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Targeting drug sensitivity predictors: New potential strategies to improve pharmacotherapy of human brain disorders

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ABSTRACT

One of the main challenges in medicine is the lack of efficient drug therapies for common human disorders. For example, although depressed patients receive powerful antidepressants, many often remain resistant to psychopharmacotherapy. The growing recognition of complex interplay between the drug targets and the predictors of drug sensitivity requires an improved understanding of these two key aspects of drug action and their potentially shared molecular networks. Here, we apply the concept of endophenotypes and their interplay to drug action and sensitivity. Based on these analyses, we postulate that novel drugs may be developed by targeting specific molecular pathways that integrate drug targets with drug sensitivity predictors.

Contents

1. Introduction

The advent of personalized medicine (Costello et al., 2014; Fabbri et al., 2014b) as well as recent proteomics, metabolomics, bioinformatics (Anticevic et al., 2013; Wang and Krystal, 2014) and genetic sequencing (Lu et al., 2014) tools have markedly improved our understanding of human pathogenesis and its risk factors. However, the lack of efficient drug therapies for various human diseases remains one of the main challenges in biomedicine. For example, depression is one of the most debilitating human disorders, and its societal and public health burden continues to grow (WHO, 2008; Willner et al., 2014). Despite the availability of potent antidepressants, depressed patients often remain resistant to pharmacotherapy (Cattaneo et al., 2013; Fabbri et al., 2014a; Fabbri et al., 2014b; Oved et al., 2012) and/or develop remission (Jakubovski and Bloch, 2014; Malki et al., 2014). Contributing to worsened patient health, such drug resistance may reflect important aspects of the disorder pathogenesis, prognosis, and risks (Bruder et al., 2014; El-Hage et al., 2013; Willner et al., 2014). Paralleling clinical evidence, experimental animal models have also been developed to study

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; BDNF, brain-derived neurotrophic factor; CHL1, cell adhesion molecule L1-like; DT, drug target; GABA, gamma-aminobutyric acid; GWAS, genome-wide association studies; GRIK4, ionotropic kainate glutamate receptor subtype 4; GRIN2B, the 2B subunit of glutamate NMDA receptor; ITGB3, integrin beta-3; NET, norepinephrine transporter; RXR, retinoid X receptor; SERT, serotonin transporter; SNARE, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor; SP, drug sensitivity predictor; SSRI, selective serotonin reuptake inhibitor; VDR, vitamin D receptor.

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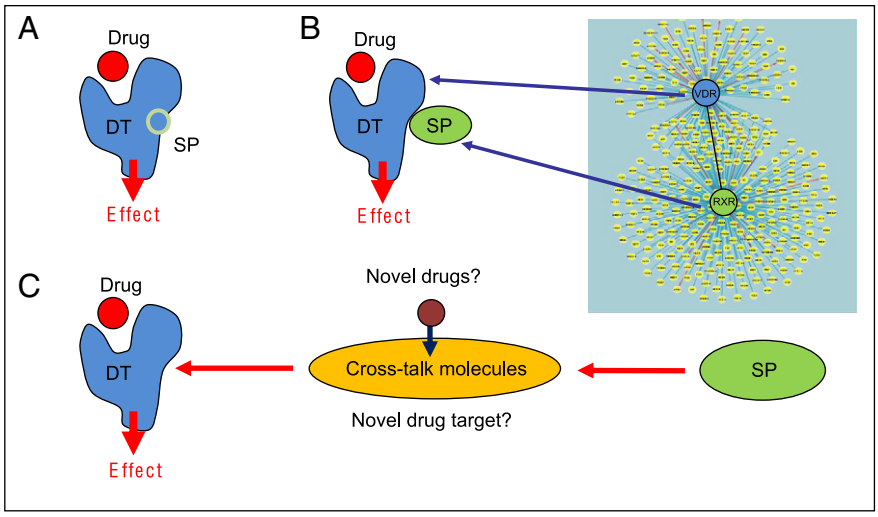

Fig. 1. Modeling drug target (DT) and drug sensitivity predictor (SP) interplay. Panel A outlines the situation in which the DT and SP sensitivity are represented by the same molecule (e.g., serotonin transporter SERT, see text for details; acting as both the target and the selective serotonin reuptake inhibitors/SSRI sensitivity predictor). Panel B illustrates the situation in which the DT and SP are two separate but directly interacting molecules: vitamin D acts via its target – the vitamin D receptor (VDR) – which requires coupling with a retinoid X receptor RXR, serving as an SP. Inset: molecular interactions between VDR and RXR, generated by the United Human Interactome database (www.unihi.org, (UHI, 2014). Note that this type of DT–SP interactions may include allosteric modulation of the DT (e.g., receptor) but can extends far beyond it, including other "binding site-unrelated" cellular phenomena, such as receptor anchoring/docking and stabilization in plasma membrane. Panel C illustrates the situation in which the DT and SP are represented by two distinct, noninteracting molecules (see Figs. 2-3 for detailed explanation) likely interlinked indirectly via a shared, cross-talk mechanism.

antidepressant action and sensitivity. Recently comprehensively evaluated elsewhere (Homberg, 2011; Lindholm and Castren, 2014; Malki et al., 2014; Shen et al., 2010), these important preclinical studies will not be discussed in-depth here.

Over the last several decades, the concept of disorder-related phenotypic traits – endophenotypes (Gottesman and Gould, 2003; Gould and Gottesman, 2006; Wang and Krystal, 2014) – has become widely accepted in biological psychiatry (Glahn et al., 2014; Kalueff et al., 2014; Lenzenweger, 2013b). Briefly, endophenotypes represent objective quantifiable and inheritable (e.g., anatomical, physiological, or behavioral) disordered traits (de Mooij-van Malsen et al., 2014; Gottesman and Gould, 2003; Gould and Gottesman, 2006). Conceptually, they are similar (but not identical) to the term "intermediate phenotypes," often used to describe quantitative traits between the genes and the disorder (Lenzenweger, 2013a, b). The potential role of complex interplay between disordered endophenotypes (e.g., via shared cross-talk mechanisms) has also been recently recognized (Kalueff et al., 2014; LaPorte et al., 2010).

As the "true" complexity of genetics underlying human disease continues to be reported (Consortium, C.-D.G.o.t.P.G., 2013, 2014; de Mooij-van Malsen et al., 2014; Fears et al., 2014; Gaugler et al., 2014; Hibar et al., 2013; Lupski et al., 2011; Malki et al., 2014), it is becoming clear that establishing the disease genes alone is not sufficient to reduce or prevent pathogenesis. Thus, the genetics of drug sensitivity and its relation to pathogenesis are also important factors to consider (Arias et al., 2014; Krasniak et al., 2014; Matsumoto et al., 2014; Serretti and Artioli, 2003; Serretti et al., 2001; Serretti et al., 2009; Walley et al., 2009).

For example, drug responsivity may represent a physiological trait linked to the disease and its risks (El-Hage et al., 2013; Walley et al., 2009; Willner et al., 2014). Therefore, the concept of endophenotypes may be logically expanded to drug-related phenotypes. For instance, it is possible to expect that drug sensitivity (with its genetic and environmental determinants) may represent an important disordered "pharmacological" endophenotype that merits further studies (Walley et al., 2009). In addition, disease-related endophenotypes may also be used to predict drug responsivity (Bruder et al., 2014). Thus, the ability of disorder-specific drugs to target disease symptoms via known mechanisms of action (drug targets, DTs) becomes as important at ensuring high drug sensitivity (Fig. 1).

Increasingly recognized in biomedicine, the distinction between DTs and the predictors of drug efficacy (sensitivity predictors, SPs) necessitates further in-depth consideration (Cattaneo et al., 2013; Gould et al., 2012). For instance, most studies focus either on DTs (Delorenzo et al., 2013) or SPs (Cattaneo et al., 2013; Costello et al., 2014), but not on their *interplay*. However, mounting evidence suggests that DT and SP may interact clinically (Bruder et al., 2014; Leuchter et al., 2009; Staeker et al., 2014). Using serotonergic antidepressants – the most prescribed CNS drugs – as examples, here we posit that disease phenotypes (regulated by drugs via DTs) and drug sensitivity (controlled by SPs) may represent two *overlapping* and clinically important endophenotypes of the disorder. We further argue that modulating overlapping molecular networks of DT-related and SP-related pathways may represent a novel strategy for pharmacotherapy of complex human disorders (Fig. 2A).

2. Drug targets and drug efficacy predictors: simple interactions

In general, multiple molecular mechanisms can underlie the interactions between the drug, DT, and SP, contributing to therapeutic outcome variability (El-Hage et al., 2013; Krasniak et al., 2014; Yamanishi et al., 2010). For example, in a simple case, DT and SP can be the same molecule (Fig. 1A). One of the best-known examples of this type of interrelationship is the serotonin transporter (SERT), the main target of selective serotonin reuptake inhibitors (SSRIs) (Murphy and Lesch, 2008). Representing the most prescribed psychotropic medication today, SSRIs selectively bind to SERT, alleviating depression (Fabbri et al., 2014b; Kalueff et al., 2010; Murphy and Lesch, 2008; Stewart et al., 2013). However, many depressed patients remain resistant to SSRIs (Oved et al., 2012), the trait strongly associated with a polymorphism of the promoter region of the *SERT* gene (Fabbri et al., 2014a; Fabbri et al., 2014b). Carriers of two "short" *SERT* alleles are not only more vulnerable to depression and anxiety but also display reduced sensitivity to the antidepressant action of SSRIs (Murphy and Lesch, 2008). In contrast, the "long" *SERT* allele carriers are both more stress-resistant and responsive to SSRI therapy (Murphy and Lesch, 2008; Staeker et al., 2014); also see additional data on *SERT* variance in predicting antidepressant action (Huezo-Diaz et al., 2009; Matsumoto et al., 2014; Serretti et al., 2001; Serretti et al., 2004). Therefore, improved knowledge of genetic and molecular processes underlying