Molecular Imaging Studies of Alcohol Use Disorder

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Abstract Alcohol use disorder (AUD) is a serious public health problem in many countries, bringing a gamut of health risks and impairments to individuals and a great burden to society. Despite the prevalence of a disease model of AUD, the

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current pharmacopeia does not present reliable treatments for AUD; approved treatments are confined to a narrow spectrum of medications engaging inhibitory γ-aminobutyric acid (GABA) neurotransmission and possibly excitatory N-methyl-D-aspartate (NMDA) receptors, and opioid receptor antagonists. Molecular imaging with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can open a window into the living brain and has provided diverse insights into the pathology of AUD. In this narrative review, we summarize the state of molecular imaging findings on the pharmacological action of ethanol and the neuropathological changes associated with AUD. Laboratory and preclinical imaging results highlight the interactions between ethanol and GABA A-type receptors ($GABA_AR$), but the interpretation of such results is complicated by subtype specificity. An abundance of studies with the glucose metabolism tracer fluorodeoxyglucose (FDG) concur in showing cerebral hypometabolism after ethanol challenge, but there is relatively little data on long-term changes in AUD. Alcohol toxicity evokes neuroinflammation, which can be tracked using PET with ligands for the microglial marker translocator protein (TSPO). Several PET studies show reversible increases in TSPO binding in AUD individuals, and preclinical results suggest that opioid-antagonists can rescue from these inflammatory responses. There are numerous PET/SPECT studies showing changes in dopaminergic markers, generally consistent with an impairment in dopamine synthesis and release among AUD patients, as seen in a number of other addictions; this may reflect the composite of an underlying deficiency in reward mechanisms that predisposes to AUD, in conjunction with acquired alterations in dopamine signaling. There is little evidence for altered serotonin markers in AUD, but studies with opioid receptor ligands suggest a specific up-regulation of the μ-opioid receptor subtype. Considerable heterogeneity in drinking patterns, gender differences, and the variable contributions of genetics and pre-existing vulnerability traits present great challenges for charting the landscape of molecular imaging in AUD.

Keywords Alcohol use disorder (AUD) · FDG · Molecular imaging · Neuroinflammation · PET · Receptors · SPECT

Abbreviations

2DG	2-[^{14}C]deoxyglucose
AUD	Alcohol use disorder
BP_{ND}	Binding potential (non-displaceable)
D1R	Dopamine D_1 receptor
D2R	Dopamine D_2 receptor
DALYS	Disability-adjusted life years
DAT	Dopamine transporter
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and statistical manual of mental disorders fifth revision

EMA	European Medicines Agency
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
GABA	γ-Aminobutyric acid
$GABA_AR$	GABA A-type receptors
NMDA	N-methyl-D-aspartate
PET	Positron emission tomography
SPECT	Single-photon emission computed tomography
TSPO	Translocator protein
VS	Ventral striatum
WCST	Wisconsin Card Sorting Test

1 Introduction

The prevalence of alcohol use exceeds 70% among adults in some countries (Degenhardt et al. 2018). The adage *dosis sola facit venenum*, attributed to Paracelsus, holds especially true for alcohol. Drinking a glass or two of wine may induce a socially acceptable disinhibition and increased verbosity, along with a blood ethanol concentration of 5–10 mM. However, a tenfold higher dose is likely to induce loss of consciousness in individuals who have not acquired tolerance, whereas a 20-fold higher dose may cause coma and death. As such, ethanol has a relatively low potency and low safety range. Excessive alcohol use is one of the leading causes for death and disability worldwide, accounting for up to 6% of deaths worldwide and approximately 5% of the global disease burden, with alcohol use being the seventh leading risk factor for death and disability-adjusted life years (DALYs) (Degenhardt et al. 2018). For all-cause mortality, there is a positive and curvilinear association with the level of alcohol consumption, with the minimum mortality risk occurring at around 100 g per week (Degenhardt et al. 2018). High concentrations of ethanol and its primary metabolite acetaldehyde induce oxidative stress and deoxyribonucleic acid (DNA) damage in cultured neurons (Lee et al. 2005) and are teratogenic for fetal mice (Webster et al. 1983). Excessive alcohol use links to over 60 acute and chronic diseases (Rehm et al. 2003). Indeed, alcohol consumption has a roughly linearly association with risk of stroke, coronary disease (excluding myocardial infarction), heart failure, fatal hypertensive disease, and fatal aortic aneurysm; those with very heavy alcohol consumption (>100 g/day for males or 60 g/day for females) have a life expectancy that is shortened by decades (Rehm et al. 2003). Chronic alcohol use has also been associated with cognitive impairments, covering a spectrum of disorders including alcohol-related dementia and the Wernicke-Korsakoff syndrome (Hayes et al. 2016).

Alcohol use disorder (AUD), which replaces the earlier terms alcohol dependence and alcoholism, refers to a condition in which drinking evokes symptoms that impair mental and physical health. According to the current classification system, the

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (https://doi.org/10.1176/appi.books.9780890425596), these symptoms include: a strong desire to drink alcohol; unsuccessful efforts to cut down or limit alcohol use; evidence of tolerance, such that increased doses of alcohol are required in order to achieve effects originally produced by lower doses; continued alcohol use despite social or interpersonal problems or clear evidence of overtly harmful physical consequences (e.g., liver cirrhosis); alcohol use in situations in which it is physically hazardous; occurrence of withdrawal symptoms when substance use has ceased or been reduced, as evidenced by a characteristic withdrawal syndrome typically including sweating, nausea, tachycardia, hypertension, tremor, but also severe events such as seizures, psychotic symptoms, and delirium tremens (National Clinical Guideline 2010).

Globally around 107 million people suffer from AUD, of whom 70% are men (James et al. 2018). Although men show higher rates of alcohol use and binge drinking, women are more susceptible than are men to deleterious health effects of AUD (Holman et al. 1996; Keyes et al. 2019). Longitudinal data from the USA also show a steeper increase in alcohol-related deaths in females, compared to males between the years 1999 and 2017 (White et al. 2020). Indeed, death rates for women with AUD are 50–100% higher than for men, reflecting alcohol-related accidents, heart disease, stroke, and liver diseases (Mokdad et al. 2004). Part of the gender differences in alcohol-related health consequences may reflect differences in alcohol metabolism and body fluid compartments (Lieber 2000).

Historically, Cloninger and colleagues (Cloninger et al. 1981) proposed a binary typology of individuals with alcoholism, with Type I alcoholism occurring in both sexes, causing few social and legal problems and either mild or severe AUD symptoms. In contrast, Type II alcoholism was said to occur predominantly in men, with earlier age at onset and causing higher rates of social and legal problems, rating high on novelty seeking temperament (Cloninger et al. 1981). Initial findings of an association with certain genetic markers, especially involving dopaminergic neurotransmission, have been reassessed due to the generally weak reproducibility of such studies (Dao et al. 2021; Jung et al. 2019). Current diagnostic systems (DSM-5, see above) have conceptualized AUD as a dimensional construct, classified as mild, moderate, or severe, according to the number of criteria met by an individual. As such, AUD is a chronic relapsing condition characterized by repeated heavy alcohol consumption despite negative consequences. While studies indicated that 5–45% of untreated individuals with AUD may achieve some improvement or remission, meta-analyses show that the average short-term abstinence rate in non-treated individuals (e.g., waiting lists) is only about 20%, versus 40% in treated individuals (Moyer and Finney 2002). Thus, there is scope for improving the general efficacy of AUD treatment. We suppose that the search for more effective treatments could benefit from an improved understanding of the individual neurobiological factors associated with AUD.

2 Treatment of AUD

In general, treatment for AUD encompasses social, psychological, and pharmacotherapeutic strategies (Kiefer and Mann 2005). Pharmacotherapeutic strategies for the acute phase of alcohol withdrawal of patients presenting with a physical dependence generally involve an adapted dose of benzodiazepines and vitamin supplementation (Kosten and O'Connor 2003) followed by long-term therapy. The sedative compounds clomethiazole and the benzodiazepines, as allosteric activators of inhibitory γ-aminobutyric acid (GABA)-A receptors ($GABA_AR$), have anxiolytic and anticonvulsant actions, thus decreasing the intensity of withdrawal symptoms and protecting against the life-threatening seizures that can occur during acute detoxification. Currently, the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) has approved three types of medication for long-term treatment of AUD. Of these, the aldehyde dehydrogenase inhibitor, disulfiram has been available since the 1940s. Disulfiram produces an aversive reaction to alcohol consumption by irreversibly inhibiting aldehyde dehydrogenase, leading to the accumulation in blood of the primary ethanol metabolite acetaldehyde, which results in flushing, sweating, nausea, and tachycardia. As such, disulfiram mimics the trait of alcohol intolerance seen in some Asian populations due to a functional polymorphism of the aldehyde dehydrogenase enzyme (Goedde and Agarwal 1987).

The other two approved medications for treating AUD are naltrexone and acamprosate. Naltrexone is an opioid-antagonist with high affinity for μ-opioid-receptors and a lesser affinity for κ- and δ-opioid receptors (Altshuler et al. 1980; Lee et al. 1988). Alcohol consumption stimulates the release of opioid peptides and μ-receptor activation, which modulates alcohol-induced dopamine release and consequent reward signaling within the nucleus accumbens and mesocorticolimbic system (Hansson et al. 2019; Mitchell et al. 2012). Alternatively, the ethanol metabolite (*R*)-salsolinol may act as an agonist at central μ-opioid-receptors, thereby contributing to behavioral sensitization and excessive alcohol intake (Deitrich et al. 2006; Quintanilla et al. 2014, 2016). For example, microinjections of salsolinol into the rat posterior ventral tegmental area increase dopamine release in the nucleus accumbens shell (Deehan Jr et al. 2013). This presents a mechanism whereby the opioid receptor antagonist naloxone could attenuate ethanol-induced increases in dopamine release in the nucleus accumbens, which theoretically should remove the incentive to consume ethanol (Gonzales and Weiss 1998). Acamprosate, a homotaurine analog, is classically considered an NMDA receptor antagonist and positive allosteric modulator of $GABA_A$ receptors (Spanagel et al. 2005; Umhau et al. 2010), thereby attenuating alcohol craving. Studies that are more recent failed to replicate effects of acamprosate on N-methyl-D-aspartate (NMDA) receptors or metabotropic glutamate receptors (Spanagel et al. 2014). Hence, the pharmacological mechanisms whereby acamprosate exerts its effects remain to be fully established.

There is emerging clinical and preclinical support for the efficacy of still unapproved medications for the treatment of AUD, notably the anti-glutamatergic compound topiramate (Blodgett et al. 2014). Other medications showing a certain

efficacy include the $5HT_3$ antagonist ondansetron (Johnson et al. 2000), the nicotinic partial agonist varenicline (Litten et al. 2013), and the GABA-B agonist baclofen (Bschor et al. 2018). For a comprehensive review of novel agents for the pharmacological treatment of alcohol use disorder, see Burnette et al. (2022). Antidepressants showed small to medium effects of depressive symptoms in patients with comorbid AUD and depression, but showed very limited effects on alcohol use (for systematic reviews, see Agabio et al. (2018); Foulds et al. (2015)). Overall, the available pharmacological treatments are supportive in the acute withdrawal phase, but of modest benefit in sustaining long-term abstinence. This implies that establishing better the molecular mechanisms underlying AUD symptomatology and addictive behavior might guide the development of improved pharmacological interventions. In this regard, molecular neuroimaging using Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) enables the probing of acute and long-term changes in the brain due to ethanol consumption.

3 GABAergic Effects of Ethanol

Some researchers have attributed the effects of ethanol and other alcohols on neuronal function to their high solubility in the plasma membrane lipid bilayer, and consequent changes in the biophysical properties of membranes (Murail et al. 2012; Patra et al. 2006), along with non-specific effects at various other targets (Eckardt et al. 1998; Harris et al. 2008; Spanagel 2009). More in keeping with classical pharmacology, ethanol and other alcohols are allosteric modulators of $GABA_A$ receptors, thus potentiating the inhibitory chloride currents stimulated by endogenous GABA (Nestoros 1980), much in the manner of benzodiazepines. The $GABA_A$ receptor is a heteropentameric ligand-gated ion channel that occurs in a wide diversity of subunit compositions; not all forms are equally sensitive to interactions with ethanol, but various $GABA_A$ receptor subtypes have sensitivity for alcohol (Mihic et al. 1997; Sundstrom-Poromaa et al. 2002). In particular, the negative modulation of $GABA_A$Rs by the imidazobenzodiazepine partial inverse agonist Ro15-4513 antagonizes the behavioral effects of low to moderate doses of alcohol (Suzdak et al. 1988), apparently by occupation of the benzodiazepine binding site on the α5-subunit of the $GABA_A$R (Sundstrom-Poromaa et al. 2002), which are notably abundant in the hippocampus.

The chemical structure of Ro15-4513 lends itself for preparation as a tracer for PET using the positron-emitting radionuclide Carbon-11 (physical half-life 20 min). Indeed, [^{11}C]Ro 15-4513 showed high uptake in brain of Cynomolgus monkeys, which was displaceable by treatment with flumazenil in cerebral cortex and basal ganglia (although not in cerebellum) (Halldin et al. 1992). Similarly, PET recordings with [^{11}C]Ro15-4513 showed relatively high accumulation in frontal cortex, temporal cortex, and hippocampus (Inoue et al. 1992b). Relative to a metabolite-corrected arterial input function, the total distribution volume of [^{11}C]Ro15-4513

in human brain ranged from 3.5 ml g^{-1} in cerebellum to 9 ml g^{-1} in anterior cingulate cortex. Rat studies showed no displacement of [^{11}C]Ro15-4513 by the $GABA_AR$ α1 subunit selective hypnotic medication zolpidem (Lingford-Hughes et al. 2002). Further studies in non-human primates confirmed the relative selectivity of [^{11}C]Ro15-4513 binding for the α5-subunit of the $GABA_AR$ in limbic cortical regions (Maeda et al. 2003). A PET study in abstinent men with AUD showed a significant decrease in [^{11}C]Ro15-4513 binding in nucleus accumbens, parahippocampal gyri, right hippocampus, and amygdala compared with a healthy control group (Lingford-Hughes et al. 2012). Furthermore, the individual extent of decreased hippocampal binding correlated with impaired performance in a verbal memory task in the patients. While the abstinence period of 6 weeks excludes any acute effect of competition from alcohol, these reductions may reflect toxicity in limbic structures, or adaptive down-regulation of $GABA_ARs$ in response to chronic ethanol exposure. One might thus expect a normalization of $GABA_AR$ binding after long-term abstinence.

Membrane binding studies in vitro with [^{3}H]Ro15-4513 showed that a line of alcohol-sensitive rats had a higher affinity (lower K_D) but no change in B_{max} relative to the alcohol-insensitive strain, in conjunction with greater sensitivity of the binding in cerebellum to displacement by diazepam (Uusi-Oukari and Korpi 1990). That result is hard to interpret, but may be consistent with a shift in the population distribution of $GABA_AR$ subtypes in relation to ethanol sensitivity. However, autoradiography with [^{3}H]Ro15-4513 showed no difference in the $GABA_AR$ availability in a strain of alcohol-preferring rats, nor did the proportions of zolpidem and diazepam-sensitive binding sites differ (Wong et al. 1996).

There seems to have been no study testing the effect of an acute ethanol challenge on [^{11}C]Ro15-4513 binding in living brain, either in experimental animals or in humans. The antagonist ligand [^{18}F]flumazenil is used more often than [^{11}C]Ro15-4513 for PET studies of $GABA_AR$. Acute ingestion of ethanol at an intoxicating dose was without effect on [^{18}F]flumazenil cerebral uptake in a small group of healthy volunteers (Farde et al. 1994). In that same report, [^{18}F]flumazenil PET estimates of the saturation binding parameters (B_{max} and K_D) did not differ significantly between healthy controls and men with AUD. Thus, the available PET tracers seem unfit to establish the acute and chronic effects of ethanol on $GABA_AR$ availability, possibly due to their inadequate selectivity for the receptor subunits involved in AUD.

4 Brain Energy Metabolism

The specific action of ethanol as an allosteric activator of inhibitory $GABA_ARs$ might predict a general inhibition of brain metabolism. The rate of cerebral glucose metabolism is measured autoradiographically from the progressive metabolic trapping of the glucose analogue 2-[^{14}C]deoxyglucose (2DG) in the brain or by PET using [^{18}F]fluorodeoxyglucose (FDG). In one 2DG study, rats administered ethanol

in their drinking water for 3 days showed a tendency toward increased 2DG uptake in the brain, whereas longer term administration evoked a global depression of metabolism (Nobrega et al. 1987). More consistent with expectations, intraperitoneal administration of ethanol evoked acute widespread reductions in cerebral 2DG uptake in alcohol-preferring rats (Strother et al. 2005). However, other studies report a dose-dependent effect, whereby 0.25 g/kg ethanol increased 2DG uptake in mesocorticolimbic and nigrostriatal circuit components, but administration of 1.0 and 2.0 g/kg ethanol evoked more circumscribed increases, primarily in the mesocorticolimbic circuit (Williams-Hemby and Porrino 1997a). We suppose that this may reflect the biphasic behavioral effects of alcohol, where a low dose can have a more distinctly stimulant profile. Furthermore, the same authors showed that treatment with a dopamine antagonist tended to block the mesocorticolimbic and nigrostriatal increases in 2DG uptake evoked by the intragastric ethanol at the 0.25 g/kg dose, but with lesser effect on the higher doses (Williams-Hemby and Porrino 1997b). Thus, the cerebrometabolic effects of low-dose ethanol may arise due to altered dopamine signaling, rather than global inhibitory effects of $GABA_AR$ activation on neuronal activity.

Other rat studies employing chronic ethanol exposure showed increased 2DG uptake in sensorimotor cortex, globus pallidus, thalamus, and cerebellum during an acute phase of alcohol withdrawal, suggesting a disinhibition of neuronal activity in these regions, which might underlie the propensity for withdrawal symptoms, *delirium tremens,* and seizures during acute detoxification (Campbell et al. 1982). In further rat studies, post withdrawal increases in 2DG uptake persisted in certain limbic structures weeks after withdrawal; these long-term changes may conceivably relate to toxicity and the risk for relapse (Eckardt et al. 1986; Smith et al. 2001). However, others reported widespread decreases in 2DG uptake during withdrawal, a difference that the authors attributed to the minimal restraint and lesser stress in their study (Clemmesen et al. 1988). However, rats trained to drink ethanol voluntarily showed decreased 2DG uptake in the hippocampal complex, habenula, anterior ventral thalamus, and mammillary bodies upon ethanol challenge, but increased uptake in the nucleus accumbens and locus coeruleus (Williams-Hemby et al. 1996). Conversely, water challenge in the alcohol-habituated rats evoked widespread increases in 2DG uptake, consistent with the disinhibition reported in other studies. Overall, the various rat 2DG studies show either decreased or increased metabolism after ethanol, depending on the dose and route of administration. However, studies in an acute withdrawal paradigm have more consistently shown increased cerebral metabolism, presumably due to disinhibition. FDG microPET imaging showed that ethanol challenge to naïve Wistar rats reduced whole-brain FDG uptake, especially in parietal cortex and cerebellum, whereas rats with ethanol exposure for 3 months showed a lesser decline, and FDG uptake in rats with 12 months exposure was unaffected by the challenge (Gispert et al. 2017). In the same rat study, the ethanol challenge increased FDG uptake in specific regions (ventral striatum and entorhinal cortex), and effect not showing signs of tolerance after long-term drinking.

In a rare human PET study with [^{11}C]glucose, which is arguably superior to FDG as a tracer for the glucose metabolic rate, there was 20–30% lower glucose metabolism in various cortical and subcortical regions in a group of nine detoxified alcoholics compared with healthy controls (Wik et al. 1988). Results of FDG-PET studies generally concur with preclinical findings using the 2DG autoradiographic method. In one human study, a low dose of ethanol evoked variable effects on FDG uptake in healthy volunteers, whereas a higher dose decreased global metabolic rate in the same subjects (de Wit et al. 1990). However, there were no clear relationships between the mood-altering effects of alcohol and altered brain metabolism. In a subsequent study in 20 healthy volunteers, a dose of 0.25 g/kg decreased global CMRglc by 10%, whereas 0.5 g/kg evoked a 23% global decrease (Volkow et al. 2006). The lower dose mainly affected the cerebral cortex, whereas the higher dose also reduced metabolism in cerebellum, mesencephalon, basal ganglia, and thalamus; these effects of rather low doses were not associated with significant impairment in performance of a cognitive test battery. An FDG-PET study in detoxified AUD subjects compared with healthy controls did not indicate any group difference in the hypometabolism evoked by a challenge with lorazepam (Volkow et al. 1997); this led the authors to conclude that the metabolic deficit seen in the baseline scans could not be attributable to GABAergic mechanisms per se. Further investigations by the same group showed that the ethanol-induced reductions in FDG uptake were offset by increases in the uptake of the alternate energy substrate [^{11}C]acetate (Volkow et al. 2013a); thus, ethanol may provoke a shift away from the usual absolute dependence of brain tissue on glucose metabolism in favor of acetate or perhaps ketone bodies. It was shown that patients with AUD show higher brain acetate metabolism and lower brain glucose metabolism compared with controls and that this shift from glucose to acetate metabolism in AUD persists beyond the acute intoxication state (Volkow et al. 2017). The authors suggested that this might result in a paradoxical energy-deficit state in the brain during alcohol detoxification, when acetate levels in plasma decrease, which in turn might drive withdrawal symptoms. In line with this hypothesis, recent data from a small pilot trial also indicated that individuals following a ketogenic diet during withdrawal from alcohol experienced reduced withdrawal symptoms and craving intensity (Wiers et al. 2021).

Alcoholism occurs more frequently in men than in women and the preponderance of molecular imaging studies of AUD has included exclusively male patients. An FDG-PET study in detoxified female AUD patients did not indicate any substantial reduction in metabolic rate, which argues against claims of greater toxicity of alcohol for the female brain (Wang et al. 1998).

There are relatively few reports on cerebrometabolic changes associated with chronic and severe AUD. An FDG-PET study of a 40-year-old individual with Wernicke-Korsakoff syndrome showed bilateral thalamic and severe bilateral temporal-parietal hypometabolism (Fellgiebel et al. 2003). After thiamine treatment and confirmed alcohol abstinence for 9 months, there was substantial recovery of clinical state along with FDG uptake in cortical regions. However, there was no recovery of FDG uptake in the thalamus during this remission. A study in 12 Wernicke-Korsakoff patients showed atrophy of the thalamus and mammillary

bodies, along with some loss of frontal lobe volume, all consistent with Papez circuit degeneration (Reed et al. 2003). FDG-PET in the same individuals showed relative declines in metabolism in white matter and in subcortical gray matter of the diencephalon. An FDG-PET case study in a patient with alcoholism-related hallucinosis showed normal uptake in the temporal lobes, but 14% reduced uptake in the left thalamus (Soyka et al. 2000). A test of the selective GABA transporter 1 inhibitor tiagabine in healthy controls did not interfere in the cerebrometabolic effects of alcohol challenge as measured by FDG-PET (Fehr et al. 2007).

5 Metabotropic Glutamate Receptors

As distinct from the inotropic glutamate receptors, which are ligand-gated ion channels, there is an important family of at least five glutamate receptor types, which mediate their effects via coupling to intracellular second messenger systems. As such, they are known as the metabotropic glutamate receptors (mGluR). We have recently reviewed the literature on molecular imaging of this important class of receptors, as well as the NMDA-type ionotropic receptors (Kim et al. 2020). A recent FDG-PET study examined the effect on cerebral glucose metabolism in alcohol-dependent rats with infralimbic cortex-specific knockdown of the type 2 metabotropic glutamate receptor (mGluR2) after pre-treatment with the mGluR2/3 agonist LY379268 or vehicle (Meinhardt et al. 2021). Results showed that, compared to vehicle treatment, the mGluR2/3 agonist LY379268 challenge led to decreased FDG trapping in the infralimbic cortex of control animals under resting state conditions, while there was no such effect of LY379268 in the mGluR2 deficient, alcohol-dependent rats. The authors interpreted these results to indicate that alcohol-dependent animals deficient in mGluR2 could not modulate their glucose utilization in the infralimbic cortex upon pharmacological receptor activation.

Initial PET studies of the type five-metabotropic glutamate receptor (mGluR5) used the ligand [^{18}F]FPEB, which is now finding increasing competition from the alternate tracer [^{11}C]ABP688. A recent dual tracer study tested the effects of an acute challenge with alcohol on the cerebral availabilities of mGluR5 to [^{18}F]FPEB PET (Leurquin-Sterk et al. 2018), while also measuring in the same moderate drinkers the effects on dopamine receptor availability to [^{18}F]fallypride, as shall be discussed in greater detail below. They reported that baseline availability of binding sites for [^{18}F]FPEB in the prefrontal cortex, temporal lobe, caudate nucleus, and thalamus correlated with "liking" of the effect of alcohol, as did declining [^{18}F]fallypride in similar regions, suggesting a link between cortical dopamine release, mGluR5 availability, and reinforcing properties of alcohol. This notion was lent support by a preclinical finding that higher baseline binding of [^{18}F]FPEB in the rat nucleus accumbens predicted future predilection to consume ethanol (de Laat et al. 2019); prolonged ethanol exposure generally decreased the mGluR5 availability in rat brain. Further clinical PET research with [^{18}F]FPEB indicated that prolonged abstinence (2–-6 months) was associated with recovery of the initially low mGluR5 availability in

brain, along with a decline in the intensity of craving (Ceccarini et al. 2020). This is encouraging with respect to the reversibility of acquired brain changes in AUD.

An [^{11}C]ABP688 PET study of 14 male AUD patients showed a significant 10% higher binding in various cortical regions as comparted to healthy controls, and an inverse relation between amygdala binding with craving scores in the AUG group (Akkus et al. 2018); this study made careful matching of non-smoking subjects, as tobacco consumption has strong independent effects on mGluR5 availability. Another [^{11}C]ABP688 PET study in a group of 12 AUD patients with prolonged abstinence showed only small decreases in mGluR5 binding in some cortical regions as compared to controls (Joo et al. 2021). An additional functional connectivity analysis using a seed placed in the inferior parietal cortex of the abstinent AUD patients showed abnormal connectivity with distal regions such as the occipital pole and dorsal visual cortex. While difficult to interpret, the result may call for more studies aiming to link AUD-related molecular imaging with functional connectivity; changes in receptor abundance may prove to weak surrogates for more behaviorally and cognitively relevant changes in network activity of the brain.

6 Neuroinflammation

There is considerable evidence for involvement of peripheral and central inflammation in the development of the AUD. Heavy alcohol consumption induces neuroinflammation either via a direct effect on microglial reactivity (De Santis et al. 2019, 2020; Fernandez-Lizarbe et al. 2008; Zou and Crews 2010) or by excitotoxicity due to GABA/glutamate imbalance (Mon et al. 2012) and resultant oxidative stress (Almansa et al. 2009). AUD patients also present with important signs of peripheral inflammation (Leclercq et al. 2012) that are partially attributable to increases in gut permeability, to alterations in the composition of the gut microbiota (Leclercq et al. 2014), and possibly to complex peripheral metabolomics changes in the body (Leclercq et al. 2020). There is extensive evidence that inflammation and neuroinflammation contribute to aspects of addictive behaviors in animal models (Robinson et al. 2014).

The translocator protein (TSPO) binding site (formerly known as the peripheral benzodiazepine receptor) is a cholesterol transporter located in the mitochondrial membrane of microglia, which are the resident macrophages of the brain. Radiotracers for the TSPO binding site can reveal microglial activation in response to neurotoxic insults, although there is some ambiguity about the cellular localization of TSPO, complicated by the caveat that most TSPO PET tracers distinguish a functional polymorphism of TSPO in human populations (Cumming et al. 2018). For example, this phenomenon explained the allelic dependence of [^{18}F]-FEPPA binding in human PET studies (Mizrahi et al. 2012), and the general requirement for genotyping of individuals, given the roughly equal abundances of binding and non-binding alleles in human populations. Roughly 10% of individuals are homozygotic for the non-binding allele, and thus show negative results with most TSPO PET tracers other than prototypic ligand, [^{11}C]PK11195.

Preclinical data indicated an increase in TSPO in alcohol-dependent rats (Tamborska and Marangos 1986). In particular, there were 20–50% increases in the binding of [^{3}H]Ro-5-4864 to cortical and cerebellar membranes, which persisted for 3 days after withdrawal, but had largely normalized at 4–7 days. There were no accompanying changes in $GABA_AR$ sites labelled with [^{3}H]-ethyl-β-carboline-3-carboxylate. In another rat study, chronic exposure to ethanol vapor increased the autoradiographic binding of the prototypic TSPO ligand [^{3}H]PK11195 in thalamus and hippocampus, with trend level increases for another TSPO ligand, [^{3}H]PBR28, compared to control rats (Tyler et al. 2019). However, corresponding [^{11}C]PBR28 PET studies did not reveal increased TSPO binding in vivo, which led the authors to question the validity of that tracer for detecting microglial activation in the alcohol-dependent model. Three young baboons underwent serial TSPO PET with [^{18}F] DPA714 PET at baseline, during a binge-drinking paradigm, and after prolonged withdrawal (Harris et al. 1996). The total distribution volume in brain at steady-state (V_T; ml g^{-1}) was nearly doubled during alcohol exposure relative to baseline and remained 50% increased after several months of withdrawal, suggesting persistence of microglial activation in that model.

Despite the disparate results in rat models, results of the non-human primate study cited above might still predict at least a transient increase in TSPO binding sites in alcohol-dependent human subjects. However, in a TSPO PET study with [^{11}C] PBR28, there was a 20% reduction in the V_T in hippocampus of a group of detoxified AUD individuals (Kalk et al. 2017). The magnitude of V_T correlated positively with verbal memory performance in the combined group of AUD and healthy controls, but not in the AUD group in isolation. Another [^{11}C]PBR28 PET experiment in groups of 15 AUD and control subjects showed 10% lower V_T in brain of the AUD groups at 1–4 days after the last drink (Hillmer et al. 2017); exploratory analysis showed a negative correlation between severity of alcohol dependence and [^{11}C] PBR28 in striatum and hippocampus. Another [^{11}C]PBR28 PET study ($n = 19$) comparing participants with AUD and a similar sized group of healthy controls did not show any group differences in V_T, except when considering only the mixed affinity subgroup (i.e., TSPO rs6971 heterozygotes) of AUD patients, who proved to show a reduction in binding (Kim et al. 2018). Furthermore, cholesterol levels in the combined group correlated inversely with [^{11}C]PBR28 binding in the brain, suggesting a functional relationship between the TSPO phenotype and inflammatory responses. Rats treated with ethanol for 2 weeks in a binge-drinking model showed twofold increases in TSPO binding to [^{18}F]DPA714 PET, but this neuroinflammatory response was substantially relieved by treatment with the opioid-antagonist nalmefene (Tournier et al. 2021).

7 Dopamine

We have seen above that antipsychotic medication could block some of the cerebrometabolic effects of a low dose of ethanol, suggesting a mechanism via effects on dopaminergic signaling. We can measure the integrity of nigrostriatal

dopamine innervations with SPECT and PET tracers for various markers for biochemical constituents of the dopamine terminals, namely synaptic vesicles, dopamine reuptake sites, and the pathway for dopamine synthesis (Doudet et al. 2006). The latter pathway is probed by [^{18}F]FDOPA, an exogenous levodopa analogue that is metabolically trapped in neuron terminals containing the enzyme DOPA decarboxylase, thus giving an index of the local capacity for dopamine synthesis. In an [^{18}F]FDOPA PET study of ten AUD patients designated a Type I according to Cloninger, the group mean analysis indicated a 28% elevation in [^{18}F]FDOPA trapping in the left putamen, and a 36% elevation in the right caudate (Tiihonen et al. 1998). These increases correlated inversely with performance in the Wisconsin Card Sorting Test (WCST). The finding of increased dopamine synthesis capacity goes against the conventional expectation of reduced dopaminergic transmission in patients with substance dependence. Indeed, the striatal [^{18}F]FDOPA influx was completely within the normal range in another study of AUD patients (Heinz et al. 2005b), although individual results correlated inversely with the degree of craving reported during abstinence. Yet another [^{18}F]FDOPA PET study showed normal influx in a group of 12 detoxified AUD patients. However, advanced kinetic analysis of the steady-state trapping of [^{18}F]FDOPA metabolites (V_D; ml g^{-1}) showed that the patient group, unlike healthy controls, showed no significant correlation between V_D in left amygdala and activation in left anterior cingulate cortex in response to aversive visual stimuli (Kienast et al. 2013). Further advanced kinetic analysis of the same data set showed that the net cerebral influx of [^{18}F]FDOPA was completely normal in the AUD group. However, the magnitude of V_D in the left caudate head was reduced by 43% relative to the controls, consistent with a 58% increase in the turnover rate of trapped [^{18}F]fluorodopamine (k_{loss}, min^{-1}) (Kumakura et al. 2013). Furthermore, the extent of craving reported at the time of PET scanning correlated with the individual magnitude of k_{loss} in the ventral striatum. Thus, advanced kinetic analysis of [^{18}F]FDOPA PET suggests intact dopamine synthesis capacity in AUD patients, but a state of elevated dopamine turnover, at least in the condition of withdrawal.

SPECT studies with dopamine transporter (DAT) ligands can establish degeneration of the nigrostriatal dopamine system in Parkinson's disease. A [^{123}I]-β-CIT study comparing 21 impulsive violent AUD patients, 10 non-violent AUD cases, and 21 age-matched controls showed increased spatial heterogeneity in the right striatum of the violent AUD group, along with absence of the normal left-to-right asymmetry in DAT (Kuikka et al. 1998). The authors interpreted this to indicate a subtle disturbance in the development of the nigrostriatal pathway in patients with AUD prone to violence. Another such SPECT study from the same group showed relatively reduced striatal DAT binding in the non-violent AUD group, versus a slight increase in the violent group, relative to healthy controls (Tiihonen et al. 1995). Others showed reduced DAT binding in the striatum of 28 AUD subjects during withdrawal and a significant restoration with prolonged sobriety (Laine et al. 1999). In that study, there was a significant correlation between reduced DAT binding and scores on a depression rating scale, irrespective of the state of withdrawal. Another study reported a positive correlation between the novelty seeking

personality trait and striatal [^{123}I]-β-CIT binding in a group of AUD patients (Laine et al. 2001). A [^{99m}Tc]-TRODAT SPECT study in AUD patients showed reduced DAT availability in striatum, which was more pronounced in proportion to the duration of alcohol abuse; this reduction in DAT availability was associated with impaired performance in the WCST (Yen et al. 2016).

In a [^{123}I]PE2I SPECT study of a group of nine AUD patients, striatal DAT availability was significantly decreased relative to the control group (Repo et al. 1999), which was seemingly confirmed in a postmortem whole hemisphere autoradiographic study with [^{123}I]PE2I (Tupala et al. 2001). Another postmortem study with [^{125}I]PE2I showed a lack of the usual correlation between age and DAT availability in AUD patients designated as Type I alcoholics, whereas there was the usual decline with age in the control material and Type II patient sample (Tupala et al. 2003). The authors speculated that the Type I group might have had a disease-related change in DAT obscuring the usual 5–10% decline per decade of healthy aging. In studies conducted in vivo using cerebral microdialysis or brain slice voltammetry, there was no sign of any differences in the alcohol-evoked dopamine release in wild-type and DAT-KO mice, indicating that effects on the dopamine system are unlikely to entail a direct interaction between ethanol and DAT (Mathews et al. 2006).

Upon release from presynaptic terminals, dopamine acts at receptors expressed on striatal medium spiny neurons and cortical pyramidal cells belonging to two pharmacological classes: dopamine D_1-like receptors (D_1R) and D_2-like receptors (D_2R). Preclinical evidence indicates that ethanol along with pentobarbital and flunitrazepam decreases the binding of the D_1R antagonist [^{3}H]Sch23390 in mouse striatum in a dose-dependent manner, without altering the binding in cerebral cortex (Inoue et al. 1992a). The pharmacological basis of the interaction is not immediately apparent.

In contrast to the sparse D_1R PET literature, there is an extensive literature on effects of alcohol and AUD on the D_2R, which has highest expression in the extended striatum, and much lower expression in cerebral cortex. Whole hemisphere autoradiography with [^{125}I]epidepride revealed decreased D_2R in cortex of Type I patients with AUD, versus a trend toward increased binding in Type II patients (Tupala et al. 2004). The kinetic analysis of uptake of the D_2R ligand [^{11}C]raclopride is amenable to quantitation as the steady-state binding potential (BP_{ND}; proportional to B_{max}/K_D) relative to uptake in cerebellum, a non-binding reference region. Notably, the magnitude of [^{11}C]raclopride BP_{ND} is influenced by competition from endogenous dopamine, such that increased dopamine release reduces the magnitude of BP_{ND} in living brain. Voxel-wise analysis of [^{11}C]raclopride BP_{ND} in healthy volunteers did not show any acute effects of intravenous alcohol administration, although individual declines in striatal BP_{ND} did correlate with the subjective responses (Yoder et al. 2007); this implies a considerable degree of variability in the dopaminergic response to a standard dose of alcohol in healthy volunteers. Furthermore, the same research group showed that alcohol infusion after neutral cues evoked a decrease in striatal [^{11}C]raclopride binding in healthy controls, consistent with unconditioned dopamine release, whereas olfactory cues not

followed by alcohol seemingly reduced dopamine release, consistent with a negative/positive reward prediction error model for dopamine (Yoder et al. 2009). On the other hand, others found that consuming an alcohol-free beer flavored beverage reduced ventral striatal [^{11}C]raclopride binding in a heterogeneous group of healthy males to an extent that was more pronounced in those subjects with close relatives suffering from AUD (Oberlin et al. 2013). Subsequent work showed that intravenous ethanol administration reduced [^{11}C]raclopride binding specifically in the left ventral striatum of heavy drinkers, whereas consumption of beer flavored drinks evoked dopamine release in the right ventral striatal; conjoint ethanol administration and beer flavored drink consumption evoked a bilateral dopamine release, suggesting the composite of conditioned and unconditioned effects (Oberlin et al. 2015). The cue-related decrease in [^{11}C]raclopride BP_{ND} in the right ventral striatum in habitual beer drinkers was associated with BOLD signal responses in the bilateral orbitofrontal cortex, consistent with a role for that region in decision making (Oberlin et al. 2016). Further [^{11}C]raclopride PET studies implicated polymorphism A118G in the mu-opioid-receptor gene as a major determinant of striatal dopamine responses to alcohol. Results showed that the striatal dopamine response to alcohol was restricted to carriers of the minor 118G allele (Ramchandani et al. 2011), which might contribute importantly to individual vulnerability to loss of control of alcohol intake.

Whereas in conventional practice, [^{11}C]raclopride administration is as a single bolus, the bolus plus continuous infusion experimental design obtains a persistent steady-state of binding during the PET session. This allows acquisition of PET recordings in the baseline and challenge conditions in a single study. Applying this method in healthy volunteers, D_2R availability at baseline in the left nucleus accumbens correlated with the subjective experience of intoxication after an ethanol infusion (Yoder et al. 2005). This could imply that low basal occupancy of these receptors by dopamine in healthy individuals predicts a greater response to pharmacological challenge evoking a release of dopamine. In another bolus plus infusion study, intravenous ethanol administration evoked a decline in [^{11}C]raclopride binding in groups of AUD patients and controls with and without family history of AUD by 6–7% in the ventral striatum and 2–5% in the caudate and putamen (Kegeles et al. 2018). There was an interaction with order of treatments, such that the subjects with family history who first received the placebo showed a relatively greater effect of the placebo, which could indicate a greater effect of expectation of alcohol infusion in these individuals, presumably indicating a greater vulnerability to its effects on dopamine release.

Using the [^{11}C]raclopride bolus plus infusion paradigm, others showed that intravenous ethanol evoked a bilateral 13% decrease in BP_{ND} in the ventral striatum, with lesser decreases also seen in the caudate/putamen (Aalto et al. 2015). The pronounced effect seen in that study may reflect the high dose, which resulted in a mean blood ethanol level of 1.3 g/L. On the other hand, intravenous infusion of ethanol at a rate clamping the blood level to 0.8 g/L (the legal limit for driving in many countries) evoked a decline in [^{11}C]raclopride binding confined to the right ventral striatum of AUD patients, but was without significant effect in a matched

group of social drinkers (Yoder et al. 2016). As such, AUD may entail a kind of sensitization to the dopamine-releasing effects of ethanol, or perhaps a greater sensitivity to alcohol-related sensory cues, even in the context of an ethanol infusion.

Comparison of a group of AUD subjects with healthy individuals indicated a 20% lower [^{11}C]raclopride BP_{ND} throughout striatum at baseline (Martinez et al. 2005). This result is consistent with a broad literature showing reduced dopamine receptor availability in various addiction conditions, including psychostimulant dependence (Volkow et al. 2007), obesity (Volkow et al. 2008), and even internet addiction (Kim et al. 2011). Furthermore, AUD subjects showed blunting of the [^{11}C]raclopride BP_{ND} reduction after pharmacological challenge with amphetamine, with only 5% displacement in the limbic striatum as compared to 13% in the control group (Martinez et al. 2005). In a combined FDG/[^{11}C]raclopride PET study, others showed blunting of the methylphenidate-induced dopamine release in a group of AUD patients compared with healthy controls (Volkow et al. 2013b). Furthermore, in that study the cerebrometabolic inhibition in striatum to FDG-PET showed a concomitant reduction in its response to methylphenidate; control and patient groups both showed strong correlations between striatal dopamine release with reduced FDG uptake in the subthalamic nucleus, anterior cingulate, and medial orbitofrontal cortex, thus implicating a disabling of limbic circuits.

In another study, the baseline and amphetamine-evoked reductions in [^{11}C] raclopride BP_{ND} did not differ in non-dependent individuals with and without family history of AUD, nor were there differences in the amphetamine-evoked cortisol and growth hormone levels (Munro et al. 2006). This suggests that the dopaminergic manifestations of AUD are more likely to be an acquired trait than genetically determined. However, a comparable [^{11}C]raclopride study in rats showed greater response to ethanol administration in Wistar rats as compared to (naïve) alcohol-preferring rats, which would be more consistent with a pre-existing genetic state of desensitization to dopamine-releasing effects of alcohol in that model (Sullivan et al. 2011).

Whereas [^{11}C]raclopride BP_{ND} reveals striatal D_2R binding, the more affine tracer [^{18}F]fallypride is also sensitive to the lower abundance extrastriatal binding, albeit with the requirement for more prolonged PET recordings. In a [^{18}F]fallypride PET study of healthy controls, intravenous infusion of ethanol was without much effect on D_2R availability (Pfeifer et al. 2017); on the other hand, baseline [^{18}F] fallypride binding in cortical regions correlated with a positive subjective experience. At baseline, a group of AUD patients showed a non-significant 8% reduction in striatal [^{18}F]fallypride BP_{ND}, and significant 10–20% reductions in thalamus, hippocampus, and insular and temporal cortex as compared to a healthy control group, thus calling attention to extrastriatal dopamine signaling in AUD (Rominger et al. 2012) (Fig. 1). The age-related decline in [^{18}F]fallypride binding was greater in the AUD group (7%/decade) than in the controls (4%/decade), but this loss was seemingly reversible; prolonged abstinence in some of the patients was associated with partial restoration of the striatal and thalamic binding (Fig. 2). Similarly, an [^{123}I] IBZM SPECT study showed that relatively higher striatal D_2R availability in detoxified inpatients predicted early relapse (Guardia et al. 2000); here, the higher

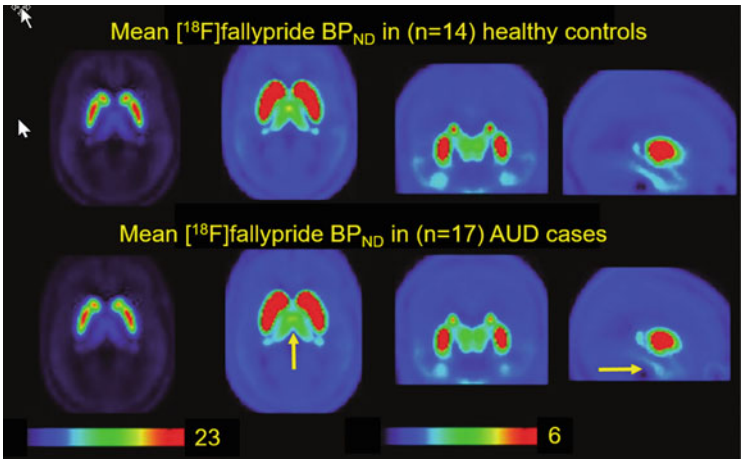

Fig. 1 Mean parametric maps of [^{18}F]fallypride BP_{ND} in groups of male healthy controls and AUD patients. The left-hand side with color scale to BP_{ND} of 23 shows little sign of altered D_2R availability in striatum of the AUD group. Contraction of the color scale to BP_{ND} of 6 shows 20% reductions in the binding in thalamus and entorhinal cortex. Figure modified with permission from Rominger et al. (2012)

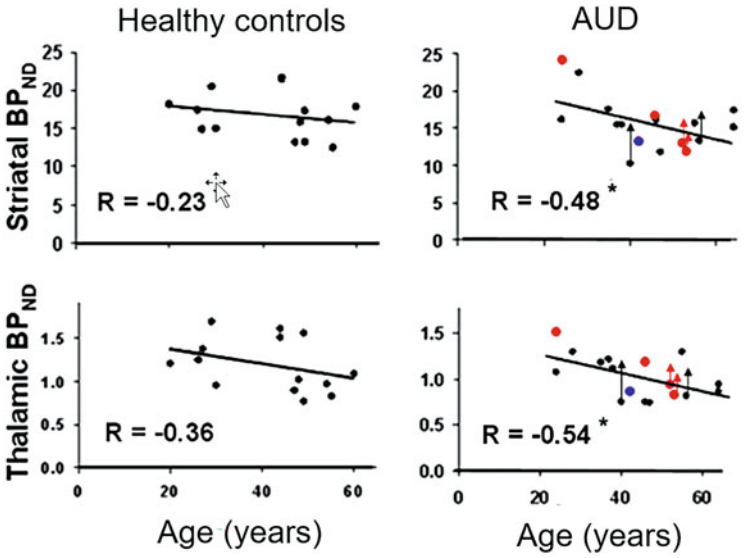

Fig. 2 Correlation of striatal and thalamic [^{18}F]fallypride binding potential (BP_{ND}) with age in (left) healthy controls and (right) AUD patients. The blue dot indicates a relapse with unaltered alcohol consumption, whereas the red dots indicate harm reduction compared to baseline consumption. The vertical arrows indicate individuals with increased BP_{ND} at long-term follow-up. Modified with permission from Rominger et al. (2012)

D_2R availability may indicate a lesser tonic occupancy by dopamine, rather than a down-regulation of D_2R per se. This distinction touches on the formal ambiguity of baseline findings with benzamide D_2R ligands, resolution of which calls for complex saturation binding studies involving administration of PET tracers at high and low molar activity (Cumming 2011).

8 Serotonin

A PET study with the serotonin selective reuptake site (SERT) ligand [^{11}C]DASB failed to show any group differences in a comparison of 30 inpatients with AUD with 18 healthy controls, nor was there any relationship with aggressive and violent characteristics of the alcoholic group (Brown et al. 2007). This result stood in contrast with findings of an earlier [^{123}I]β-CIT SPECT study, notably a study in 23 male AUD patients reporting a 30% lower availability of brainstem serotonin transporters relative to age-matched healthy controls (Heinz et al. 1998). This discrepancy may reflect the lesser sensitivity of [^{123}I]β-CIT SPECT, which is nearly ambivalent with respect to its affinity for DAT and SERT, and has lower specific binding than the SERT-selective PET ligand [^{11}C]DASB. PET studies with the controversial serotonin synthesis tracer α-[^{11}C]-methyl-*L*-tryptophan (Cumming 2014) showed cortical regions with elevated or decreased tracer uptake in a group of non-depressed AUD patients relative to controls (Nishikawa et al. 2009).

A PET study with the serotonin 2_AR antagonist ligand [^{18}F]altanserin did not show any relationship with alcohol (or tobacco) consumption in a large population of healthy volunteers (Erritzoe et al. 2009). The pre- and post-synaptic serotonin $5HT_{1A}$ receptors were studied in an [^{18}F]MFWAY PET study in non-human primates using a chronic alcohol self-administration model (Hillmer et al. 2014). Relative to the baseline condition, there were widespread increases in the availability of $5HT_{1A}$ receptors after 3 months of self-administration, notably in the dorsal raphe nuclei, where they represent presynaptic autoreceptors on serotonin neurons. This result suggested that low autoreceptor availability could predict the acquisition of ethanol self-administration.

9 Opioid Receptors

The clinical efficacy of opioid-antagonists, such as naltrexone and naloxone, in the treatment of AUD has motivated a series of PET investigations of opioid receptors, recently benefiting from the emergence of tracers that are selective for the μ, δ, and κ-opioid receptor subtypes. However, the first phase of the research used non-selective ligands such as [^{11}C]diprenorphine. In one such study, the [^{11}C]diprenorphine V_T was marginally increased in a group of early abstinence AUD patients (Williams et al. 2009); however, there was a significant correlation between

increased binding in the anterior cingulate cortex with the severity of craving, which is a predictor of relapse. In another study, AUD patients had relatively increased binding in the ventral striatum and other brain regions of the μ-selective agonist ligand [^{11}C]carfentanyl, but no differences in the uptake of the δ-selective ligand [^{11}C]methylnaltrindole (Weerts et al. 2011). In another [^{11}C]carfentanyl study, μ-opioid receptor availability was elevated in the ventral striatum and nucleus accumbens in AUD patients compared to healthy controls; this increase persisted after 5 weeks of abstinence and correlated with intensity of alcohol craving, which is predictor for relapse (Heinz et al. 2005a). In AUD patients under treatment with naltrexone (FDA-recommended dose of 50 mg daily), there was nearly complete occupancy at μ-opioid receptors labelled with [^{11}C]carfentanyl, but only 21% occupancy at δ-sites labelled with [^{11}C]methylnaltrindole (Weerts et al. 2008). In an extension of those study, the naltrexone-evoked increases in plasma cortisol levels showed a negative correlation with [^{11}C]methylnaltrindole in ventral striatum and other limbic brain regions of healthy subjects, whereas AUD subjects showed no such relationship (Wand et al. 2013). Similarly, there was a significant correlation between plasma cortisol response and baseline [^{11}C]carfentanyl binding in brain of healthy subjects, but no such relationship in the AUD group (Wand et al. 2012). The reason for these dissociations between brain receptor levels and cortisol release after naloxone challenge remains uncertain. A subsequent [^{11}C]carfentanyl PET study in alcohol-dependent patients compared the effects of naltrexone versus placebo treatment on relapse risk, and examined whether such effects are moderated by the A118G μ-opioid-receptor polymorphism (Hermann et al. 2017). They indeed found a significant interaction between the μ-opioid-receptor polymorphism, [^{11}C]carfentanyl binding in the ventral striatum, and relapse risk. More specifically, in carriers of the less common G-allele, lower striatal [^{11}C]carfentanyl binding was associated with a higher relapse risk, an effect that was especially pronounced in the group treated with naltrexone. The authors concluded that the low [^{11}C]carfentanyl binding in the ventral striatum might indicate a low tonic opioid signaling at μ-opioid-receptors, thus explaining the ineffectiveness of naltrexone treatment in this subgroup.

Occupancy by naltrexone at κ-opioid receptors labelled with [^{11}C]-LY2795050 by a dose of 100 mg naltrexone, which exceeds the FDA-recommended daily dose of 50 mg, correlated negatively with the reduction in alcohol consumption and correlated positively with craving in a mixed gender group of AUD patients treated with naltrexone (de Laat et al. 2020). The authors attributed these results to the competing effects of naltrexone at μ- and δ-opioid receptors. In another [^{11}C]-LY2795050 PET study, AUD patients had significantly reduced κ-opioid receptors in amygdala and pallidum compared to healthy controls and absence of the normal age-related decline in κ-opioid binding sites (Vijay et al. 2018). Naloxone-precipitated opioid withdrawal evoked increased [^{11}C]raclopride displacement in the dorsal striatum of opioid-dependent males (Shokri-Kojori et al. 2021) suggesting a link between opioid receptors and dopamine release in substance abuse. Moreover, the magnitude of this effect correlated with the aversive experience evoked by opioid receptor blockade.

10 Discussion and Conclusions

In reviewing the molecular imaging of AUD, we have focused on the effects of challenge with ethanol on brain metabolism and receptor availability, and the corresponding long-term changes encountered during withdrawal in AUD patients. Molecular neuroimaging studies have contributed to elucidating the mechanisms of alcohol on brain neurochemistry, receptor systems, reward processing, and the neurobiological basis of AUD symptomatology. Their results demonstrate widespread dysregulation in dopaminergic, opioid, serotonergic, and GABAergic systems in AUD. The presented results indicate that these changes are dynamic and dependent on the severity of the addiction, the time since last alcohol use and the individual history of alcohol exposure. This dynamicity might also explain the divergent results of molecular neuroimaging studies. In addition, individual patient characteristics, such as gender and smoking status, which have not been investigated systematically in molecular neuroimaging studies yet, but were repeatedly associated with different alcohol use patterns and treatment trajectories, might explain variability in presented study results.

Effects of ethanol on the GABAergic system mediate ethanol's acute sedating and anxiolytic effects. The reduction in $GABA_AR$ availability observed in animal and human PET studies suggests a down-regulation of these receptors or changes in receptor affinity, which might in part explain differences in ethanol sensitivity and development of tolerance toward ethanol's effects. However, the interpretation of such results is made complicated by subtype specificity of the available tracers. With regard to withdrawal states, the available preclinical and clinical data – mainly derived from spectroscopic and microdialysis studies – have indicated that disturbed balance between GABAergic and glutamatergic systems results in a hyperglutamatergic state, which drives withdrawal symptoms (Hermann et al. 2012; Roberto and Varodayan 2017). Currently, the lack of NMDA receptor tracers limits the capacity of molecular neuroimaging studies to document specific changes in the glutamatergic neurotransmission system.

The available molecular neuroimaging PET and SPECT studies consistently show changes in dopamine D_1R and D_2R availability, as well as changes in DAT availability in patients with AUD. Results from animal and human data converge in demonstrating significant ethanol-induced displacement of dopamine-tracer BP_{ND}s in striatal regions, which are associated with a subjective ethanol-induced "high" and thus support a key role for dopamine in mediating the rewarding properties of alcohol. Presented data are compatible with the occurrence of a dynamic change from a hypodopaminergic state during early withdrawal to a hyperdopaminergic state during longer abstinence. This seems consistent with the findings of a recent meta-analysis of human and animal data (Hirth et al. 2016), also matching with the theoretical conceptual neurobiological framework of addictive disorders proposed by Koob and Volkow. Dynamic changes occur in dopaminergic neurotransmission proceeding from acute intoxication and binge stages, through the withdrawal and negative affect stage, to the preoccupation and anticipation stage of dependence.

Hypodopaminergic and hyperdopaminergic states might both represent dysfunction of the reward processing system that drives alcohol use and relapse in patients with AUD. As the functional state of the dopaminergic system has been associated with increased craving in individuals with AUD, the potential dynamic regulation of the dopamine system in AUD should have consequences for pharmacological treatments. Depending on the current state of the dopaminergic system, direct pharmacological interventions with agonists or antagonists of D_1R or D_2R would yield variable behavioral effects. Perhaps in line with this hypothesis, clinical studies investigating direct dopamine receptor antagonists did not yield consistent effects (Hutchison et al. 2006; Schmidt et al. 2002; Wiesbeck et al. 2001). New approaches that consider receptor internalization and desensitization might help to elucidate the complex dynamics of the dopaminergic system in AUD.

Molecular neuroimaging studies have significantly contributed to our understanding of the role of the opioid systems in AUD and the neurobiological effects of pharmacological treatment with opioid-antagonists, such as naltrexone. The available data from studies that used selective tracers for the μ, δ, and κ-opioid receptor subtypes indicate a higher μ-opioid receptor availability in the ventral striatum, nucleus accumbens, and anterior cingulate cortex in patients with AUD and a significant positive association between μ-opioid receptor availability and alcohol craving, which predicted subsequent relapse. In contrast, data indicated a decrease in κ-opioid receptors in amygdala and pallidum in individuals. Regarding the effects of opioid-antagonists, study data showed that FDA-recommended doses of 50 mg naltrexone produced a near complete inhibition of the μ-opioid receptor in recently abstinent patients with AUD, while there was a lower inhibition and greater variability of δ-opioid receptor blockade, which may contribute to individual differences in treatment outcomes to naltrexone. In addition, higher doses of naltrexone (100 mg per day) yielded a κ-opioid receptor occupancy above 90%, which was associated with higher craving and fewer reductions in alcohol use. This might indicate that especially the actions of naltrexone at μ-opioid receptors (and to a lesser extent at δ-opioid receptors) might confer its beneficial effects on relapse risk and drinking outcomes, while κ-opioid receptor blockade, as seen with higher doses, might be associated with lesser efficacy. This biphasic effect could also provide a framework for explaining the observations that lower doses of naltrexone can have greater clinical efficacy in patients with AUD.

The limited molecular neuroimaging data on the serotonergic system in AUD indicate changes in serotonin transporter availability and availability of $5HT_{1A}$ receptors in the brainstem. From a clinical perspective, the serotonergic system is of interest, due to the high comorbidity of AUD and depressive disorders. In addition, treatment with antidepressants has had inconsistent effects on depressive symptoms and drinking behavior in clinical trials, which draws attention to the likely importance of individual differences in the serotonergic systems of patients with AUD (Agabio et al. 2018). Furthermore, ionotropic $5\text{-}HT_3$ receptors may represent a viable pharmacological treatment target in AUD, due to their role in regulating dopamine release in the mesolimbic system (Kilpatrick et al. 1996). In line with that finding, a preliminary clinical trial indicated a significant effect of the $5\text{-}HT_3$

receptor antagonist ondansetron on alcohol use in patients with AUD (Johnson et al. 2000). Here molecular neuroimaging studies that target the serotonergic system might contribute to a better understanding of the variable treatment effects observed in patients with comorbid AUD and depression. After a long moratorium against clinical research with ibogaine and classical hallucinogens, we are seeing new interest in their potential for relieving AUD (Barsuglia et al. 2018; Cameron et al. 2021).

Regarding the detrimental effects of alcohol on brain metabolism and brain structure, molecular neuroimaging studies provided proof for a dose-dependent effect of ethanol on cerebral metabolism, with higher doses of ethanol resulting in widespread hypometabolism. In addition, studies indicated an ethanol-induced TSPO-dependent activation of microglia in the brain and following neuroinflammatory responses as a potential mediator of ethanol's detrimental effects on cerebral metabolism and brain structure. By probing acute and chronic changes in cerebral metabolism and neurotransmission, we may come to establish better the nature of dependence and the correlates of abstinence and relapse, perhaps delivering a more individualized medicine that can support improved outcomes for those living with AUD.

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