The Role of Neurotransmitter Systems in Eating and Substance Use Disorders

3

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Abstract

Eating disorders (ED) as well as substance use disorders (SUD) commonly start during adolescence and young adulthood, an important time of brain maturation that includes neurotransmitter receptor expression. Increasing attention should be paid to neurobiological mechanisms and brain circuit alterations that may be shared across those potentially related disorders. Studies in ED suggested lower cerebrospinal fluid (CSF), serotonin (5-HT), and dopamine (DA) metabolite levels, neurotransmitters involved in the regulation of eating, mood, and anxiety, among other functions. Higher 5-HT metabolite levels after recovery suggested that this could be a trait alteration. The body of CSF neurotransmitter research in SUD is small. However, alcoholism may be associated with reduced CSF 5-HT metabolites, and acute substance use may increase 5-HT release but also inhibit 5-HT neuronal activity through auto-inhibition, while withdrawal from most substances is associated with reduced extracellular 5-HT. More recent research in ED using brain imaging implicated neurotransmitter receptors such as the 5-HT_{1A} receptor, 5-HT_{2A} receptor, and 5-HT transporter or DA D2/3 receptors, which predicted high anxiety and harm avoidance. Studies in SUD suggested 5-HT and DA receptors may undergo adaptive changes during stages of the illness. Other addictive disorders include tobacco use and gambling behavior, and their neurobiology has been linked to reward and DA pathways. Overall, research suggests that 5-HT and DA are involved in the neurobiology ED and SUD as well as behavioral addictions, and comparative research across disorders should be undertaken to identify underlying mechanisms.

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3.1 Introduction

The eating disorders (ED) anorexia (AN), bulimia nervosa (BN), and binge-eating disorder (BED), as well as the substance use disorders (SUD), commonly start during adolescence or young adulthood (American Psychiatric Association, 2013), a time full of changes in brain biology and maturation (Rumsey & Ernst, 2009). Advances in technology have allowed us to examine aspects of central neurotransmitter systems that could be related to eating and addictive disorder pathophysiology. Older studies have focused on cerebral spinal fluid (CSF) to examine metabolite levels of various neurotransmitters such as serotonin (5-HT), dopamine (DA), norepinephrine (NE), and opioids, as well as other indirect measures of central neurochemical concentration and activity, such as platelet studies and pharmacologic challenge studies. Since then, various brain imaging techniques have been employed to examine brain neurotransmitter receptor availability, especially positron emission tomography (PET), which uses radio tracers that bind to specific neurotransmitters in the brain. In the more recent past, brain imaging techniques such as functional magnetic resonance imaging (fMRI) have used behavioral paradigms that stimulate specific neurotransmitter circuits, an approach that helps tie brain neurotransmitters to disorder-relevant behaviors. One such approach is the study of the brain reward system. Both food and substances of abuse provide powerful stimulation of brain reward circuits (Kelley & Berridge, 2002; Kelley, Schiltz, & Landry, 2005), and hence, there should be significant overlap in the neurobiology of neurotransmitters across those disorders (Kaye et al., 2013). This chapter will review past neurotransmitter research in ED and SUD as well as describe recent developments that may help identify altered brain circuits that may be shared between those disorders.

3.2 Serotonin

3.2.1 Anorexia Nervosa

Several authors have reviewed evidence for 5-HT dysregulation in individuals who were ill with AN and BN (Brewerton, 1995; Jimerson, Lesem, Kaye, Hegg, & Brewerton, 1990; Jimerson et al., 1997; Kaye, Strober, & Jimerson, 2004; Steiger, Gauvin, et al., 2001; Treasure & Campbell, 1994). Brain 5-HT is involved in mood, anxiety, feeding, and sleep regulation among other processes (Naughton, Mulrooney, & Leonard, 2000). Early studies used CSF 5-HT metabolite levels to approximate 5-HT *brain* levels (Stanley, Traskman-Bendz, & Dorovini-Zis, 1985).

Ill restricting-type AN subjects had a significant reduction in CSF of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) compared to control women (Jimerson, Lesem, Hegg, & Brewerton, 1990; Kaye, Ebert, Gwirtsman, & Weiss, 1984; Kaye, Gwirtsman, George, Jimerson, & Ebert, 1988). Interestingly, a recent study has found increased 5-HT but also DA metabolites in obesity (Markianos, Evangelopoulos, Koutsis, & Sfagos, 2013), indicating that symptomatic AN and OB may be on opposite ends of a neurobiological spectrum. In comparison, recovered restricting-type AN subjects had elevated concentrations of CSF 5-HIAA, proposing the possibility that elevated 5-HT could be a premorbid trait. 5-HT neuronal pathways play a role in the expression of anxiety and fear, obsessional behaviors, and depression (Charney, Woods, Krystal, & Heninger, 1990; Kaye et al., 2008; Price, Charney, Delgado, & Heninger, 1990), and increased 5-HT activity may be related to harm-avoidance traits (Kaye et al., 2008). By depleting tryptophan, the dietary precursor of 5-HT (Fernstrom & Wurtman, 1971), food restriction may produce anxiolytic effects for those predisposed to ED development. In fact, studies have found that depletion of tryptophan (TRP) may reduce dysphoric mood in ill and recovered AN subjects (Kaye et al., 2003), and food reduction may thus produce "self-medicating" effects.

Neurotransmitter receptor imaging studies assess the "functional availability" of 5-HT receptors in the brain. In particular, the 5-HT_{1A} and 5-HT_{2A} receptors are believed to be involved in the modulation of mood, feeding, impulse control, sleep, and anxiety. Using PET and the radioligand [11C]WAY, 5-HT_{1A} receptor binding has been found to be elevated across most brain regions in a mixed group of symptomatic restricting- and binge-eating/purging-type AN subjects compared to healthy controls, as well as in binge-eating/purging-type AN after recovery (Bailer et al., 2005). In contrast, recovered restricting-type AN individuals showed normal brain 5-HT_{1A} binding (Bailer et al., 2005). In addition, there appears to be reduced 5-HT_{2A} binding in the frontal, parietal, and occipital cortices in both ill and recovered AN individuals (Audenaert et al., 2003; Frank et al., 2002). In summary, after recovery, 5-HT_{1A} receptor binding seems to differentiate AN subtypes, whereas 5-HT_{2A} receptor binding is reduced in both restricting and binge-eating/purging AN in various brain regions. Since these disturbances occur after recovery, they may reflect either trait disturbances or scars from the illness.

Some progress has been made to tie such neuroreceptor abnormalities to ED-related behaviors. Harm avoidance, a behavioral correlate of anxiety, has been found to be positively correlated with mesial temporal cortex (amygdala and hippocampus) 5-HT_{2A} binding in recovered binge-eating/purging AN, and with mesial temporal cortex 5-HT_{1A} binding in recovered restricting-type AN. Most recently, the interaction of 5-HT transporter binding with DA receptor availability was associated with harm avoidance in AN after recovery (Bailer et al., 2013), suggesting that interaction of those two neurotransmitter systems contributes to the modulation of complex behaviors such as anxiety.

The 5-HT_{1A} receptor has been implicated in food reward modulation (Carli & Samanin, 2000), while the 5-HT_{2C} receptor may in part transmit "reward signals" (Higgins & Fletcher, 2003). Serotonin brain levels influence weight in rodents,

there is cross talk with reward modulating sites (Konkle & Bielajew, 1999), and 5-HT is implicated in delay of reinforcement and reward processing (Cardinal, Winstanley, Robbins, & Everitt, 2004). Furthermore, 5-HT may be involved in the learning and "appraisal" of rewarding stimuli (Merali, Michaud, McIntosh, Kent, & Anisman, 2003). Thus, the 5-HT system appears to take part in cognitive, emotional, and salience aspects of eating modulation.

Some, but not all, genetic studies support altered 5-HT receptor function in AN (Collier et al., 1997; Enoch, Greenberg, Murphy, & Goldman, 2001; Hinney, Ziegler, Nothen, Remschmidt, & Hebebrand, 1997; Nacmias et al., 1999; Sorbi et al., 1998), and the possibility that genotype could contribute to 5-HT receptor function in AN will need further study.

3.2.2 Bulimia Nervosa

Ill individuals with BN have normal CSF 5-HIAA levels, but the more severely affected present with lower CSF 5-HIAA levels (Jimerson, Lesem, Kaye, & Brewerton, 1992). In contrast, recovered BN individuals showed elevated CSF 5-HIAA (Kaye & Weltzin, 1991). This suggests that abnormally high 5-HT brain levels could be a trait marker for AN as well as BN. Considerable evidence also exists for a dysregulation of 5-HT processes in BN. Examples include blunted prolactin response to the 5-HT receptor agonists m-chlorophenylpiperazine (m-CPP), 5-hydroxytrytophan, and DL-fenfluramine and enhanced migraine-like headache response to m-CPP challenge (Brewerton & George, 1993; Brewerton, Mueller, et al., 1992; Monteleone, Brambilla, Bortolotti, Ferraro, & Maj, 1998). Acute perturbation of 5-HT tone by dietary depletion of tryptophan has also been linked to increased food intake and mood irritability in individuals with BN compared to healthy controls (Bruce et al., 2009), which further suggested that this neurotransmitter system could be involved in the psychopathology of BN.

Brain imaging studies (Kaye et al., 2001) have found reduced orbitofrontal 5-HT_{2A} receptor binding in recovered BN using PET and the radioligand [18F] altanserin. A number of studies have implicated the orbitofrontal cortex in inhibitory processes (Robbins, 2005) and in the representation of food-related affective values (Kringelbach, O'Doherty, Rolls, & Andrews, 2003). Thus, orbitofrontal alterations may contribute to behavioral disturbances associated with BN, such as impulsivity and altered emotional processing (Steiger, Young, et al., 2001), although this has not been explored empirically yet using specific behavior tasks with 5-HT-related probes. BN women failed to show the negative correlations of age and 5-HT_{2A} binding found in normal controls (Kaye et al., 2001), and this lack of correlation may reflect a scarring effect from the illness. Symptomatic BN patients have also shown reduced 5-HT transporter binding in the thalamus and hypothalamus (Tauscher et al., 2001), but increased 5-HT_{1A} receptor binding (Tiihonen et al., 2004), most prominently in the medial prefrontal cortex, posterior cingulate, and angular gyrus of the parietal cortex. After recovery, patients with BN had increased 5-HT_{1A} binding compared to healthy controls as well (Bailer et al.,

2011), and 5-HT_{1A} binding in BN predicted measures for inhibition. The dynamics between 5-HT receptor expression and synaptic 5-HT are not well understood. Reduced 5-HT_{2A} binding in recovered BN subjects may be related to higher level of endogenous 5-HT in the synaptic cleft or a downregulation of the receptor. With the same schema, increased 5-HT_{1A} receptor binding during the symptomatic state may reflect reduced 5-HT synaptic level and an upregulation of the receptor (Enoch et al., 1998; Jimerson et al., 1992). In addition, reduced 5-HT transporter availability in ill individuals with BN may be an adaptation in response to lowered 5-HT concentrations in the premorbid state. Of interest, selective 5-HT reuptake inhibitors (SSRIs) are effective in the treatment of BN, but symptomatic BN requires higher doses of such medications compared to, for instance, patients being treated for depression. This relative resistance to SSRI treatment may be related to an upregulation of 5-HT_{1A} autoreceptors, which inhibit 5-HT release.

3.2.3 Binge-Eating Disorder

A new ED, binge-eating disorder (BED), was just introduced in the last edition of the DSM (American Psychiatric Association, 2013). That disorder is characterized by binge episodes as in bulimia nervosa but lacks compensatory mechanisms, and BED is therefore typically associated with obesity. BED individuals share high depression and anxiety in addition to preoccupation over shape and weight with AN and BN. The use of the 5HT reuptake inhibitors fluoxetine and sertraline showed some promise reducing binge-eating symptoms and body weight in BED (Leombruni et al., 2008), but it is yet unclear whether the use of such medication is in fact targeting binge eating or rather depression and anxiety, with eating behavior changes as secondary effects (Akkermann, Nordquist, Oreland, & Harro, 2010). A small study with ten BED subjects studying prolactin response to the 5HT stimulating challenge drug D-fenfluramine did not find a difference on this measure compared to controls (Monteleone, Brambilla, Bortolotti, & Maj, 2000). The supplement chromium effects mood and eating behavior and has shown some promising pilot results, but larger studies will be needed for confirmation (Brownley, Von Holle, Hamer, La Via, & Bulik, 2013).

3.2.4 Substance Use Disorders

Studying neurotransmitters in addictive disorders is similarly difficult as in ED, as the biological effects here of drug or alcohol interact with existing predisposing biological factors, and teasing apart short-lived state from illness determining trait factors is complex. This has complicated human research in this area, and most of the knowledge stems from animal studies, although they might not reflect "real-life" circumstances. However, it is known that acute administration of substances such as alcohol, stimulants, cocaine, and opioids increases extracellular 5-HT but in return decreases 5-HT neurotransmission via either 5-HT_{1A} receptor auto-inhibition

(in response to alcohol, cocaine, stimulants) or gamma-aminobutyric acid (GABA) action (in response to opioids) in the brain (Kirby, Zeeb, & Winstanley, 2011). Interestingly, 5-HT neuronal response tends to normalize again during chronic use, while withdrawal has been associated with decrease of extracellular 5-HT, and thus possibly contributing to dysphoria and craving during removal of the substance from the organism (Kirby et al., 2011).

The body of literature on neurotransmitter research in humans with SUD problems has been small and is not always easy to interpret with respect to disorder pathology. CSF studies have found a variety of results across alcohol and substance addictions. 5-HIAA levels of alcoholics 1–2 months after their last drink were significantly lower compared to healthy controls or alcoholics within 1–2 days after their last drink (Ballenger, Goodwin, Major, & Brown, 1979). Others found reduced platelet 5-HT content, uptake, and CSF 5-HIAA secondary to chronic alcohol use, which was hypothesized be related to anxiety and depression associated with alcohol use (Tollefson, 1989). However, another study did not find 5-HIAA levels in CSF in alcohol dependence different from controls, and there was also no group difference in DA or NE metabolites (Agartz, Shoaf, Rawlings, Momenan, & Hommer, 2003). More than ten brain imaging studies have assessed the 5-HT transporter in alcohol dependence, but no uniform picture has emerged, that is, studies found increased, normal, or decreased transporter availability (Cosgrove, 2010).

A study in cocaine addiction found no significant relationships between cocaine craving scores and CSF 5-HIAA concentrations, but that study did not report on a comparison group (Roy, Berman, Gonzalez, & Roy, 2002). Ecstasy users however showed lower CSF 5-HIAA compared to controls (Stuerenburg et al., 2002). The number of studies that has investigated CSF neurotransmitters including 5-HT is small, but chronic alcohol or substance use may be associated with lower 5-HT metabolites in CSF compared to controls. How this contributes to illness behavior is uncertain. However, ED and SUD are associated with alterations in 5-HT system activity, and this could contribute to mood and anxiety problems that could prolong the illness or promote relapse. Brain imaging of the 5-HT transporter found increased availability in the brain stem of cocaine-dependent individuals during acute abstinence, which could indicate a compensatory upregulation (Jacobsen et al., 2000). In contrast, in alcoholism, 5-HT transporter availability was lower in some studies (Heinz et al., 1998; Szabo et al., 2004) but normal in another (Brown et al., 2007) compared to controls. Importantly, tobacco smoking may have an important confounding role in those studies by apparently suppressing 5-HT transporter availability in alcoholism (Cosgrove et al., 2009).

3.2.5 Other Addictive Disorders

Gambling disorder is new in DSM-5, and tobacco use has now the same criteria as the other SUD. A multitude of neurotransmitter systems are involved in gambling, including 5-HT (Leeman & Potenza, 2013), but whether for instance increase

(Cuomo et al., 2013) or depletion (Koot et al., 2012) of 5-HT promotes the behavior is uncertain. The highly addictive substance nicotine acts on nicotinic acetylcholine receptors and 5-HT among transmitters such as adenosine, cannabinoids, DA, and glutamate, but the exact mechanisms need further study (Wooters, Bevins, & Bardo, 2009).

3.2.6 Summary

While our understanding of 5-HT in the pathophysiology of those disorders is limited, there may be important overlap between the importance of 5-HT in ED and SUD. As mentioned above, 5-HT has been associated with high anxiety and inhibition in ED. In SUD and addictions, high impulsivity has been associated with disease risk, and 5-HT might have an important role in this trait behavior (Winstanley, Dalley, Theobald, & Robbins, 2004; Winstanley, Olausson, Taylor, & Jentsch, 2010). For instance, individuals vulnerable to addiction may show higher "impulsive choice," a construct that includes the inability to await larger rewards in the future, instead selecting smaller but immediate rewards (Ainslie, 1975; Reynolds, 2006). Clinically, this could be translated into the inability to work toward the benefits of long-term recovery and rather chose the immediate, short-term perceived benefits from substance or alcohol use. Therefore, neurobiologically, AN and addictive disorder individuals could be on opposite ends of a spectrum of low to high impulsivity, possibly mediated at least in part by 5-HT function. The BN population is somewhere in the middle in this framework with aspects of both inhibition and disinhibition, which is reflected phenotypically in binge/purge episodes alternating with food restriction (Tozzi et al., 2005). AN, BN, and SUD populations have heightened sensitivity to salient stimuli (Brunelle et al., 2004; Jappe et al., 2011; Lyvers, Duff, Basch, & Edwards, 2012; Wagner et al., 2006). How those potential traits interact with high anxiety and inhibition in ED (Fig. 3.1) but frequently low inhibition and high impulsivity in SUD will require further careful and comparative study.

3.3 Dopamine

The DA pathways are a neuromodulatory system that arises from cells in the midbrain (Kapur & Remington, 1996). These midbrain neurons release DA, which acts on DA receptors. DA function contributes to the modulation of motor activity (Alexander, Crutcher, & DeLong, 1990), weight and feeding behaviors (Halford, Cooper, & Dovey, 2004), and reinforcement and reward (Volkow, Fowler, & Wang, 2002). There is some indication that AN responds to typical and atypical neuroleptics (Brewerton, 2004; Brewerton, 2012; Cassano et al., 2003), which may indicate alterations in the DA system in that disorder.

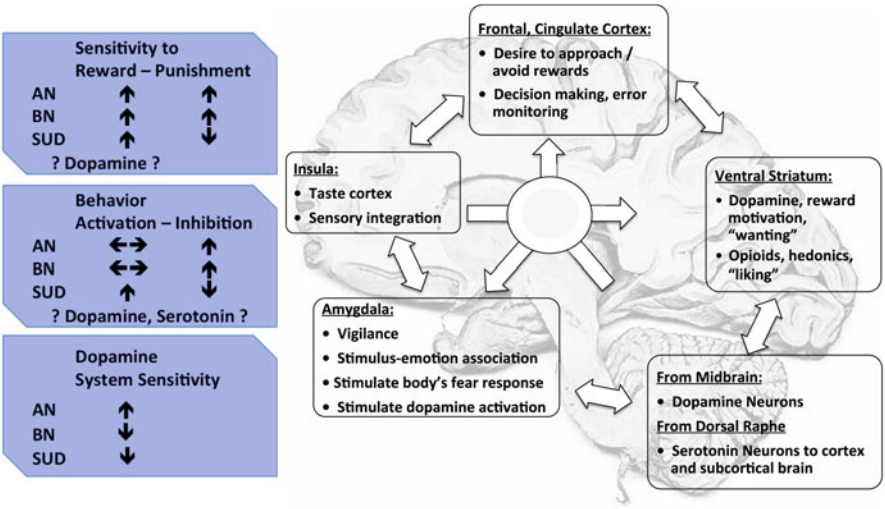

Fig. 3.1 To the left are behavioral and biological aspects that could drive eating and substance use disorder behaviors. To the right is a schematic of brain structures involved in reward processing. *AN* anorexia nervosa, *BN* bulimia nervosa, *SUD* substance use disorder

3.3.1 Anorexia Nervosa

In ill AN, CSF homovanillic acid (HVA), the major DA metabolite, was reduced by about 30 % compared to controls (Kaye, Ebert, Raleigh, & Lake, 1984). In addition, recovered restricting-type AN subjects had significantly reduced concentrations of CSF HVA compared to controls and other ED subjects (Kaye, Frank, & McConaha, 1999). Whether individuals with restricting-type AN have an intrinsic disturbance of DA (James & Starr, 1980; Kapur & Remington, 1996; Ugedo, Grenhoff, & Svensson, 1989) remains uncertain. A mixed group of recovered restricting-type and recovered binge-eating/purging-type AN women had increased DA D2/D3 receptor binding potential (BP) in the anteroventral striatum (Frank et al., 2005), while decreased D2/D3 receptor binding has been found in obese subjects (Wang, Volkow, Thanos, & Fowler, 2004). That finding supports the possibility that D2/D3 receptor binding may be inversely related to weight and eating, with restricting-type AN on one end and obesity on the other end of the spectrum. Thus, increased D2/D3 receptor availability in AN may contribute to a drive to become emaciated. Increased DA D2/D3 receptor binding in AN might help explain the underlying mechanism for why individuals with AN are able to lose weight, resist eating, and overexercise, are protected from substance abuse, and are insensitive to natural rewards. It is worth noting that food restriction sensitizes D2/D3 receptors in rats, and if the same mechanism happens in AN then this could be a factor complicating recovery (Carr, Tsimberg, Berman, & Yamamoto, 2003). The mentioned PET imaging studies tested available DA receptor profiles, but they could not test the

functionality of those receptors in relation to actual behavior. Others found increased eye blink compared to controls (Barbato, Fichele, Senatore, Casiello, & Muscettola, 2006) that suggested heightened DA sensitivity (Karson, 1983) in AN, which could provide important clues that a downregulation of receptor sensitivity might be important, despite the notion of low extracellular DA in AN.

3.3.2 Bulimia Nervosa

The early research indicated that CSF HVA is normal in individuals with BN when they are ill (Kaye et al., 1990). A very recent study found that BN individuals had a trend to lower DA D2/3 receptor binding in the striatum compared to controls, and BN individuals showed less DA release compared to controls in response to methylphenidate application (Broft et al., 2012). While this body of research is small, it suggests that food restriction in AN may increase, and episodic binge eating in BN could reduce DA pathway activity.

3.3.3 Binge-Eating Disorder

Having the addiction model in mind as in BN, research in BED has also focused on brain DA function. A fairly solid model exists that describes DA in the mechanism of binge eating (Avena, Bocarsly, & Hoebel, 2012) suggesting an addictive quality **(see Chaps. 1 and 13)**. Further, human studies have found higher DA release in relation to binge eating (Wang et al., 2011), and the DA D2 receptor may be involved in this disorder (Davis et al., 2012). A recent study in rodents supports that notion (Halpern et al., 2013). Another recent study using the DA reuptake inhibitor bupropion in BED led to short-term lower body weight, but did not improve behaviors such as binge eating or food craving (White & Grilo, 2013). All in all, the BED population is neurobiologically very heterogeneous, and no clear recommendations can be given for pharmacologic intervention (Marazziti, Corsi, Baroni, Consoli, & Catena-Dell'Osso, 2012).

3.3.4 Substance Use Disorders

DA has been extensively studied in animal models of addictive disorders. This stems from the understanding that this neurotransmitter is intimately involved in the processing of and response to salient, "rewarding or punishing" stimuli (Kelley & Berridge, 2002; Ross & Peselow, 2009). Studying brain circuits that are related to DA models in the context of brain reward function is particularly interesting for several reasons. First, within brain reward circuits, DA is critically associated with providing signals regarding the presence and amplitude of rewards (Kelley, Baldo, Pratt, & Will, 2005; Schultz, 2002). Such signals facilitate reinforcement learning (Daw & Doya, 2006) and have been found to code the value of a stimulus (Daw,

Gershman, Seymour, Dayan, & Dolan, 2011; Jocham, Klein, & Ullsperger, 2011), which may even include the metabolic value of food (de Araujo, Ren, & Ferreira, 2010). Second, computer models for DA neuron reward activation exist that can be related to human in vivo brain function (Sutton & Barto, 1998), helping in the study of in vivo dynamics of human DA function.

Alcoholism was not associated with alterations in HVA levels compared to controls in an early study (Ballenger et al., 1979), in a small follow-up study (Sjoquist & Borg, 1984), or in a larger more recent investigation (Agartz et al., 2003). One study though found higher HVA levels in early onset alcoholics compared to controls or late onset alcoholic subjects, but HVA levels were unrelated to craving measures (Petrakis et al., 1999). In contrast, cocaine-dependent individuals showed significantly higher CSF HVA than did the healthy controls, as did short-term abstinent cocaine-dependent individuals (Roy, Berman, Gonzalez, et al., 2002; Roy, Berman, Williams, Kuhn, & Gonzalez, 2002). Thus, in alcoholism DA metabolites do not seem to reflect the addiction pathophysiology, although the time of onset of the alcohol disorder could be related to HVA levels. There may be more to be learned from CSF HVA in cocaine addiction, but the research body is small and cannot be interpreted without using great caution.

DA transporter availability was in most studies increased in cocaine addiction compared to controls (Crits-Christoph et al., 2008; Jacobsen et al., 2000; Malison et al., 1998). It was hypothesized that this would be a compensatory upregulation, and this was supported by the gradual decline in receptor levels during abstinence. The DA D2/3 receptor was found to be lower compared to controls in most cocaine dependence studies, possibly a sign of downregulation in response to overstimulation (Martinez et al., 2004; Volkow et al., 1993; Volkow et al., 1990). In contrast, lower DA D2/3 receptor availability seems to be a more consistent marker for alcohol dependence (Cosgrove, 2010). Importantly, lower DA D2/3 receptor availability may be related to greater alcohol craving (Heinz et al., 2004) and higher consumption (Martinez et al., 2005), as well as predict treatment outcome or relapse (Guardia et al., 2000).

3.3.5 Other Addictive Disorders

As stated above, multiple neurotransmitter systems are involved in addictions including tobacco and gambling. This is complicating treatment development, and effective treatments were frequently found by chance, while systematically studied compounds that promised success in animal models have failed (Pierce, O'Brien, Kenny, & Vanderschuren, 2012). Gambling disorder is new to the field of addictions and as there are only moderately well-formed concepts of neurotransmitter involvement. Similarly to tobacco use, careful study will be required to identify key neurotransmitters that can become targets for pharmacologic intervention. DA appears to be the obvious first neurotransmitter, but as above in SUD, its involvement is intertwined with many other systems in the brain.

3.3.6 Summary

DA function is a particularly interesting neurotransmitter system to study across ED, SUD, and other addictive disorders. There is a clear overlap between natural rewards such as food and substances of abuse and addiction with respect to activation of the reward pathways (Kelley & Berridge, 2002). Prospective studies in rodents that were exposed to over- or underconsumption of food (Avena, Rada, & Hoebel, 2008; Carr, 2007; Johnson & Kenny, 2010) suggest adaptive DA-related changes to food intake with sensitization to food restriction but desensitization to excessive food ingestion quality (see Chaps. 1 and 13). Similar models have been proposed for addictive disorders, where the organism eventually desensitizes so much that exposure to alcohol or drugs only improves the mood state toward "normal" without providing the "high" when first using (Koob & Le Moal, 2005). For the addiction field a so-called reward deficiency model has been established, proposing that such a reduced reward response could drive excessive use (Blum, Gardner, Oscar-Berman, & Gold, 2012; Comings & Blum, 2000). This model could fit the proposed psychopathology in BN and BED with a downregulation of response to food stimuli and excessive sensitivity in AN after deprivation. Importantly, such adaptations could be targeted when in search for neurobiological treatments for those disorders.

3.4 Norepinephrine

NE is part of the body's stress system, which is also closely linked to the corticoid system and corticotropin-releasing factor (CRF). Foods, as well as substances of abuse, are regularly used by individuals in response to stress, while in AN food *restriction* may be used in an attempt to handle stress better. Animal research has shown that during withdrawal of substances of abuse anxiety increases, the responsiveness to rewards is lowered, DA system function is reduced, and this is accompanied by increases of CRF in the amygdala (Koob, 2010, 2013). Thus this biologic system around stress may be highly important as a trigger for behaviors that involve eating or alcohol and drug use. Other behaviors and central functions that norepinephrine is involved are learning and memory, sleep–wake cycle, reinforcement, and general body metabolism, functions that have been associated with eating behavior (Cooper, Bloom, & Roth, 2003).

3.4.1 Eating Disorders

The CSF levels of NE in underweight AN individuals and in these patients a few weeks after weight restoration were similar to those in normal subjects, while long-term (20 ± 7 months) weight-recovered AN individuals had a 50 % decrease in CSF NE levels compared with those of controls (Kaye, Ebert, Raleigh, et al., 1984), which could point toward trait alterations. A study in obese individuals did not find

alterations in NE metabolites (Markianos et al., 2013), while another study found that obese individuals compared to controls had reduced NE metabolite methoxyhydroxyphenylglycol (MHPG) levels in addition to reduced corticotropin-releasing hormone, beta-endorphins, and neuropeptide Y (Strombom et al., 1996).

Bulimic patients had a significantly lower mean CSF NE concentration, while CSF 5-HIAA and HVA were normal compared to controls (Kaye et al., 1990).All in all, there may be alterations in ED with respect to the body's stress system, but the data are too few to draw meaningful conclusions at this point.

3.4.2 Substance Use Disorders

The available basic research in SUD and NE is larger, and theoretical models exist on how this system could be involved. Most prominently, stress may be involved in a reduced ability to experience rewards, causing a "reward deficit" which may promote use (Koob, 2013). Clinically, alcohol-dependent individuals without overt autonomic nervous system signs showed no change in MHPG in an earlier (Fujimoto, Nagao, Ebara, Sato, & Otsuki, 1983) and a more recent study (Agartz et al., 2003), but there was a positive correlation between CSF MHPG and intensity of withdrawal symptoms in one study (Fujimoto et al., 1983). Yet another study that explored family background in alcohol-dependent individuals showed that CSF MHPG correlated negatively with subjective reported ethanol consumption as well as presence of first-degree relatives with alcohol problems and presence of memory lapses (Valverius, Hogstrom-Brandt, & Borg, 1993).

3.4.3 Summary

Most research on the relationship between stress-related neurotransmitters and hormones in the control of ED and SUD or addiction has been done in animals. However, this neurotransmitter system may provide a very promising avenue of research in targeting cognitive-emotional factors that contribute to those disorders.

3.5 Opioids

While DA has been mostly associated with the drive to approach rewards or so-called wanting, the opioids may be particularly involved in the hedonic ("liking") aspects of food and other rewarding stimuli (Berridge, Robinson, & Aldridge, 2009; Kelley & Berridge, 2002). One could then speculate that individuals with trait-related attenuation in this system might be prone to excessive need for hedonic stimulation, or if that system were overly expressed, it could be highly able to resist both food and alcohol or drug stimuli.

3.5.1 Eating Disorders

A small sample of subjects ill with AN showed significantly lower CSF concentrations of the opioid beta-endorphin, as well as beta-lipotropin and adrenocorticotropic hormone (ACTH), all derived from the same precursor molecule, proopiomelanocortin (POMC) (Kaye et al., 1987). However, those alterations remitted with recovery (Kaye, 1987). Another investigation found higher levels of CSF opioids in severely underweight patients with AN compared to controls and the same patients after weight restoration, while chronic AN with mild underweight had normal levels of CSF opioids (Kaye, Pickar, Naber, & Ebert, 1982). In light of those studies, it could be that food restriction sensitizes opioid activity in AN. This could be consistent with research in BN that found less mu-opioid receptor binding in the left insular cortex compared to controls while binding correlated inversely with recent fasting behavior in that study, suggesting that the episodic excessive food intake downregulates this receptor (Bencherif et al., 2005; Bencherif et al., 2004; Brewerton, Lydiard, Laraia, Shook, & Ballenger, 1992; Stoeckel et al., 2008).

3.5.2 Substance Use Disorders

Mu-opioid receptor binding has been found to be increased in active cocaine users, as well as during immediate abstinence, but then decline, with the steeper the decline indicating a longer time to relapse (Gorelick et al., 2005; Zubieta et al., 1996). This receptor may have a critical role in craving and relapse in cocaine users. In alcohol dependence, mu-opioid receptor availability may be increased or decreased (Bencherif et al., 2004; Heinz et al., 2005), and more research is needed to study the relevance of this neurotransmitter system in alcoholism.

3.5.3 Summary

There is a strong theoretical framework describing how the opioid system could be involved in ED and SUD. There is a large body of research in animals but a small amount of human work with respect to brain imaging. In contrast, a variety of studies have used opioid receptor active agents as potential treatments, although models of action for this receptor are still under development (Spetea, Asim, Wolber, & Schmidhammer, 2013). Interestingly, more commonly μ-opioid receptor agonists are used in the treatment of drug addiction, while antagonists have provided some but only modest success (Tetrault & Fiellin, 2012). Most recently, an opioid receptor antagonist showed some promise in altering brain response to images of food in binge-eating individuals (Cambridge et al., 2013), suggesting that this receptor could become an important treatment target, at least in eating-related disorders.

3.6 Brain DA and Reward Function to Advance Neurotransmitter Research in Eating and Substance Use Disorders

The use of CSF samples and radioligand brain imaging to study neurotransmitter systems has given us directions for further research; however, how those systems are related to actual behavior continues to be largely obscure. The combination of functional imaging that applies disorder-relevant tasks that have been associated with specific neurotransmitter function has been a current approach for human clinical in vivo research to answer such questions. Studying brain circuits that are related to DA models in the context of brain reward function could be particularly important here, as DA is critically associated with providing signals regarding the presence and amplitude of rewards (Kelley, Baldo, et al., 2005; Schultz, 2002), facilitates reinforcement learning (Daw & Doya, 2006), and has been found to code the value of natural and drug reward stimuli (Daw et al., 2011; de Araujo et al., 2010; Jocham et al., 2011; Kelley, Schiltz, et al., 2005). Second, computer models for DA neuron reward activation exist that can be related to human in vivo brain function. Predictions of brain neurotransmitter response can be compared with actual brain activation and compared across pathologic or control groups. Such a model is the temporal difference model (Sutton & Barto, 1981). This model is a theoretical framework for computational reward learning that predicts brain DA neuron response. This model has been previously tested for unexpected reward receipt and omission in animal studies (Schultz, Dayan, & Montague, 1997) and later validated for human brain imaging (D'Ardenne, McClure, Nystrom, & Cohen, 2008; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003). In brief, DA neurons exhibit a phasic burst of activation in response to the presentation of an unexpected rewarding stimulus (the primary, unconditioned reward stimulus US). After repeated presentation of an additional arbitrary stimulus (the conditioned stimulus CS) preceding the US, the phasic activation of DA neurons transfers in time to the presentation of the CS. Thus, the CS elicits a conditioned DA response. This conditioned response is thought to reflect a *prediction* regarding *upcoming* rewards, so that after presentation of the CS, there is a high likelihood of a reward appearing. As it is thought to be a prediction, such a prediction can be violated. If the CS (and therefore the conditioned DA response) is not followed by the expected reward (US), then there is a violation of the prediction, and as a consequence at the time of expected but omitted reward, there is a decrease in DA tone. This relationship between CS and US is termed a "prediction error," the difference between the value of the reward stimulus received and that predicted.

Most recently 21 underweight, restricting-type AN (age M 22.5, SD 5.8 years); 19 obese (age M 27.1, SD 6.7 years); and 23 healthy control women (age M 24.8, SD 5.6 years) were studied using functional magnetic resonance brain imaging (fMRI) together with a reward-conditioning task that elicits the prediction error response (Frank et al., 2012). The DA model reward-learning signal distinguished groups in the anteroventral striatum, insula, and prefrontal cortex, with brain responses greater in the AN group, but lower activation in the obese group,

compared to controls. These results suggested that brain reward circuits are more responsive to unexpected food stimuli in AN but less responsive in obese women. A study using the same task in BN found reduced presumably DA-related response in insula, ventral putamen, amygdala, and orbitofrontal cortex, and binge/purge frequency in BN inversely predicted reduced TD model response (Frank, Reynolds, Shott, & O'Reilly, 2011). Those results suggest that there may be adaptive changes in response to under- or overeating in ED as seen in the animal studies described above (Avena, 2013). The stronger response in AN but lesser activation in BN and obese also indicates that those groups have differences in strength of learning signals derived from DA-related activation provided to the prefrontal cortex. A few studies have investigated prediction error response in addictive disorders. For instance, methamphetamine has been shown to enhance the brain response during prediction error stimulation (Menon et al., 2007). Most recently, research in alcohol dependence has now shown that those individuals have a functioning prediction error response but that the prefrontal cortex does not adequately learn from those signals (Park et al., 2010). Thus, this model provides the opportunity to study a variety of potential brain circuitry alterations including subcortical stimulus-reward associations and higher-order learning-related pathways. As the prediction error response has been associated with specific DA receptors, namely, the D1 and D2 type, there could be important avenues for future drug interventions (Maia & Frank, 2011).

Conclusion

Research over the past 30 or years has provided a variety of important findings with respect to 5-HT, DA, NE, and opioid neurotransmitter system alterations across ED and SUD populations. There are no studies that investigated how those disorders overlap from a neurobiological level. The neurotransmitter system that may have the biggest promise to reveal similarities across disorders may be the DA system, as there is strong neuroscience-based knowledge, especially regarding its involvement in reward processing. However, 5-HT function may also be a strong candidate as it is involved in impulsivity and inhibition, behaviors relevant to both ED and SUD, and research into the NE system could provide important markers that relate to cognitive-emotional triggers for pathologic eating or substance use in the context of stress. More comparative research will be needed to disentangle interactions between these disorders and neurotransmitter systems.

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