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Brief Report

# Treatment of addictions with special reference to anorexia nervosa

Henry C. Tuckwell

School of Electrical and Electronic Engineering, University of Adelaide,
Adelaide, South Australia 5005, Australia

E-mail: henry.tuckwell@adelaide.edu.au; henrytuckwell@hotmail.com
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## Abstract

Anorexia nervosa (AN) is a disease affecting mainly young women. It involves a pathological desire to be thin and has a complex etiology. Treatments, which have varying degrees of success, focus on medication or supervised counseling, sometimes in a hospital setting. AN has several possible co-morbidities, including obsessive-compulsive disorder, depression, and anxiety. In this article, it is hypothesized that since AN has characteristics in common with those of addiction, it could possibly be treated with supplements, such as N-acetylcysteine (NAC), which act to restore glutamate homeostasis in the nucleus accumbens and have been successfully employed in the treatment of substance abuse and various addictive behaviors.

***Keywords:*** Anorexia nervosa, eating disorder, behavioral addiction, eating disorder treatment, food behavior, glutamate, N-acetylcysteine, pharmacological therapy, psychostimulants

## 1. Introduction

Anorexia nervosa (AN) is characterized by an obsession with maintaining a weight well below normal. Two subtypes are distinguished, one in which there is a severe restriction of food intake, whereas in the other there is a bulimic component. Bulimic nervosa is similar in that after food there is purging but it is not associated with severe weight loss (Kaye et.al., 2005). In the United States, lifetime prevalence rates for AN are approximately 0.3 % for men and 0.9% for women (Striegel-Moore & Bulik, 2007). The etiology of AN is complex and generally considered to be unknown with neuropsychiatric, metabolic and cultural components (Bailer et.al., 2004; Avena & Bocarsly, 2012; Duncan et.al., 2017).

## 2. Mechanisms of AN

In an early study (Garner, 1993) several pre-disposing factors to AN were discussed including depression, anxiety, and psychological and physical trauma. The latter include intrusive behaviors of relatives and friends and sexual abuse. Anorexia nervosa is often comorbid with obsessive-compulsive disorder (OCD) (Halmi et al., 1991), and such comorbidity was found to have a genetic basis (Duncan et al., 2017). It was posited that the neurobiological mechanisms involved in AN may intersect with those of OCD.

The behavior of AN sufferers has characteristics of a habit learned, usually in adolescence. Anorexia nervosa fits the two key factors defining many types of addiction given by Goodman (2008), namely failure to control the behavior and persistence with the behavior despite harmful consequences. The compulsivity of AN has parallels with that of OCD (Steinglass & Walsh 2006) and addictive behaviors such as substance abuse (Zink & Weinberger, 2010). However, Godier & Park (2014) remark that there was a lack of empirical evidence that habit formation was an integral component of AN.

The addictive behavior associated with AN is unusual in that the outward manifestation of the reward is of being thin and under normal weight; as such, it involves being obsessed with eating less, which for many individuals, especially obese ones, would be a painful rather than pleasurable process. It is possible that in AN, the reward comes from the gratification of achieving the goal of thinness (Selby et al., 2014).

Rolls (2007) explains the brain mechanisms involved in appetite control, including dopamine release and several hormones. Disturbances in dopaminergic systems occur in AN as evidenced by the increased levels of the DA metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF) of AN patients (Castro-Fornieles et al., 2008). Furthermore, increased binding to D2/D3 dopamine receptors in the anterior ventral striatum (Frank et al., 2005) and reduced homovanillic acid concentration in the CSF (Kaye, 1999) in those recovered from AN.

Leichner (1986) commonly observes increases in cortisol and decreases in gonadotropins in subjects with eating disorders. Kaye et al. (2004) related the increase in corticotropin-releasing hormone (CRH) in AN to the discovery by Glowa & Gold (1991) that the intracerebroventricular administration of CRH led to many characteristics of AN. These observations point to a role for stress or anxiety as a factor either accompanying or causal in AN.

Dysregulation in serotonergic pathways in cortical and limbic structures has been found in AN (Kaye et al., 2005), including changes in the serotonin receptors 1A and 2A, both of which are involved in feeding behavior, and the serotonin transporter. A comprehensive account of alterations in serotonergic and dopaminergic systems in AN is given in Godier & Park (2014).

Park (2014) summarizes the neuronal circuitry underlying impulsive and compulsive behavior, with the main components being striatal (nucleus accumbens, caudate nucleus) and cortical (orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex). Neuroimaging studies support the idea that AN may result from abnormal reward processing, so there is a disturbance in the balance between bottom-up circuits involving reward and top-down circuits controlling behavior (Kaye, 2009; Park et al., 2011; Park et al., 2012).

## 3. Treatments and a hypothesis

Various treatments for AN, some with cognitive therapy and counseling and others with medication, have been proposed but have had limited success (Zipfel et al., 2000; Byrne et al., 2017). Long delays in admission to the hospital after the appearance of the symptoms of AN tended to lead to poor outcomes (Zipfel et al., 2000). Medications employed have included antidepressants and neuroleptics. SSRIs are not useful in hospitalized AN patients but may help prevent relapses after weight gain (Kaye et al., 2005). The neuroleptic olanzapine, which is used to treat schizophrenia, produced modest but less-than-expected weight gains in a 16-week program for AN patients (Attia et al., 2019). A recent meta-analysis indicated that olanzapine could be useful for older AN patients but not for adolescents (Han et al., 2022).

The fact that SSRIs and antipsychotics are not particularly effective in treating AN may indicate that the serotonergic and dopaminergic disturbances in schizophrenia differ from those in AN. This claim is supported by the findings that dopamine and serotonin metabolites are not significantly altered in schizophrenia (Tuckwell & Koziol, 1993, 1996) but are, as seen above, in AN. Deep brain stimulation has also been successfully treated AN (Godier & Park, 2015).

In the last 20 years or so, significant advances have been made in understanding the dynamics of habit formation and addiction and methods for treating them. Glutamate was found to play a fundamental role in both the development and expression of addictive behaviors (Kalivas & Volkow, 2005; Kalivas et al., 2009; Olive et al., 2012; Scofield et al. (2016). The dynamics of the synapse between cortico-striatal glutamate afferents and the GABAergic medium spinal neurons of the nucleus accumbens core plays a key role, though more recent expositions (Beloate & Kalivas, 2019; Chioma et al., 2021, 2021) include involvement of signaling in the extracellular matrix. A simplified picture of the basic elements involved is shown in **Figure 1**, adapted from Figure 4 (Scofield et al., 2016). **Figure 1** of that reference is a circuit diagram showing afferents involving 7 types of neurotransmitters from 8 brain structures and 20 sub-structures to the nucleus accumbens.

et al., 2012; Reissner et al 2015; Baker et al 2003;

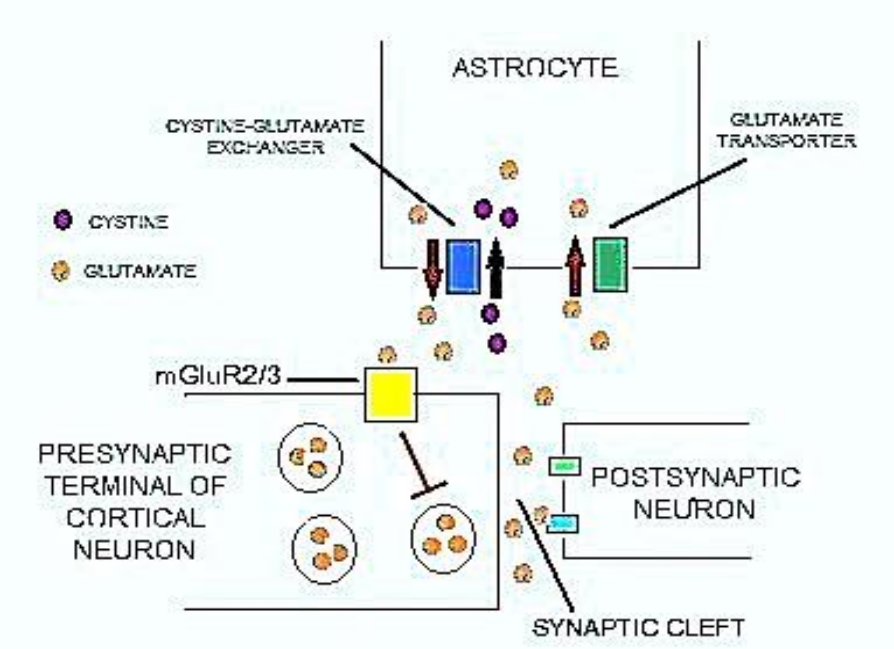


**Figure 1**: Key elements of cortico-MSN synapse involved in action of Nacetylcysteine. mGluR2/3 are metabotropic glutamate receptors which inhibit synaptic glutamate release. See text for further details. (Adapted from detailed figure in Scofield et al., 2016).

In the current **Figure 1,** there are two sources of glutamate, one being due to the release of vesicles into the synaptic cleft where glutamate activates receptors such as NMDA and AMPA on the dendrites of postsynaptic cells. The other source of glutamate is from the cystine-glutamate exchanger, often referred to as xc-, on neighboring astrocytes (Lebourgeois et al., 2019), which is the main source of glutamate (50 - 60% (Scofield et al., 2016; Lebourgeois et al., 2019) in the extracellular space away from the synaptic cleft (Scofield et al., 2016; Lebourgeois et al., 2019). Glutamate released from presynaptic terminals is removed from the extracellular space by the glial glutamate transporter GLT-1, which is responsible for 90% of glutamate uptake in the brain (Scofield et al., 2016).

Chronic administration of drugs such as cocaine which result in addiction, leads to reduced levels of glutamate in the nucleus accumbens in animals (Kalivas & Volkow, 2005; Scofield et al., 2016; Murray et al., 2012; Reissner et al., 2015) and humans (Engeli et al., 2021). It has also been found that chronic drug use leads to a downregulation of both the cystine-glutamate exchanger and the transporter GLT-1, both in animals (Kalivas & Volkow, 2005; Scofield et.al., 2016; Murray et.al., 2012; Reissner et.al 2015; Baker et.al 2003; Moran et.al 2003) and humans (Engeli et.al., 2021). The reduced activity of the exchanger accounts for the decline in glutamate levels (Scofield et al., 2016) during chronic drug taking or administration.

After withdrawal and reinstatement of drug-seeking the glutamate levels rise (Scofield et al., 2016; Engeli et al., 2021), and possibly quite dramatically (Murray et al. 2012). Such increases arise because the functioning of both the transporter GLT-1 and the exchanger are impaired. Reduced xc- activity means that mGluR1/R2 receptors are less activated, and their inhibitory effect on synaptic release is impeded. Reduced GLT-1 activity results in less clearance of released glutamate, so there is an “overflow” of glutamate in the synaptic cleft, which leads to excessive stimulation of postsynaptic glutamate receptors. Thus, glutamate homeostasis is lost.

Experimentalists have devised clever ways to ameliorate these deleterious effects of addictive drugs through the discovery of treatments with substances that restore the functioning of the exchanger and the transporter. Two such substances are N-acetylcysteine (NAC), which is an acetylated derivative of the amino acid cysteine and ceftriaxone (CEF), which is an

antibiotic commonly used to treat bacterial meningitis. There are numerous accounts of the successful treatment with NAC of various addictive substances, such as alcohol, cocaine, methamphetamine, nicotine and marijuana and addictive behaviors including gambling, internet/pornography, impulsive-compulsive disorder as well as psychiatric disorders such as depression, schizophrenia and bipolar disorder (Olive et al., 2012; Murray et al., 2012) and in addition (Scofield et al., 2016; Lebourgeois et al., 2019; Reissner et al., 2015; Engeli et al., 2021; Duailibi et al., 2017; Israel et al., 2021). The curative properties of NAC also derive from its contribution to the synthesis of the antioxidant glutathione. It has long been used for the treatment of acetaminophen overdose (Aldini et al., 2018) and for preventing hepatic toxicity by N-methyl-$\alpha$-methyldopamine (MDMA or "ecstasy") (Carvalho et al., 2004).

According to Olive et al. (2012) and Engeli et al. (2021) and many other articles, it is highly likely that there is a considerable intersection of the neurobiological basis of addiction to drugs, including alcohol, and that of addictions classified as the behavioral type. It was well founded that disruption of glutamate homeostasis plays a key role in substance abuse and that treatment with NAC (or CEF) restores the homeostasis by effects including those on the cystine/glutamate exchanger and the glutamate transporter. Furthermore, as stated above, there is considerable evidence that NAC is useful in the treatment of several diverse types of addictive behavior.

Although the studies on which this latter claim was made involve relatively small sample sizes (Olive et al., 2012), the evidence that NAC has anti-addictive properties is very strong. In support of this claim, the author is familiar with a case where an addiction that could not be overcome for over 20 years was cured by the administration of NAC, starting with 3g/day and tapering to 1g/day in the course of a few weeks. In another case, a behavioral addiction that lasted 4 months and showed no signs of abating was similarly overcome with NAC. These events confirm that of the antioxidants that have proven of benefit in treating many addictions, NAC has been one of the most successful.

Since AN qualifies as an addictive type of behavior, it is possible that it too involves, amongst other neurobiological changes, disrupted glutamate homeostasis. A recent article by Reyes-Ortega et.al. (2022) has shown that glutamate-glutamine homeostasis in the prefrontal cortex of young female rats is disrupted in AN. Thus, it is hypothesized that NAC could be an effective treatment for AN. Indeed, a suggestion was made by Park et.al (2014) that clinical trials on the use of NAC in the treatment of AN would be useful. This is also the case for other drugs, such as CEF, which act on glutamate dynamics in a similar way to NAC. However, NAC is readily available without prescription. It is also relatively inexpensive and is considered safe and without harmful side effects.

As a final note, although underlying disturbances in neuroanatomy, neurophysiology and neuropharmacology may be the primary causes of AN, AN victims develop habits which are guided by their imposed abnormal desire to be thin. A treatment that reduces the impact of such habits should assist in the treatment of the disease by amelioration of the symptoms and possibly lead to a reduction in the influence of underlying pathology.


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