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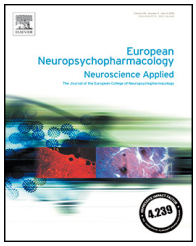

Network-based drug repositioning: A novel strategy for discovering potential antidepressants and their mode of action

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Abstract
Current target-oriented paradigm for novel antidepressant discovery has been difficult to succeed and the failures always bring huge economic losses. Although abundant ledge of disease related genes and drug action targets has been accumulated, the successful application of the knowledge for new drug discovery is limited. Here, we predicted and validated potential antidepressants and molecular targets from DrugBank recorded drugs using a novel network-based drug repositioning approach. This approach predicted relationships between drug and targets through network-based integration of drug chemical similarity, therapeutic similarity and protein-protein interactions. We predicted genome-wide relations of drugs and targets, and then screened drugs that connect to depression-related targets of known antidepressants. Six drugs were predicted and experimentally validated to have antidepressant-like effects in the tail suspension test (TST) and forced swimming test (FST) in mice. Alverine, which is a gastrointestinal antispasmodic drug, was further validated to display antidepressant-like effects in the learned helplessness and chronic unpredictable stress models of depression. Four targets, including serotonin transporter, norepinephrine transporter, serotonin 1A receptor and serotonin 2A receptor, were included in the predictable system and confirmed as primary sites of action for alverine. The results suggest that alverine may be an effective antidepressant drug

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and the network-based drug repositioning may be a promising drug discovery paradigm for complex multi-genetic diseases such as depression.

1. Introduction

Depression is a complex disease, which affects 322 million people worldwide with high rate of morbidity, recurrence, suicide, and heavy burden (WHO, 2017). The current antidepressants are often criticized for their unsatisfactory efficacy, multiple side-effects, and late onset of effect. Moreover, most of their patents have expired. Thus, there are strong clinical and commercial requirements for new drugs. Unfortunately, Bristol-Myers Squibb, Teva, and Eli Lilly and Company recently announced that they would abandon their depression projects for BMS-820836, armodafinil, or edivoxetine, respectively, in light of their negative results in phase II or III clinical trial studies.

The target-oriented paradigm is facing significant challenge in discovering novel drugs for complex psychiatric disorders, such as depression (Harmer et al., 2017; Hendrie et al., 2013). Advances in systems biology suggest that phenotypes may undergo modification when multiple biomolecules or biological processes are regulating simultaneously (Hopkins, 2007; Li, 2007,2009). In fact, evidence showed that the first-generation antidepressants with multiple targets provide better efficacy compared with subsequent antidepressants with a single target (Anderson, 1998, 2001; Laux, 2001; Millan, 2006).

Drug repositioning is one of the most economic strategies for new drug development and is expected to decrease the cost and reduce the failure risk associated with unwanted adverse effects (Ashburn and Thor, 2004). Traditionally, drug repositioning mainly relies on infrequent "happy accidents", whereas network-based approaches have inspired efforts to predict drug–target associations, which provides a more fast and effective method for drug repositioning (Ashburn and Thor, 2004; Bisgin et al., 2012; Guney et al., 2016). Network pharmacology uses a network approach to elucidate complex molecular mechanisms underlying actions of drugs and explore new indications for drugs (Hopkins, 2008; Li, 2007). Network-based drug repositioning aids in the understanding of the mode of action, and drugs predicted via this method may reduce risky events induced by negative efficacy results (Hopkins, 2008; Li, 2007; Li and Zhang, 2013). In our previous study, we proposed a network-based approach, which has been successfully applied in the discovery of bioactive compounds (Qi et al., 2016) and the analysis of pharmacological activities for complex herbal formulae, such as Liu-Wei-Di-Huang Pill (Liang et al., 2014) and Qing-Luo-Yin (Zhang et al., 2013) in traditional Chinese medicine. This approach can systematically unveil pharmacological activities of drugs and promote the study of drug repositioning.

In this study, we aimed to predict potential antidepressants from known small molecular drugs in the DrugBank database using a network-based framework, drugCIPHER. This approach is regarded as a representative method of emerging network pharmacology (Barabasi et al., 2011). Six drugs were predicted and then experimentally validated to exhibit antidepressant-like effects in the tail suspension test (TST) and forced swimming test (FST) in mice. Given the satisfactory pharmacological and safety profiles, alverine was selected as a candidate, and we performed *in silico* drug–target interaction prediction. We further validated its antidepressant activity using oral administration in the TST, FST, the learned helpless model in mice and the chronic unpredictable stress (CUS) model in rats. More importantly, we validated some key target predictions, including serotonin transporter (SERT), norepinephrine transporter (NET), serotonin 1A receptor (5-HT_{1A}R) and serotonin 2A receptor (5-HT_{2A}R), which may be essential for its effects. Network-based drug repositioning provides an effective method to discover a potential antidepressant, alverine, and helps us better understand its mode of action.

2. Experimental procedures

2.1. Target prediction of drug candidates

For *in silico* screening of antidepressants, potential targets of drug candidates in the DrugBank database were predicted by drugCIPHER, a state-of-art network-based algorithm for global prediction of drug targets developed in our previous study (Knox et al., 2011; Zhao and Li, 2010). First, a network closeness measure that describes how close are two proteins in terms of network distance is calculated in the protein-protein interaction (PPI) network. Then, linear regression models are proposed to quantify the concordance score that the network closeness is related to drug similarities. Drugs and proteins with high concordance scores are more likely to exhibit drug–target interactions.

2.2. Computational analysis of drug repositioning

Drug bioactivity resemblance could be further defined based on the similarity between concordance scores of drug pairs. To identify antidepressant candidates, hierarchical clustering analysis of target lists was applied to determine potential antidepressants by measuring the drug bioactivity resemblance between known drugs and 3817 DrugBank recorded drugs. In total, 34 FDA-approved antidepressant drugs were collected (Table S1). Standard hierarchical clustering dependence on predicted targets of drug candidates and known antidepressant drugs was performed.

2.3. Animals

Male ICR mice weighing 18–20 g were purchased from Beijing SPF animal laboratory animal technology company (Beijing, China). Male Wistar rats weighing 220–240 g were

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