyT1, Myelin Transcription Factor 1; MRI, magnetic resonance imaging; NA, noradrenaline; Nac, nucleus accumbens; PFC, prefrontal cortex; SNP, single nucleotide polymorphisms; SUD, substance use disorders; SURPS, Substance Use Risk Profile Scale; VTA, ventral tegmental area; WT, wild type

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with alcohol consumption (Spanagel et al., 2005; Desrivieres et al., 2011; Schumann et al., 2011, 2016; Stacey et al., 2012; Talukdar et al., 2016; Müller et al., 2019). These factors may determine how an individual instrumentalizes the alcohol in order to improve other, non-drug related behaviours or cope with environmental conditions (Bradizza et al., 1999; Clarke and Schumann, 2009; Dong et al., 2011). The same factors, but in other expression, determine the risk of alcohol addiction development and maintenance (Treutlein et al., 2006; Bleich et al., 2007; Blomeyer et al., 2008; Lenz et al., 2012; Wang et al., 2012; Easton et al., 2013; Müller and Homberg, 2015; Walters et al., 2018). It is important to note that the single steps of addiction development, and possibly also single addiction-related behaviours, are under the control of distinct genetic factors. As such, there appears little overlap between the factors that contribute to the establishment of drinking and those that contribute to the escalation of alcohol consumption and the transition to alcohol addiction. Independent from the genetic factors, there are non-pharmacological, environmental factors during development that contribute to the risk of alcohol addiction, such as the availability of different drugs, alternative rewarded behaviours, stress and adverse lifetime events (Ahmed et al., 2020). In addition, those factors may individually contribute to the distinct stages of addiction development. Since the behaviour of an individual is throughout the whole life span genetically determined as well as under environmental, social and cultural influence (Bierut et al., 1998; Müller, 2020), there is also a causal factor that results from the G x E interaction (Blomeyer et al., 2008; Clarke and Schumann, 2009).

The concept of personality allows to group individual humans and animals according to their displayed behaviour to better predict future behaviours. This is based on the observation of personality clusters. Human beings do not show completely unique behavioural profiles, but groups of people appear to share certain behavioural traits. It is assumed that the similarity in behavioural traits results from shared neurobiological traits. This may apply for normal behaviours, but can also be useful to predict the risk of psychiatric disorders (Kalinichenko et al., 2019). For alcohol use, abuse and addiction, previously defined personality dimensions had been used and tested for whether they allow a prediction of how an individual may develop alcohol use, abuse and addiction.

Personality traits associate with alcohol use and addiction are sensation seeking, impulsivity, hopelessness, and anxiety sensitivity (Castellanos-Ryan and Conrod, 2012; Pihl and Peterson, 1995). Sensation seeking/novelty seeking is characterized by low tolerance to boredom, a strong need for stimulation, and a willingness to take risks for the sake of having novel and varied experiences, and low trait anxiety in novel environments (Arnett, 1994; Zuckerman, 1996). High sensation seeking is associated with drug and alcohol abuse in general (Earleywine and Finn, 1991; Magid et al., 2007), and an early onset of alcohol use in particular (Dom et al., 2006). Impulsivity is a trait that comprises diminished reflectiveness, rapid decision making and action, and a failure to inhibit a behaviour (Baumeister and Vohs, 2004). Impulsivity is also associated with externalizing and conduct problems in general (Krueger et al., 2002; Tremblay et al., 1994; Khan et al., 2005). In addition, hopelessness is associated with alcohol abuse and addiction. This trait is also linked to self-reported drug instrumentalization in order to cope with anxiety and depression (Woicik et al., 2009; Müller, 2020). Anxiety sensitivity describes the fear of anxiety-related physical sensations with disastrous consequences (Reiss et al., 1986). It is also linked to negative reinforcing effects of psychoactive drugs (Stewart and Kushner, 2001) and alcohol abuse problems (Conrod et al., 1998; Castellanos-Ryan et al., 2013).

2. Measuring personality traits and alcohol use and addiction in animal models

Recreational use of alcohol is widespread, yet, only a minority of individuals develops alcohol use disorder (AUD) (American Psychiatric Association, 2013). According to WHO, the prevalence of AUD in Europe is estimated to 14.8 % and 3.5 % among men and women respectively (WHO, 2018). It is therefore clinically relevant to elucidate which factor characteristics predispose individuals to lose control over alcohol use and ultimately develop addiction. Human studies indicate that certain personality traits, such as high impulsivity (Verdejo-Garcia and Clark, 2008; Kreek et al., 2005; Lejuez et al., 2010; Moeller et al., 2001; Whelan et al., 2014), novelty and sensation seeking (Aliev et al., 2015; Cloninger et al., 1995; Ducci et al., 2007; Howard et al., 1997; Kreek et al., 2005; Lange et al., 2010; Lukasiewicz et al., 2008) and anxiety (Kreek et al., 2005; Kushner et al., 2000) are serious risk factors for alcohol use early in live and development of AUD. Still debatable is whether these traits predict vulnerability to addiction or are induced by prolonged alcohol use. The research on animal models of alcohol use may help to answer this question. The experimental data gathered to date the most extensively describe a cocaine addiction-prone phenotype in rats (Belin-Rauscent et al., 2016; Belin et al., 2008; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). This phenotype may be, however, very different from the phenotypes susceptible to compulsive use of alcohol or other drugs (McNamara et al., 2010). Thus, great effort have been made to identify and characterize alcohol-prone phenotypes in mice and rats (Augier et al., 2018; Barrenha and Chester, 2007; Correia et al., 2009; Fee et al., 2004; Kliethermes et al., 2007; Logue et al., 1998; Meyer et al., 2010; Oberlin and Grahame, 2009; Radwanska and Kaczmarek, 2012; Wilhelm et al., 2007) and to develop animal models that mimic different aspects of human alcohol dependence (Augier et al., 2018; Radwanska and Kaczmarek, 2012; Spanagel, 2009; Spanagel and Hölter, 2000; Vengeliene et al., 2009). Identifying behavioural traits that predispose to compulsive alcohol drinking in laboratory animals could narrow down the neural and molecular substrates of alcoholism and provide models to develop and test new therapies for this disease. Here, we review the studies questioning whether three main personality traits linked with AUD in people - impulsivity, novelty seeking and anxiety, predispose to alcohol use and AUD in animal models.

2.1. High impulsivity

Research suggests that people with impulsive, risk-taking personality are more prone to develop addiction (Verdejo-Garcia and Clark, 2008; Ersche et al., 2010; Kreek et al., 2005; Moeller et al., 2001). Animal studies, in which human impulsivity was operationalized as a diminished ability to delay action before performing an appropriate response (impulsive action) (Dalley et al., 2011; Dick et al., 2010; Fineberg et al., 2010; Perry and Carroll, 2008), also supported this notion. High impulsivity in rats predicted escalation of cocaine intake during extended access to the drug (Dalley et al., 2007), compulsive cocaine self-administration (Belin et al., 2008) and relapse to cocaine use after protracted abstinence (Economidou et al., 2009). Similarly, both in rats and mice exposed to alcohol self-administration, high impulsivity score predicted increased ethanol consumption (Hammerslag et al., 2019; Loos et al., 2013; O'Tousa et al., 2015; Poulos et al., 1995; Sanchez-Roige et al., 2014). A significant correlation between impulsivity and ethanol consumption was found in 13 inbred strains of mice (Logue et al., 1998) as well as in the protein kinase C gamma null mutant mice (Bowers and Wehner, 2001) and $GABA_A$ receptor subunit, ɣ2, knockout mice (Stojakovic et al., 2018). Mice and rats selectively bred for high alcohol consumption exhibited higher choice impulsivity and increased risk-taking (Oberlin and Grahame, 2009), as well as impaired response inhibition (Wilhelm et al., 2007). (-)-OSU6162 (OSU6162) is a monoamine stabilizer, which stabilizes dopaminergic activity depending on the prevailing dopaminergic tone. OSU6162 improved motor impulse control, attenuated voluntary alcohol consumption, operant alcohol self-administration, alcohol withdrawal symptoms and cue-induced reinstatement of alcohol seeking in rats (Fredriksson et al., 2019; Steensland et al., 2012). To test the

correlation between impulsivity and AUD in mice, a behavioural screening protocol was designed in the IntelliCage system (TSE Systems, Bad Homburg, Germany). It measured impulsive action, as the premature responses produced before signaled reward availability, and addiction-related behaviors defined by DSM-5 (American Psychiatric Association, 2013). These included the high motivation for persistent and compulsive alcohol seeking and alcohol intake, even when an individual was subjected to punishment. It also covered the relapse after alcohol withdrawal. This study supported earlier findings and demonstrated that high impulsivity predisposes to high alcohol drinking and addicted phenotype in mice (Radwanska and Kaczmarek, 2012). Contrary to cocaine use and alcohol consumption, high impulsivity in rats did not predict the escalation of heroin self-administration (McNamara et al., 2010), indicating possibly different vulnerability mechanisms underlying opioid addiction.

2.2. Sensation seeking/ novelty seeking

Novelty seeking, defined as the seeking of a novel and intense experience and sensations, is a crucial vulnerability factor for alcoholics (Cloninger et al., 1995; Ducci et al., 2007; Ersche et al., 2010; Howard et al., 1997; Lange et al., 2010; Lukasiewicz et al., 2008). In animal studies, this human trait was operationalized either as novelty-induced locomotor activity or as novelty-induced place preference. The role of novelty seeking as a risk factor in alcohol use has been only partially replicated in animal studies. Novelty-induced locomotor activity was shown to be a predictor of either the cocaine use- or alcohol use-prone phenotype, and novelty-induced place preference has been shown to be a predictor of the cocaine addiction-prone phenotype in rats (Belin et al., 2011; Nadal et al., 2002). Other studies found, however, no correlation between the novelty-seeking trait and alcohol drinking and amphetamine use in mice and rats (Kliethermes et al., 2007; Meyer et al., 2010). In experiments in which novelty-induced activity was measured as the number of exploratory visits to the corners during the first hour in the novel IntelliCage system, mice with a lower novelty-seeking trait were later diagnosed with higher addiction scores (Radwanska and Kaczmarek, 2012). This finding contrasts with the previous studies of alcohol- and cocaine-taking rats (Belin et al., 2011; Nadal et al., 2002) and may indicate important differences in the mechanisms leading to compulsive drug taking in rats and mice.

2.3. High anxiety

Compulsive, out-of-control alcohol use despite adverse consequences is a hallmark of AUD (American Psychiatric Association, 2013). Alcohol use disorders are often co-morbid with anxiety disorders in humans (Ducci et al., 2007; Kessler et al., 1997; Kushner et al., 2000; Kushner and Sher, 1990; Low et al., 2008), and with obsessive-compulsive disorder occurring most frequently (Echeburúa et al., 2005; Regier et al., 1990). In animal studies, the anxiety trait was operationalized as a reaction to stressful factors (high ultrasound vocalization in reaction to electric shock or air puff) (Naito et al., 2003; Sánchez, 2003), a tendency to avoid stressful situations (low exploration of open or brightly lit areas in the open field test, elevated mazes, or the light/dark transfer test) (Pawlak et al., 2008; Ramos, 2008), or suppression of feeding behavior in response to stressful situation (novelty induced suppression of feeding) (Bodnoff et al., 1988). The link between anxiety and alcohol consumption was only partially confirmed by animal studies. No correlation was found between anxiety level in mice and their preference for ethanol intake (Barkley-Levenson and Crabbe, 2015; Correia et al., 2009; Fee et al., 2004). However, mice selectively bred for high alcohol preference showed greater fear-potentiated startle than mice selectively bred for low alcohol preference (Barrenha and Chester, 2007). Moreover, prenatal and adolescent stress and social isolation led to increased anxiety and alcohol consumption in animal models (Caruso et al., 2018; Dong et al., 2018; Evans et al., 2019; Moonat et al., 2013; Rodriguez-Arias et al., 2016), while an enriched environment, which has anxiolytic effects (Ragu Varman and Rajan, 2015; Sztainberg et al., 2010), reduced compulsive drinking (Rodríguez-Ortega et al., 2018). The overexpression of the Myelin Transcription Factor 1 (MyT1) in the dentate gyrus attenuated anxiety-related behaviors in the elevated plus maze and open field test. It also reduced ethanol intake and preference in rats (Bahi and Dreyer, 2017). Based on the classic model, anxiety-related resistance to punishment was measured in the IntelliCage, by calculating the reduction in sucrose consumption when it was associated with anxiogenic air-puff punishment (Radwanska and Kaczmarek, 2012). High anxiety predicted an increased alcohol consumption and a high addiction score. Additionally, it was found that high persistence in sucrose seeking during signaled sucrose non-availability, which resembles compulsive behaviors (repetitive and inflexible), also precedes high alcohol drinking (Radwanska and Kaczmarek, 2012). Thus, these data indicate that a high level of anxiety-related traits and compulsive behavior may be a critical factor that drives animal compulsive alcohol consumption.

Importantly, the analogy exists between the human and animal studies as far as the role of brain circuits that control compulsive alcohol consumption is concerned. In human fMRI studies, impaired response inhibition was correlated with the function of fronto-striatal circuitry and is predictive of future compulsive alcohol use in adolescents (Mahmood et al., 2013; Whelan et al., 2014). Similar findings were observed in binge-drinking mice, as the activity pattern of medial prefrontal cortex neurons projecting to the brainstem was shown to be predictive of compulsive alcohol self-administration (Siciliano et al., 2019).

Altogether, research in animals indicates that high levels of anxiety-related traits, e.g. low novelty seeking, low resistance to punishment and a high level of compulsive behaviours, and possibly high impulsivity may readily predict addiction-like alcohol drinking. However, the drug use-prone phenotype was not fully consistent across different species and drugs of abuse. Thus, it is important to acknowledge both genetic predispositions and epigenetic effects that may underlie vulnerability to different drugs of abuse.

3. Impulsivity as a neurocognitive marker for alcohol use disorders

Over the last decades, much research has focussed on uncovering risk factors that may predispose to SUD and AUD. In this regard, there is growing evidence that deficits in cognitive functioning play a key role in the development, the course, and relapse to use in SUD and AUD.

Indeed, cognitive impairments including impaired behavioural control have consistently been found in AUD, and diminished cognitive functioning in AUD has been related to reduced treatment response and early relapse (e.g. Bates et al., 2002, 2006; Finn et al., 1994). In further support of the idea that cognitive functioning is involved in the development of AUD, are the findings from several prospective studies that demonstrate a strong association between diminished behavioural control capacities in early childhood years (ages 3–5) and problematic use of alcohol as well as other illicit drugs during adolescence (ages 15–17) (Nigg et al., 2006; Tarter et al., 2003; Wong et al., 2006). Thus, these studies suggest that the vulnerability for alcohol and drug abuse could already have its origin in childhood years and the poorer control over one's behaviour during that age could affect motivational processes later in life. In a sense, these data echo the ground breaking work of Walter Mischel, who demonstrated that delay of gratification behaviour in childhood years, is a stable trait that lasts through life and can influence motivational and cognitive functioning (Casey et al., 2011). A scientific explanation for the interrelationship between impaired cognitive functioning and substance abuse was postulated in an influential landmark paper by Jentsch and Taylor (1999). In this review, which generated much interest in this field of research, the authors argued that prolonged substance use leads to reduced frontal cortical

functioning, which in turn impairs behavioural control ultimately contributing to increased drug consumption and drug seeking behaviour. It is, therefore, perceivable that impaired control over behaviour as neurocognitive risk factor extends to various stages of the 'downward spiral' of SUD and AUD, including the onset and maintenance of these disorders (Winstanley et al., 2010).

From a broader perspective, diminished behavioural control, i.e. the control over one's behaviour, is an expression of increased impulsivity. There is general agreement that impulsivity as a behavioural construct consists of distinct forms and accompanying behavioural expressions with (partly) separable neuroanatomical circuits and neurochemical pathways (see for reviews, e.g. Evenden, 1999; Dalley and Robbins, 2017; Moeller et al., 2001; Pattij and Vanderschuren, 2008; Winstanley, 2011). One important form of impulsivity is the ability to inhibit/ withhold behavioural responses or to cancel ongoing behaviour. The overarching term that is oftentimes used for these behavioral expressions of impulsivity is impulsive action. An example of impulsive action in daily life is, for instance, the ability to withhold speaking before one's term. On the other hand, impulsivity can also result from altered decision making and a changed evaluation of the outcome of one's behaviour. This form of impulsivity is mostly referred to as impulsive choice, and often captured by delay aversion, i.e. the increased preference for short-term outcomes/results over reduced preference for delayed and more beneficial outcomes of behaviour. A daily life example of impulsive choice is, for instance, postponing or avoiding the periodical visit to the dentist. On the short term, this could provide relief, but on the long term, it may mean neglected teeth and an according unpleasant treatment. Together, impulsive action and impulsive choice represent the main forms of impulsivity that will be referred to in this section (although one can also distinguish forms of 'stopping' and 'waiting' impulsivity, see e.g. Dalley and Robbins, 2017). Importantly, neuropsychological tasks in humans and translational animal models adopted from these tasks can be used to measure these different forms of impulsivity, and do so reliably across species (Broos et al., 2012). Whereas stop-signal tasks, Go-NoGo tasks and the translational 5-choice serial reaction time task are widely used to measure impulsive action in humans and animals, delay discounting tasks are mostly used to measure impulsive choice (e.g., Eagle and Baunez, 2010; Winstanley, 2011).

Over the last decade much work has been conducted to unravel the interrelationship between different forms of impulsive behaviour and SUD/ AUD (for reviews, see De Wit, 2009; Ersche and Dalley, 2019; Pattij and De Vries, 2013; Potenza and De Wit, 2010). In this regard, a recent review from this journal eloquently discussed the role of impulsivity in AUD (Herman and Duka, 2019). Indeed, in many clinical studies interrelationships between alcohol (ab)use according to DSM-5 and measures of impulsivity (e.g. with delay or effort discounting tasks) have been reported showing increased impulsivity in AUD. In addition, it was found that interventions that simultaneously change alcohol consumption and/or alcohol-related reactivity measures might reduce measures of impulsivity (e.g., Joos et al., 2013; Leeman et al., 2014; MacKillop et al., 2011; Petry, 2001; Phung et al., 2019). A limitation of these clinical findings is that it is difficult to infer causality, and for this purpose, translational animal models are highly suited to get a better understanding of the interrelationship between impulsivity and drug/ alcohol (ab)use. Particularly, animal studies can provide more insight into whether impulsivity predates the onset of drug/alcohol consumption and can further unravel neurobiological mechanisms.

As aforementioned, various animal models reliably measure impulsivity. To investigate aspects of drug/alcohol (ab)use, the volitional drug self-administration and reinstatement model of drug relapse is often used. In this model, animals self-administer drugs or alcohol and the model is able to measure several aspects of drug/alcohol consumption, including motivation to self-administer, drug sensitivity as well as extinction of drug seeking and cue-induced/ drug-induced relapse to drug seeking (Shaham et al., 2003). Most translational animal work has focussed on the interrelationship between impulsivity and self-administration of psychostimulant drugs such as cocaine, methylphenidate and nicotine. This collective work has convincingly shown that both impulsive action and impulsive choice predict drug seeking and –consumption, and relapse to drug seeking (Anker et al., 2009; Belin et al., 2008; Broos et al., 2012; Dalley et al., 2007; Diergaarde et al., 2008; Economidou et al., 2009; Marusich and Bardo, 2009; Perry et al., 2008). Interestingly, in addition to psychostimulant self-administration, impulsive action also has been found to predict sucrose consumption (Diergaarde et al., 2009). By striking contrast, the picture seems to be different for heroin, as several studies found that impulsive action and impulsive choice did not predict consumption and relapse of this drug (McNamara et al., 2010; Schippers et al., 2012). Altogether, a conclusion one can draw from this work is that elevated impulsivity is a neurocognitive risk factor for the onset of psychostimulant drug and sucrose self-administration, as well as the maintenance of this behaviour. A question that then arises is whether reducing impulsivity is an effective strategy for treating substance use disorder. Recent work demonstrated that, whereas impulsive choice strongly predicts relapse to cocaine seeking, acute pharmacological challenges with methylphenidate to decrease impulsive choice concurrently increased relapse to cocaine seeking in the same animals (Broos et al., 2012). Moreover, sub-chronic treatment with the noradrenaline reuptake inhibitor atomoxetine that has been shown to reduce impulsivity in rats (Robinson et al., 2008), was found to reduce relapse to cocaine seeking without concurrent effects on impulsive choice (Broos et al., 2015). Thus, these data stress the interrelationship between impulsivity and relapse vulnerability, and indicate that acute pharmacological treatment of (state) impulsive choice is not necessarily effective in suppressing the propensity to relapse. Perhaps behavioural approaches to reduce (trait) impulsivity, such as working memory training (Bickel et al., 2011; Stein et al., 2016) would be more effective in achieving this.

The interrelationship between impulsivity and alcohol self-administration from translational animal work is equivocal and has been less thoroughly studied. Early work has indeed supported this association and demonstrated that impulsive choice predicts alcohol consumption in rats (Poulos et al., 1995). Yet, later studies were not able to replicate these findings and found no evidence that impulsive action or impulsive choice predicts different aspects of alcohol self-administration and relapse (Diergaarde et al., 2012; Pattij et al., 2020; Stein et al., 2015). It is of interest, that behavioural genetic approaches in rats and mice more strongly indicate an interrelationship between impulsivity and alcohol consumption. For instance, as described earlier in this review, inbred mouse strains and recombinant strains of mice with an impulsive phenotype also had a higher preference for alcohol (Radwanska and Kaczmarek, 2012; Sanchez-Roige et al., 2014), consumed more alcohol (Logue et al., 1998; Loos et al., 2013), and displayed higher relapse to alcohol seeking (Loos et al., 2013). Moreover, selectively bred alcohol-preferring mice and rats were more impulsive in terms of impulsive choice (Oberlin and Grahame, 2009; Wilhelm and Mitchell, 2009) and to a lesser extent impulsive action (Wilhelm et al., 2007). Nonetheless, the latter finding were in contrast to other work that failed to report increased impulsive action in alcohol-preferring rats (McMillen et al., 1998; Peña-Oliver et al., 2015). Regarding these positive behavioural genetic data, it would be highly interesting to investigate whether the observed associations between impulsivity and alcohol reward can be attributed to shared or distinct genetic loci.

In conclusion, based on the available evidence to date the verdict is still out whether impulsivity is neurocognitive risk factor for AUD. There are certainly strong indications to suggest that reducing impulsivity could have beneficial effects in AUD (Leeman et al., 2014), which holds promise for novel therapeutic interventions for AUD. In this regard, the findings from behavioural genetic studies in translational animal models are encouraging and potentially will help to uncover novel genes or signalling pathways that can be targeted. For this to happen, it is first of utmost importance that causality is understood in

more detail to ensure efficacy of novel treatment targets.

4. Sensation-seeking and alcohol abuse

Sensation-seeking and low anxiety, are personality traits that are associated with high risk taking behaviour (Zuckerman, 1990, 1996). This includes also an earlier onset of alcohol consumption, higher amounts of consumed drug and an enhanced risk to develop an alcohol addiction (Nadal et al., 2002; Stautz and Cooper, 2013; Bidwell et al., 2015).

Mice with a deletion of the D4Wsu27e gene coding for the EF hand domain containing 2 (EFhd2, also known as Swiprosin-1) protein, showed an enhanced sensation-seeking behavioural phenotype characterized by potentiated exploratory activity in a novel open field and reduced anxiety in the elevated plus maze test (Mielenz et al., 2018). Depression-related behaviour was reduced in the forced swim test and in the novelty suppressed feeding test, while the consumption of a hedonic food stimulus was not changed in these mice (Mielenz et al., 2018). Sensation seeking is linked to arousal and attentional processing (Blanchard et al., 2009; Peritogiannis, 2015). In line with this was the finding that EFhd2 KO mice not only showed an enhanced exploratory response to a novel environment, but also enhanced tissue noradrenaline (NA) levels in the nucleus accumbens (Nac) and prefrontal cortex (PFC). This may suggest a higher baseline arousal level in EFhd2 KO mice. In a translational analysis, the findings in mice were confirmed in a human sample of healthy adults. Humans showed an association between the intronic SNP rs112146896 from the EFhd2 coding region with anxiety traits as measured by the mean response from anxiety sensitivity items of the Substance Use Risk Profile Scale (SURPS) (Mielenz et al., 2018).

EFhd2 is a Ca^{2+} sensor protein originally discovered in lymphocytes (Vuadens et al., 2004; Mielenz et al., 2005; Dütting et al., 2011; Hagen et al., 2012). It consists of an N-terminal region of low complexity with an alanine stretch, a functional SH3 binding motif, two functional EF hands and a C-terminal coiled-coil domain (Dütting et al., 2011; Hagen et al., 2012). EFhd2 binds directly to F-actin where it controls its turnover (Huh et al., 2013; Kwon et al., 2013; Mielenz and Gunn-Moore, 2016), suggesting that it might affect synaptic plasticity (Gu et al., 2010). EFhd2 is widely expressed in the human and mice brain, with highest expression in the cortex and hippocampus (Borger et al., 2014; Purohit et al., 2014). In the brain, it is found in neurons, particularly in axons, dendrites and synaptic complexes (Borger et al., 2014; Purohit et al., 2014). In neurons EFhd2 controls axonal transport and kinesin-mediated microtubule gliding (Purohit et al., 2014), as well as pre-synaptic density composition (Borger et al., 2014).

Maclaren and Sikela (2005) compared inbred short sleep (ISS) with inbred long sleep (ILS) mice for their gene expression profiles and the sensitivity to the sedative effects of alcohol. They reported a significantly higher EFhd2 expression in the cerebellum of ILS compared to ISS mice. ISS mice were also more sensitive to the sedating effects of alcohol. This evidence suggested EFhd2 as a potential resilience factor for alcohol. In a free-choice paradigm, EFhd2 KO mice drink more alcohol than controls. Moreover, EFhd2 KO mice spontaneously escalate their alcohol consumption (Mielenz et al., 2018). Sub-chronic treatment with the anxiogenic inverse benzodiazepine receptor agonist β-carboline enhanced the anxiety level of EFhd2 KO mice to wild type (WT) level. At the same time, it normalized the high alcohol preference of these mice. These findings suggested an EFhd2-driven relationship between personality traits and alcohol preference (Mielenz et al., 2018). In addition, this relationship was confirmed in a translational analysis in humans. In a human sample of healthy adolescents, a positive association of the D4Wsu27e SNP rs112146896 with lifetime drinking was reported (Mielenz et al., 2018).

In mice, reduced EFhd2 function attenuated extracellular DA levels in the Nac, but enhanced dopaminergic response to alcohol in this structure. This effect was region specific, restricted to the Nac and not observed in the PFC (Mielenz et al., 2018). In EFhd2 KO mice, gene expression was reduced for tyrosine hydroxylase, Eomes and Pax6. The later are important genes for cortical development. These findings were confirmed in an EFhd2 knockdown model in *Xenopus* tadpoles. Magnetic resonance imaging (MRI) in mice showed that a lack of EFhd2 led to lower cortical, but not subcortical brain region volumes when measured at an adult age (Mielenz et al., 2018). A human MRI study confirmed also the negative association between lifetime alcohol drinking and superior frontal gyrus volume (Mielenz et al., 2018). Altogether, these findings suggest a common genetic base for the personality traits of sensation-seeking/low anxiety and an enhanced risk for escalating alcohol consumption. It also showed brain mechanisms that may explain the development of those specific personality traits and in parallel a higher susceptibility for the rewarding effects of alcohol (Kogias et al., 2019).

A subsequent study investigated whether the resilience role of EFhd2 also applies to other drugs of abuse, like the psychostimulants cocaine and methamphetamine (METH). Sensation-seeking and low anxiety are personality traits also associated with a higher risk to consume those drugs (Blanchard et al., 2009). A study by Kogias et al. (2020) showed that EFhd2 plays no major role for the establishment of the conditioned rewarding effects of cocaine or METH, as measured in a conditioned place preference test. While the lack of EFhd2 caused hyperactivity in a novel environment, it reduced the METH-induced locomotor activation. METH even partially normalized the low anxiety trait in the EFhd2 KO mice towards wild type level (Kogias et al., 2020). EFhd2 controlled the amplitude of the DA- and 5-HT increase after both drugs in a resilience-like way. In that, EFhd2 reduced the DA- and 5-HT responses predominantly in the Nac and, to a smaller degree, in the PFC (Kogias et al., 2020). The lack of EFhd2 enhanced the excitability of ventral tegmental area (VTA) dopaminergic neurons. In EFhd2 KO mice, the dopaminergic neurons displayed a higher rate of spontaneous firing. There was also an enhanced firing rate after stimulation of VTA dopaminergic neurons lacking EFhd2 (Kogias et al., 2020). This observation was in line with the enhanced extracellular DA responses after psychostimulant drug application. VTA dopaminergic neurons of EFhd2 KO mice showed a stronger hyperpolarizing response to the DA D2 receptor agonist quinpirole locally applied to the VTA. This may suggest that neurons without EFhd2 are more sensitive to DA D2 auto-inhibitory control (Kogias et al., 2020). These findings expanded the common genetic base for a distinct personality trait with alcohol addiction also to psychostimulant abuse and addiction (Kogias et al., 2019).

5. Anxious/depressive personality and alcohol instrumentalization

Alcohol is frequently instrumentalized by individuals with a pronounced personality of high anxiety and depression-like behaviour (Müller, 2020), which often results in a co-morbid psychiatric disorders of major depression and alcohol addiction (Room, 2000; Schuckit et al., 1997, 2006, 2007; Boden and Fergusson, 2011). This can be investigated in animal models that pick up emotional behaviour, alcohol-related behaviours as well as the effect of alcohol exposure on emotional regulation (Müller, 2017). Recent findings demonstrated that a disruption of the sphingolipid rheostat in the brain may first lead to an anxious/depressed personality, which gives rise to a high alcohol consumption in order to self-titrate the neurochemical imbalance and to attenuate adverse behavioural traits (Müller and Kornhuber, 2017).

Mice over-expressing the enzyme acid sphingomyelinase (ASM; tgASM mice) displayed a phenotype characterized by high anxiety and depression-like behaviour (Gulbins et al., 2013; Kornhuber et al., 2014). The ASM mediates the turnover of sphingomyelin to ceramide in lysosomes and the plasma membrane. While several sphingomyelinases have been identified according to their optimal pH for enzyme activity so far (Henry et al., 2013; Kornhuber et al., 2015), for personality traits

only the ASM has been extensively characterized (Gulbins et al., 2018). It was shown that the enhanced activity of ASM in the brain leads to an increase in hippocampal ceramide, which can directly attenuate local neurogenesis, neuronal maturation, and neuronal survival (Gulbins et al., 2013, 2015). This is a neurobiological marker previously associated with a depressive phenotype in rodent models (Santarelli et al., 2003). These observations have been confirmed in pharmacological studies in that many commonly prescribed antidepressant drugs were shown to work as functional ASM inhibitors (Kornhuber et al., 2010, 2011). Moreover, this ASM inhibition is a necessary requirement for the antidepressive effects of these drugs (Gulbins et al., 2013). Antidepressant drugs can also attenuate the depressogenic effects of chronic unpredictable stress on behaviour in wild type and tgASM mice. They lose their efficacy in mice lacking ASM (ASM KO). These findings suggested that a dysbalance in the sphingolipid rheostat, as it may be caused by chronic unpredictable stress in short term (Oliveira et al., 2016; Miranda et al., 2019) or by genetic mutation life-long, may give rise to an anxious/depressive personality (Kornhuber et al., 2014; Müller et al., 2015; Schneider et al., 2017).

Animal models showed that voluntary alcohol self-administration may reduce depressive symptoms in depressed mice. In rodents, this effect may be the major factor that sustains high alcohol consumption over long time (Ciccocioppo et al., 1999; Tizabi et al., 2018). Mice with a genetically enhanced ASM activity in the brain were not only depressed, but drank also significantly more alcohol in a free-choice paradigm. They also escalated their consumption after repeated withdrawal periods (Müller et al., 2017). Only the voluntary self-titration with alcohol, but not a forced exposure, normalized the depressive behavioural symptoms in these animals towards wild type levels. In the depressed mice, alcohol attenuated the genetically enhanced ASM activity in the brain, while it had no effect on ASM activity in wild type controls. ASM hyperactivity reduced the levels of the most abundant sphingomyelin species in the Nac and dorsal hippocampus (DH). Alcohol drinking in WT mice also led to a reduction of sphingomyelin species. In tgASM mice, the self-administered alcohol yielded a paradoxical effect. It attenuated the sphingomyelin deficit in the Nac, but not in the DH. Depressive tgASM mice displayed largely reduced levels of monoaminergic innervation with dopamine and serotonin in several brain areas (Müller et al., 2017), which is in line with an inactive and depressed phenotype (Carey et al., 2008; Krishnan and Nestler, 2008). In contrast, the dopaminergic responsiveness, i.e. the induced increase in extracellular DA levels, to an acute alcohol challenge was enhanced (Kalinichenko et al., 2019), which may further explain the amplified incentive value of the alcohol in these animals (Müller et al., 2017). Alcohol drinking reversed the monoamine tissue deficit in the tgASM mice almost completely, but had rather opposite effects in WT mice (Müller et al., 2017). These studies suggest that alcohol self-titration may have distinct effects depending on personality type. While it can induce depression in healthy individuals (Schuckit et al., 1997), it may have rather paradoxical effects in anxious/depressed individuals. In them, it partially reverses some of the adverse behavioural traits together with the neurobiological mechanisms that caused those (Kalinichenko et al., 2018).

6. Conclusions

While an association of distinct personality traits with high alcohol and drug use, abuse and a higher addiction rate has been known for a long time, psychological and neurobiological mechanism have largely resisted exploration. In recent times, however, better models that explicitly focused on the role of personality traits allowed for a more focused interrogation. These models have revealed now that distinct personality dimensions, which all associate with higher alcohol and drug consumption, do this by rather distinct psychological and neurobiological mechanisms. Distinguishable personality traits arise from different working modes of the brain that are shaped by genetic/epigenetic, environmental and developmental factors. As such, alcohol and other drugs hit rather different brain systems, which look similar in their macrostructure, but differ largely in their microstructure, when consumed by different personality types, and, not surprisingly, may yield distinct effects. Those effects may be more beneficial in certain personality types than in others and allow selective instrumentalization of a psychoactive drug, e.g. to self-medicate and control aversive and non-desired personality traits. The neurobiological base of how different personalities may initially benefit from a drug and later develop addiction is now increasingly understood. Multiple distinct molecular pathways emerged which, at the same time, shape personality traits and responses to psychoactive drugs. Together with a psychological assessment of personality types, neurobiological markers may in the future help to identify an enhanced risk personality at an early age and improve selective prevention strategies against addiction. It may also help for a more personalized pharmaco-treatment once a rather personality specific addiction has developed.

Broos et al. (2011) and Crabbe (2010).

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