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RESEARCH HIGHLIGHT

How Can Network-Pharmacology Contribute to Antiepileptic Drug Development?

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Network-pharmacology is a field of pharmacology emerging from the observation that most clinical drugs have multiple targets, contrasting with the previously dominant *magic bullet* paradigm which proposed the search of exquisitely selective drugs. What is more, drug targets are often involved in multiple diseases and frequently present co-expression patterns. Therefore, useful therapeutic information can be drawn from network representations of drug targets. Here, we discuss potential applications of drug-target networks in the field of antiepileptic drug development.

Keywords: drug-protein networks; network analysis; epilepsy; drug repositioning ; drug repurposing

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Introduction

Two decades ago, the prevailing paradigm in the drug discovery field proposed the development of maximally selective ligands acting on a single disease target. Selectivity and potency were thus essential aspects to decide whether a drug candidate would progress into further development phases. Such reductionist approach was founded on two notions: a) highly specific drugs would avoid off-target side-effects, thus leading to safer therapeutics and; b) at least some diseases could be adequately treated using a single target intervention (*"one gene, one drug, one disease"* paradigm). However, recent discoveries have challenged the earlier paradigm in favor of a more holistic approach in line with the philosophy of systems biology.

First, most of the approved drugs interact with more than one target [1]. Drugs developed or discovered using "black box", phenotypic screens are in fact, frequently, multi-functional (multi-target) therapies, with more and more action mechanisms being uncovered each day [2]. Second, multi-target drugs usually affect their targets only partially, that is, they present only low affinity interactions with many of their targets [2]. Contrary to previous beliefs, low-affinity multifunctional drugs may represent and advantage: weak links may stabilize the systems, buffering changes after system perturbations. Third, due to redundant functions and compensatory mechanisms, phenotypes are robust, i.e. resilient to perturbation [3].

Under this novel perspective, disease can be regarded as a breakdown of the robustness of normal physiological systems and the re-establishment of also robust (and potentially progressive) disease states [1]. This modern conception of disease might well sound familiar in the area of epilepsy: acquired epilepsy is typically initiated by a brain insult followed by a silent period during which molecular, biochemical and cellular alterations (including adaptive remodeling of neural circuits) occur in the brain and eventually lead to the recurrent spontaneous seizures

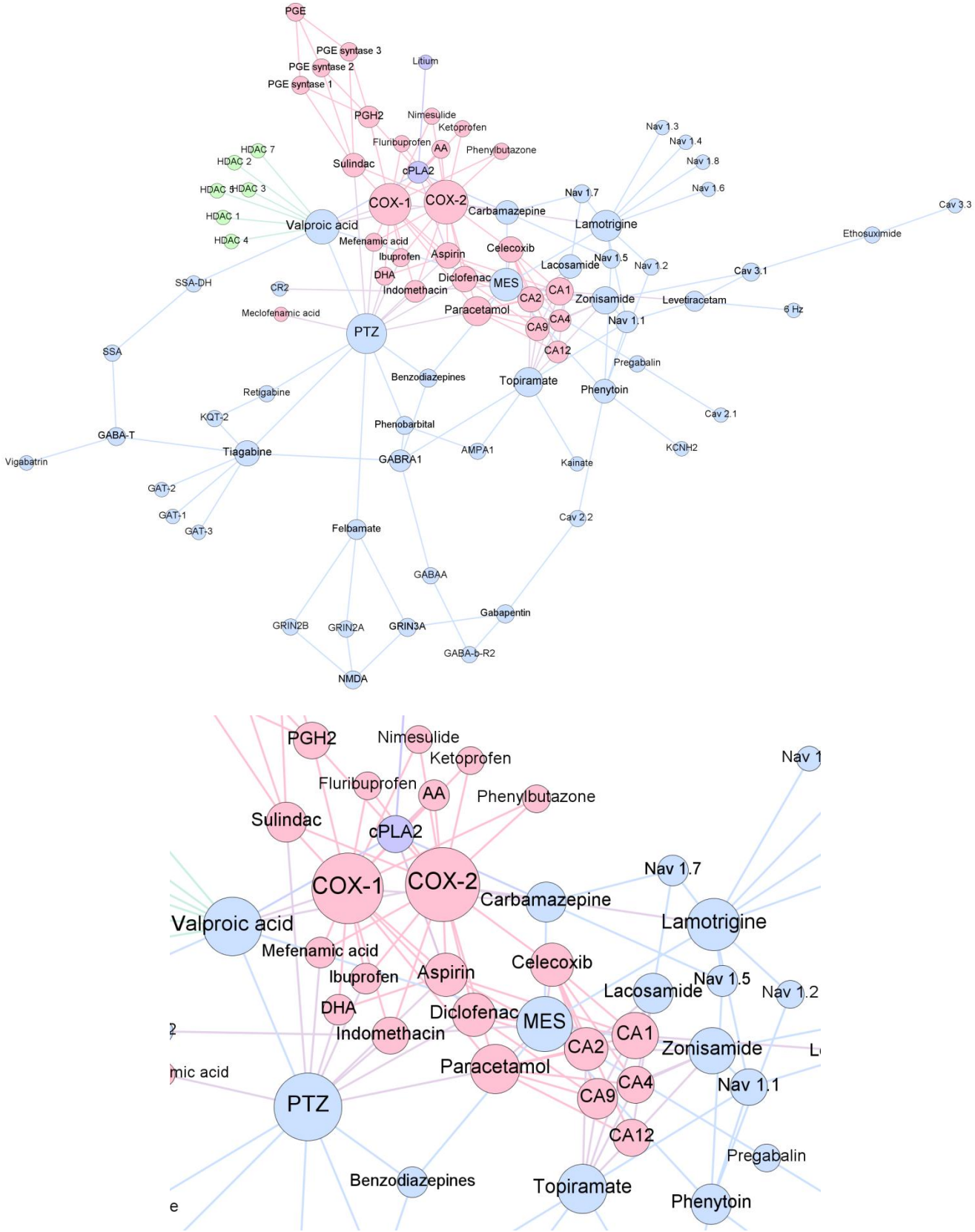

Figure 1. Drug-target network considering antiepileptic, anti-inflammatory and mood stabilizer drugs (up) and a zoom in on the interface between antiepileptic and anti-inflammatory agents.

that characterize the chronic condition [4-6]. It has been suggested that the degree of neural reorganization during epileptogenesis might be linked to the tractability of chronic disorder [6, 7].

In the light of the observation that redundancy and compensatory mechanisms limit the phenotypic impact of single perturbations to biological systems, disease will more probably manifest whenever multiple perturbations occur simultaneously. Remarkably, those disorders with significant unmet clinical needs are etiologically complex and often involve a combination of environmental and intrinsic factors (e.g. Alzheimer disease, epilepsy, cancer) [8, 9].

There are many good reasons to consider applications of drug-target networks in the field of antiepileptic drug discovery. Inconclusive but persuasive evidence suggests that some refractory patients may achieve seizure remission on poly-pharmacy, with isobolographic studies in animals and clinical experience indicating that combinations of drugs with distinct primary action mechanisms tend to be beneficial [10-13]. On the other hand, the normal function of neural networks may be more likely preserved by multiple small adjustments than by a single, strong perturbation, reducing not only the likelihood of central side-effects but also the induction of counter-regulatory processes related to drug resistance [14]. Furthermore: many currently used antiepiletic drugs are in fact unintended multi-target agents -from a drug-protein network analysis perspective, antiepileptic agents are highly connected nodes that bridge several targets- [12, 14] and much interest has been given to the broader range of therapeutic effects possessed by many antiepileptic drugs [15, 16].

The potential contribution of drug-target network to epilepsy

Today, scientific information is produced at an unprecedented rate. Before it can be regarded as knowledge (and thus exploited) such information must be organized. Particularly, the ligand-drug and protein-protein interactomes (i.e. the set of molecular interactions) have revealed themselves so complex that they often have to be either summarized or condensed through the use of manageable representations, or explored with the help of computational resources. Networks deal with complexity by simplifying complex systems: system elements are represented as nodes while relationships between nodes are represented as edges [17]. In such representation –strongly linked to mathematical Graph Theory- functional and dynamic features of the nodes are often lost and emphasis is given to the connectivity between the nodes, i.e. the topological architecture of the net.

The general philosophy of network science is then to drive attention to the wood, not the trees. Drug-protein networks have a number of practical applications which goes from rational drug repurposing (finding second medical uses of already known drugs) to prediction of side-effects [18, 19].

Figure 1 shows a partial representation of a *drug-protein-animal model* network focused on antiepileptic drugs; this network is currently under development within our research group. It is intended to guide drug repurposing (either to propose new indications for antiepileptic drugs or to reposition drugs from other therapeutic categories as antiepileptics), and to predict potential safety issues of antiepileptic drug candidates. To the moment, it includes three node types: a) approved drugs; b) drug targets that are either directly or indirectly modulated by such drugs and; c) animal models used in phase I of the NIH's Anticonvulsant Drug Development Program. It is possible, however, to expand the network by including drug candidates under investigation or withdrawn drugs and additional seizure or epilepsy models, in the future. In the figure, the nodes have been distributed in arbitrary modules (distinctively colored according to the original therapeutic indication of the included drugs); identification of topological models through network clustering algorithms blind to the function of individual nodes will be performed once the whole network is completed. In order to illustrate the potential of the network we have isolated the modules that correspond to non-steroidal anti-inflammatory agents (red), antiepileptic drugs (blue) and bipolar disorder therapies (purple). Essentially, two approaches can be used to capture interactions between the nodes [17]. The first involves compilation and curation of existing experimental data available in the literature. The second consists of predicting (often with the help of cheminformatic and bioinformatic tools) the interactions. More details on these approaches and a clear illustrative example are presented separately in the next section of the article. Interactions shown in Figure 1 have emerged from curated literature and from the Supertarget database [20]. Since all the edges have been established from experimental data, we have weighted them all alike; however, important additional information could be obtained by considering other types of bridges and by incorporating a weighting scheme which reflects either the strength of the interaction (e.g. using inhibition constants as references) or its nature (experimental versus predicted interactions). The sizes of the nodes are proportional to their degrees.

There is solid scientific ground to choose the connection between inflammation and epilepsy to illustrate the potential of the drug-network approach. Contributing factors to epilepsy such as trauma, malignancies and infections are accompanied by different levels of central nervous system inflammation and abundant evidence points to the role of inflammation in epilepsy generation and exacerbation [21-23]. Note the profuse connectivity and the presence of hubs (highly connected nodes, here represented as larger nodes) in the interface between antiepileptic and anti-inflammatory agents. The inclusion of nodes representing animal models of seizure (MES, scPTZ and 6 Hz) has been critical to detect the relative abundance of nodes in this region, which reflects the fact that many approved non-steroidal anti-inflammatory drugs have shown either anticonvulsant or proconvulsant effects in both MES and scPTZ tests [24-29]. The molecular basis of such effects remains largely unexplored. The inhibition of inflammatory mediators through downregulation and/or inhibition of cytosilic phospholipase A2 (cPLA2) and cycloxygenase (COX) isoforms (and the consequent reduction of proinflammatory cytokines) by chronic administration of carbamazepine, valproate and lamotrigine have been postulated as mechanisms of actions that may be involved in the effectiveness of these antiepileptic agents on bipolar disorder [30-32]; these actions are shared with classical bipolar disorder treatment (lithium) and justify the ongoing clinical trials of aspirin (which decreases pro-inflammatory mediators synthesis and stimulates anti-inflammatory signals) as a treatment for bipolar disorder [33]. Another interesting observation is that both antiepileptic and anti-inflammatory agents share actions on different carbonic anhydrase (CA) isoforms. It has been demonstrated that some CA isoforms may play a role in experimental febrile seizure exacerbation [34], while inhibition of CA isozymes is linked to weight loss [35,36]. Randomized clinical trials have recently been performed to establish the efficacy of topiramate and zonisamide as anti-obesity treatments[37,38]. In late 2012, a combination of topiramate and phentermine gained FDA approval for the treatment of obesity.

Finding regular links (patterns) between certain therapeutic categories pose relevant questions in the field of drug discovery and drug repositioning. E.g. should in-development anticonvulsant candidates be systematically screened as CA inhibitors or anti-inflammatory agents? In such case, should both acute and chronic models be used? Is it worth screening therapeutics from other categories related to antiepileptic drugs (e.g. anti-obesity drugs, anti-inflammatory agents) as potential anticonvulsants? As a matter of fact, our group has shown a growing interest in testing our anticonvulsant prototypes as CA inhibitors during the last few years, with encouraging results [39, 40].

Different approatches to establish links between drugs and targets

So far, the observations derived from Figure 1 are merely descriptive, since to the moment the network only condensates available experimental data. So… how can network analysis be used to develop new knowledge?

A helpful example to answer this question has recently been presented in the 2012 report from Talevi et al. on anticonvulsant effect of non-nutritive sweeteners [41]. A previously reported descriptor-based QSAR model [42] predicted that a number of artificial sweeteners (acesulfame, cyclamate, saccharin) might have anticonvulsant effect in the MES test. Subsequent bibliographic revision showed that one of them, saccharin, had already been tested in MES test in 1979 with positive results [43]. The model's predictions were later validated experimentally, and both cyclamate and acesulfame showed protective effects in the MES test. The results made us wonder whether a structural link could exist between the sweet taste receptor and one or more molecular targets of antiepileptic drugs. Literature revealed that a family of proteins named T1R is the major mediator of the sweet and umami responses in mammals [44, 45]. Sweet flavor is elicited by a heterodimer formed by T1R2 and T1R3, while umami flavor is detected by the combination of T1R1 and T1R3. Noteworthy, one of the main stimuli sensed by the umami receptor is no other than glutamate, and response to glutamate flavor is totally abolished in T1r3 KO mice [46]. We searched for similar sequences to T1R3 in the NCBI non-redundant protein database, in order to investigate the possible link between T1R3 and molecular targets of antiepileptic drugs. BLAST showed that several of the significantly aligned sequences corresponded to metabotropic glutamate receptors (mGlu) from different species, among them rat, mouse and human. Interestingly, subtypes of mGlu that were retrieved in the BLAST search (mGluR1 and mGluR5) are upregulated in epileptogenesis and kindling models of epilepsy, and in patients with complex partial seizures [47-49]. They are also linked to augmented activity of NMDA receptors, release of arachidonic acid, excitotoxicity and neuronal injury [50-51]. A synthesis of the previous analysis is depicted in the network of Figure 2. The relationships that had been experimentally

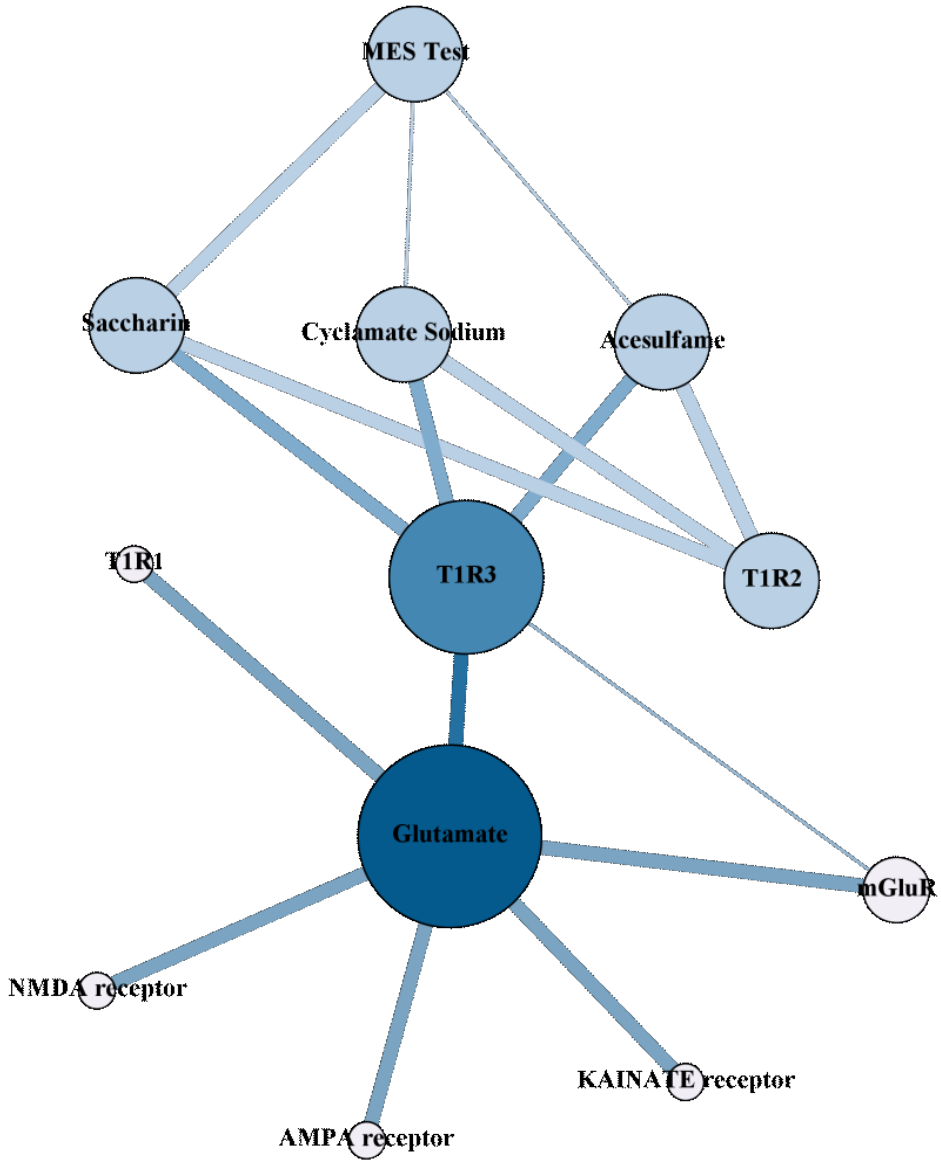

Figure 2. The thick lines in the network illustrate experimentally corroborated links; the thin lines correspond to cheminformatic (cyclamate-MES test, acesulfame-MES test) and bioinformatic (T1R3-mGluR) predictions. The first two predictions were later validated experimentally.

established previously to the report from Talevi et al. are presented as thick edges, while the associations that were predicted with computational (cheminformatic, bioinformatic) tools are presented as thin edges.

The previous example integrates the three general strategies to establish unknown (non-experimental) interactions between network nodes: a) cheminformatic predictions (e.g. predictions from automatic machine learning algorithms, molecular docking or molecular similarity searches); b) bioinformatic predictions (e.g. sequence alignment, functional relationships established from gene-order conservation, and others) and; c) literature analysis. This later approach relies on Swamson´s ABC model. Briefly, Swamson´s ABC model describes the possibility of linking different scientific disciplines though intermediate (shared) concepts [52]. Consider three separate scientific concepts A, B and C, where A is reported to be linked to B in one set of publications and B is reported to be related to C in other, while A is not reported to be directly associated to C. The relationships A-B and B-C allow inferring that A may be indirectly related to C. The unknown A–B–C relation may constituted a new finding. A practical and elegant example of the application of Swamson's ABC model in the field of network-based drug discovery is presented in ref. [18], were the importance of a predicted relationship between two nodes depends on the share node count and the share node weight, and this share node weight depends, in turn, of the connection probability.

Conclusions

Due to the multifactorial nature of epilepsy, and having in mind that most antiepileptic drugs are in fact multi-target (multifunctional) agents, it is highly probable

that drug-protein analysis will provide exciting advances in the field of antiepileptic drug discovery. Many antiepileptic drugs have already gained approval for other therapeutic indications, which suggests that development and analysis of drug-protein networks focused on antiepileptic drugs may reveal or reinforce connections between antiepileptic drugs and members of other therapeutic categories. Such knowledge might be useful to guide systematic screening of second or further medical applications of antiepileptic drugs and screening of drugs from other categories in seizure and/or epilepsy models. Prediction or explanation of side effects to antiepileptic drugs may also emerge from network analysis.

Conflict of interest

The authors declare no conflict of interest related to this article.

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