Repurposing buspirone for drug addiction treatment

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Introduction

There has been considerable interest in modulating dopaminergic transmission for drug dependence treatment. However, the fact that dopamine (DA) acts through different receptor subtypes that may have different, perhaps opposing, properties have made the development of viable treatment strategies complex and challenging. It was initially thought that only two receptor subtypes, D1 and D2 receptors, defined on the basis of their direct transduction mechanisms and pharmacological profiles, mediated the pleiotropic actions of DA. However, soon after D1 (Monsma et al. 1991) and D2 (Bunzow et al. 1988) receptors were cloned, D3 (Sokoloff et al. 1990), D4 (van Tol et al. 1991) and D5 (Sunahara et al. 1991) receptors were also discovered. Those five DA receptor subtypes, termed DRD1–DRD5, are categorized as either D1-like (DRD1 and DRD3) or D2-like (DRD2, DRD3 and DRD5) based on sequence homology and pharmacology (Le Foll et al. 2009). Among those receptors, we and others have proposed that targeting the DRD2 (Heidbreder & Newman, 2010; Le Foll et al. 2005; Newman et al. 2005) and DRD4 (Yan et al. 2012) may be a novel strategy for treatment of drug dependence. However, despite the recent development of promising molecules (particularly DRD1 ligands) by multiple pharmaceutical drug companies, the translational move forward to the clinic has been stalled, in part because of the loss of interest by pharmaceutical companies, of research in the area of neuropsychiatric disorders. In this context, the report recently published by Bergman et al. (2012) suggesting that buspirone binds to DRD3 and DRD4 (among other targets), and may thus aid drug-use cessation, is exciting and timely, especially considering that buspirone is an already-approved medication with a known side-effect profile, which may hasten potential clinical translation (Bergman et al. 2012).

Several factors have contributed to the growing popularity of the DRD3 as a key player in addiction. First, the anatomy of the DRD3 system suggests that it might be involved in addiction. While the DRD2 receptor is associated with mesocortical and mesohippocampal DA systems, DRD3 is associated with the ventral forebrain mesolimbic DA system (Sokoloff et al. 1990). As such, the DRD3 is particularly well positioned to influence reward, emotion and motivation and, by extension, drug-seeking and relapse mechanisms. Second, compared to DRD2, the DRD3 receptor subsystem is subject to a unique, perhaps opposing, functional response to repeated DA agonism, as occurs in drug abuse. Studies using animal models of addiction have previously shown lower D2-like receptor expression, and positron emission tomography (PET) imaging studies in humans addicted to cocaine, methamphetamine, alcohol and nicotine have echoed these findings (for review, see Volkow et al. 2009). In contrast, preclinical data show an up-regulation of DRD3 expression following exposure to DA-elevating drugs, including cocaine, nicotine and alcohol (for review, see Heidbreder & Newman, 2010; Le Foll et al. 2005). Third, several post-mortem studies have reported consistent findings in humans, showing higher levels of DRD3 in the brain of cocaine overdose fatalities compared to control cases who did not use cocaine (Mash, 1997a, b; Segal et al. 1997; Staley & Mash, 1996). Fourth, recent PET data from our group suggest that DRD3 levels are higher in individuals who abuse psychostimulants (Boileau et al. 2012). This effect occurs in DRD3-rich areas including ventral pallidum, substantia nigra and globus pallidus. Finally, in animal models, DRD3-selective antagonists have been shown to decrease seeking of and relapse to a
variety of drugs of abuse, including psychostimulants, nicotine, alcohol and heroin, and it has been hypothesized that the DRD₃ modulates the motivation to seek drugs and notably contributes to the relapse phenomenon (Heidbreder et al. 2005; Le Foll et al. 2005).

The findings reported by Bergman et al. raise the possibility that buspirone may be a readily available (and currently the only) DRD₃ antagonist available in the clinic. This could be surprising for clinicians who have been using buspirone for years. Buspirone was initially developed as an antipsychotic drug acting on DA DRD₂ receptors (Apter & Allen, 1999). However, its lack of antipsychotic activity and ability to reduce aggressive behaviour and anxiety led to its use for anxiety disorders. Its anxiolytic effects are believed to be mediated through its partial agonist properties at the 5-HT₁A receptor. However, since one PET study in humans has shown low occupancy (<26%) of the 5-HT₁A by buspirone in clinical doses (Rabiner et al. 2000), and since the DRD₃ has been recently implicated in anxiety (Diaz et al. 2011), some therapeutic effects of buspirone may be mediated through the DRD₃. The in vitro data indicate a 2-fold affinity selectivity and an 11-fold functional selectivity of DRD₃ over 5-HT₁A, and 70-fold affinity selectivity over DRD₂ (Kula et al. 1994). One previous occupancy PET study in non-human primates showed that buspirone occupies 70–90% of the 5-HT₁A receptors with a single dose of 5 mg/kg, showing an ED₅₀ of 2.2 mg/kg (Bruning et al. 1989; Farde et al. 1997; Kula et al. 1994). Based on the occupancy and ED₅₀ for 5-HT₁A, and the in vitro selectivity of DRD₃ over 5-HT₁A, it can be estimated that buspirone administered in a dose approved for clinical use (around 1 mg/kg) will occupy between 50–85% of the DRD₃. This question can now be addressed in humans in vivo, as our PET centre has developed the agonist radiotracer [¹¹C]-(+)-PHNO, a DRD₃/DRD₂ PET agonist radiotracer for use in humans (Willeit et al. 2006). [¹¹C]-(+)-PHNO has high in vitro affinity for the DRD₂ and DRD₃ and shows preferential affinity and selectivity in vivo for the DRD₃ (Narendran et al. 2006). Recent studies showing that the fraction of [¹¹C]-(+)-PHNO binding attributable to DRD₃ varies by region (Tziortzi et al. 2011) confirm that [¹¹C]-(+)-PHNO is a D₃ preferential PET radiotracer in some areas and suggest that this tracer can be used to collect information on the occupancy of DRD₃ by buspirone. This information will be critical in expanding the findings of Bergman et al. to humans and could guide the clinical development of buspirone for addiction treatment.

It also appears very important to determine in future studies what downstream receptor(s) mediate(s) the effects of buspirone. In addition to the known pharmacological effects at the serotonin receptors, Bergman et al. report that buspirone and some of its metabolites have significant antagonist properties for the DRD₂ and DRD₄. Careful pharmacological studies and use of transgenic animals will allow us, in the future, to define the downstream receptors responsible for the effects of buspirone. Of particular interest is the potential role of DRD₄. We have recently reported that the selective DRD₄ antagonist (L-745, 870) significantly attenuates reinstatement of nicotine seeking induced by both nicotine-associated cues and nicotine priming, while having no effects on nicotine taking (Yan et al. 2012). This suggests that blocking the DRD₄ could attenuate drug-seeking behaviour, a phenomenon that may be reflected in the effects of buspirone. It is clear that this is the beginning of the exploration of buspirone in different models of drug addiction. Determining precisely how selective those effects are, and whether they are maintained after chronic administration, will be among the critical new information to be collected in the coming years.

It is notable that the findings by Bergman et al. appear at a time of crisis for development of new medications for psychiatric disorders. Several pharmaceutical drug companies, in part deterred by increasing litigation hazards over side-effects of new drugs, long development times and high failure rates, have taken clear steps to decrease their investment in this area. In response, the National Institutes of Health recently announced the creation of a new institute, the National Center for Advancing Translational Sciences. One of the first initiatives of this new centre is a partnership with industry to speed up discovery of new therapeutic uses for existing molecules. This strategy has numerous advantages over the investments made into new molecules, which may eventually be stopped in their development for lack of effectiveness in their target indications or other reasons. The findings of Bergman et al. are a timely reminder that seeking alternative uses for existing molecules, including recently developed drugs as well as drugs available in the clinic, can be a worthwhile enterprise.

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