

RESEARCH ARTICLE

Drug Resistance in Epilepsy: Which Prospect to Tame its Stubbornness?

Author

Doru Georg Margineanu, Ph.D.

Department of Neurosciences

Faculty of Medicine and Pharmacy

University of Mons, Mons, Belgium

E-mail: Doru.Margineanu@skynet.be

Abstract

Epilepsy is a major health problem, it being among the most common chronic neurologic pathologies. Its basic therapy is via anti-seizure drugs (ASDs), of which nearly two dozen are currently available for symptomatic treatment of epileptic seizures. But, notwithstanding the increasing ASD options, about one-third of epileptic patients remain drug-refractory, and this fraction did not diminish over decades. This paper reviews the subject of drug resistance in epilepsy (DRE), in view of exploring the prospect to overcome its persistence. The survey of various hypotheses about DRE origin and mechanisms notices that any of them alone does not fully account the DRE, their multitude deriving from the lack of solution to this bad medical need. The non-pharmacological (neurosurgical, brain stimulation, focal treatments and dietary) approaches of drug-intractable epilepsy are also surveyed, with the sober conclusion that, in a predictable future, the mainstay of epilepsy therapy will likely remain the drugs. The vast multiplicity of molecular changes associated with DRE suggests that its pharmacological resolution might arise only from integrative, systemic approaches, beyond the reductionist single-target paradigm that dominated the ASD discovery, in the last several decades. A conceivable lessening of DRE might be brought about by precision (personalized) medicine, assisted by complex systems biology description of individual epileptic pathology. In a longer run, the emergent network pharmacology might led to genuine innovative multi-potent antiepileptic drugs, able to treat distinct subpopulations of current refractory patients.

Keywords: mechanisms of drug resistance; non-pharmacological antiepileptic treatments; precision medicine; network pharmacology; multi-potent drug.

1. Introduction

Epilepsy, a chronic neurologic pathology that currently affects some 70 million people worldwide,¹ was a fearsome companion of all documented human history, it being one of the earliest diseases mentioned in writings. An Akkadian tablet from earlier than 2000 BC describes accurately a person with epileptic convulsions,^{2,3} and thousand years later, a Babylonian diagnostic manual compiled several seizure types, each attributed to a particular demon having invaded the body.²⁻⁴ But, at the same period, a more realistic causality of convulsions was stated in Egypt, the famous Edwin Smith Papyrus, from around 1600 BC, describing a man with a deep wound in his head, which “would shudder exceedingly” when the wound was palpated.^{2,4} In the 5th century BC, Hippocrates rejected the mystical view of epilepsy and demythologized the then-called “sacred disease”, by suggesting a brain disorder as natural causation.⁵ He blamed the doctors who attributed epilepsy to divine intervention,³ suggested that epilepsy is hereditary, and noted post-traumatic epilepsy by observations of head trauma.^{2,3,5} His school’s therapy for epilepsy was based on diet instructions, including complete abstinence from food and other drinks but water.³ Chinese traditional medicine, treated epilepsy with herbs, acupuncture, and massage, based on principles of “Yin-Yang”.⁶ Twenty two centuries passed from the insightful Hippocratic description of epileptic seizures until the first non-folk anticonvulsant drug – the potassium bromide – was introduced in medical practice in 1857, as only in the 18th century the medical progress led to largely consider epilepsy an idiopathic disease of the brain. In the 19th century started neurosurgery procedures for curing epilepsy⁷ and Hughlings Jackson’s 1873 definition “*epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter*” is widely considered as inaugurating the modern era of epilepsy.⁸

Neurosurgery being highly invasive and risky, by far the commonest therapy of epilepsy is via anti-seizure drugs (ASDs). Beyond the early bromide, the panoply of ASDs expanded during the whole 20th century, currently more than 20 ASDs being available for symptomatic treatment of epileptic seizures, a dozen of them licensed in this 21st century. But, despite the wealth of ASD options, one-third of epileptic patients remain drug-refractory,^{9,10} and – intriguingly – the fraction of patients with pharmaco-refractory seizures did not decline since more than half a century. Thus, this review paper revisits the subject of drug resistance in epilepsy (DRE), aiming to explore the prospects of taming its obstinate persistence.

2. The DRE in clinical and mechanistic terms

2.1. Definitions and terms

According to consensus definitions proposed in 2005 by the International League against Epilepsy (ILAE), *epilepsy* denotes a diverse family of chronic functional disorders of the brain characterized by an *enduring predisposition to generate epileptic seizures* and by the neurobiological, cognitive, psychological, and social consequences of this condition. Also, an *epileptic seizure* denotes a transient occurrence of signs and/or symptoms due to *abnormal excessive or synchronous neuronal activity in the brain*.¹¹ Then in 2014, ILAE accepted the recommendation of a task force to consider epilepsy a disease of the brain defined by any of the following conditions: *i*) at least two unprovoked (or reflex) seizures occurring >24 h apart; *ii*) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years, and *iii*) diagnosis of an epilepsy syndrome.¹² Beyond the details of its definition, the epilepsy is a severe, often life-threatening condition and a

major health problem as it is one of the most common neurological pathologies.^{1,13}

While the prognosis is good for a majority of patients, a significant percentage (over 30%) of epileptics continue to have seizures uncontrolled by drug therapy.¹⁴⁻¹⁶ The general concept of drug resistance might seem obvious, but it is not easy to get an operational definition of DRE,¹⁷ due to debatable points concerning how many drugs should be tried before a patient is considered intractable, how long should be the time needed for concluding on an actual drug resistance, and to which extent side-effects may be acceptable, setting limits to dose escalation. ILAE has adopted a global consensus definition of DRE as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.¹⁸ As stated by the group of specialists that proposed it, this definition is to be considered just a framework in progress. Notice that when the term “antiepileptic drugs” was or still is used, this is simply by convention, because it is widely long-recognized that all current drugs are merely “anti-seizure”, not “antiepileptic”.

Also notice that alternative terms equivalent to DRE are “refractory” or “intractable” epilepsy. These terms are readily interchangeable, but searching them in literature databases gives fairly different results. Thus, a search of April 14, 2021 in the PubMed publication data base of NIH, National Library of Medicine ([PubMed \(nih.gov\)](https://pubmed.ncbi.nlm.nih.gov/)) indicated, from 1946 to date 6862 entries (of which 5,056 in the last 10 years) for “drug-resistant epilepsy”, 14,286 entries (8,897 in the last 10 years) for “refractory epilepsy”, and 13,597 entries (7,367 in the last 10 years) for “intractable epilepsy”. These vast figures impose overtly acknowledging that the references quoted in this article are solely illustrative, with no claim of exhaustiveness. Purposely for the sake of coverage, the references herein quoted are mostly reviews.

2.2. Presumed origins of DRE

Whether the pharmacoresistance develops as a result of disease progression, or it rather exists since the early stage of the disease is difficult to settle.¹⁹ The natural history of epilepsies may be complex, the clinical observations supporting three possibilities of evolution of the drug resistance, as expressed by the time to onset of intractability: 1) de novo continuous DRE, 2) a later development of pharmacoresistance, and 3) a stuttering course of remitting-relapsing [as it is often the case of mesial temporal lobe epilepsy (TLE)].^{15,16, 20}

Conceivably, the patho-mechanisms of DRE might derive from either *genome variability* (e.g. gene polymorphisms) leading to alterations in drug metabolism, targets and/or drug transporters, or *disease-related mechanisms*, such as etiology and progression of the disease, disease-induced structural alterations in the brain, and alterations in drug target(s) and drug uptake into the brain, or *drug-related mechanisms*, such as loss of therapeutic efficacy (functional tolerance), induction of drug-metabolizing enzymes (metabolic tolerance) or induction of drug transporters.

Some of the DRE-associated changes in the brain have been described in sufficient detail, in animal models and in human brain tissue (from resective neurosurgery) to become part of several articulate hypotheses,^{10,15,21-23} briefly sketched below, while details are readily accessible in the review references quoted. Moreover, one has to notice that any of the current mechanistic hypotheses alone does not actually account the DRE,^{10,22,23} very likely since the pharmacoresistance could be as multifactorial and heterogeneous as the epileptic pathology itself, deriving from both genetic and environmental factors.

2.2.1. Environmental origins of DRE

Every drug systemically administered in view of acting on the neurons in the brain has to traverse the blood-brain barrier (BBB), to enter in the brain parenchyma and to bind to its

target molecules on the neurons. This obvious reality made that the main hypotheses for the mechanism of DRE, that attracted most attention^{10,21-24} are a “*transporter hypothesis*” and a “*target hypothesis*”.

The “*transporter hypothesis*” posits that ASDs fail to act because of their concentrations falling below clinically effective thresholds, conceivably due to genetic or induced over-activity and/or over-expression of multidrug transporter (MDT) proteins, such as the P-glycoprotein (P-gp) and the multidrug resistance-associated proteins (MRPs), whose normal role is to prevent the entrance of toxic compounds or xenobiotics from blood to brain by an active (ATP-driven) efflux mechanism.²⁵ That hypothesis logically derives from the fact that the patients with DRE are refractory to treatment with various ASDs that have different mechanisms of action, so that drug resistance likely arises from some non-drug-specific mechanism. Such a mechanism would be the overexpression in the endothelial cells of brain capillaries of MDT proteins that preclude drugs to attain sufficient concentrations in the brain for getting their therapeutic effects. A practical corollary would be that co-administration of MRP inhibitors might render the ASDs more efficacious. A wealth of experimental data in animal models and some observations in resected human brain tissue endorse the assumptions of the transporter hypothesis, but the clinical proof is largely lacking. Moreover, not all the ASDs are transported by P-gp and MRPs, a classic drug not substrate to MDTs being the valproate.²⁶ Likewise, at difference from mouse P-gp, currently involved in experimental studies, human P-gp hardly transports any major ASD.²⁷

The “*target hypothesis*” assumes that either intrinsic, disease-related, or acquired by seizures- and/or treatment-induced alterations in the molecular targets of ASDs render them drug-insensitive. This possibility is prompted by the fact that the largely admitted mechanisms of a vast majority of the current

ASDs involve actions on voltage-gated ion channels and neurotransmitter receptors. It was put forward upon observing such changes of voltage-gated Na⁺ channels in resected hippocampal tissue from patients with DRE and in animal models of chronic epilepsy.²⁸ Quite a few experimental studies reported changes in ion channels transcription, altered post-translational processing of ion channel proteins, or altered modification of channels triggered by seizures, reducing the pharmacosensitivity of ASD targets.²⁹ While those data support the target hypothesis of DRE, others show however that it cannot fully account this fairly frequent condition. Thus, in TLE neurons, the loss of use-dependent block of the fast sodium current is produced by the reference ASDs carbamazepine and phenytoin – this being their admitted mechanism of action – but not by lamotrigine³⁰ which, however, binds to the same site on voltage-gated Na⁺ channels. Additionally, no correlation of the pharmacosensitivity of channel targets with sensitivity to ASDs *in vivo* could be observed in experimental models of epilepsy.

Since neither the access of ASDs to their molecular targets in the brain (*transporter hypothesis*), nor the alterations of the drug targets (*target hypothesis*) can fully account for clinical DRE, it is conceivable that in some resistant patients other mechanisms might prevail. Consequently, an *intrinsic severity hypothesis* of DRE was formulated, on the assumption that more severe epilepsy is more difficult to treat with AEDs.³¹ It is based on admitting that there are neurobiological factors that confer phenotypic variation among individuals with etiologically similar forms of epilepsy, namely that common factors would underlie both epilepsy severity and drug resistance, the seizures easily triggered, thus frequent, being difficult to suppress.³² This assumption derived from epidemiological indications that more frequent seizures in the early phase of epilepsy, before treatment, are a major risk factor of drug resistance. But, though biologically plausible, this is

insufficiently supported by proven mechanistic link between the severity and the response to ASDs. Also, more importantly, it can hardly account for the cases when the drug resistance has a fluctuating pattern.^{10,33}

Consequently, other hypotheses have been put forward within the last fifteen years. Thus, starting from some observations of persistently low levels of the ASDs in the plasma of two patients with refractory epilepsy and an increased hepatic clearance of the substrate of P-gp in a group of eight patients with refractory epilepsy, it was proposed a *pharmacokinetic hypothesis* of DRE.³⁴ Distinct from the transporter hypothesis' assumption that ASDs fail to reach effective concentrations in brain neurons of DRE patients due to overexpression of MDT proteins in brain capillaries, the pharmacokinetic hypothesis attributes the insufficient arrival of ASDs in brain neurons to overexpression of efflux transporters (P-gp a.s.o.) in the peripheral organs such as intestine, liver, and kidney, decreasing the ASD plasma levels in DRE patients.

Another proposed mechanism, the "neural network hypothesis"³⁵ assumes that seizure-induced structural changes in the brain (selective neuronal death, neurogenesis, gliosis, axonal sprouting and synaptic reorganization) led to formation of abnormal neuronal networks, with hyper excitable circuits lacking endogenous inhibitory mechanisms and preventing the ASDs from access to neuronal targets. This hypothesis seems supported by the fact that hippocampal sclerosis is common in patients with drug-resistant TLE, and about 60% of them become treated with ASDs after resection of the affected temporal lobe. But, alterations in the neural network do not lead to refractoriness in all epilepsy patients.²²

2.2.2. Endogenous origins of DRE

The above outlined hypotheses assume for DRE patho-mechanisms disease-related or/and drug-related, i.e. arising from *environmental* causes. But, the causes might also be *genetic*,

such as rare mutations producing drug resistance, or presumptively more common genetic causes expected to underlie drug resistance in the majority of patients with common types of epilepsy, such as TLE. The genetics of DRE relates to the more general subject of epilepsy genetics, but cannot be confounded with it. A variety of studies – of familial aggregation, twin studies, linkage, association, and gene identification studies – suggested a genetic contribution to the epilepsies, the genetics of human epilepsy being a very active field since several decades.³⁶⁻³⁹

The genome being the best understood source of internal variation in people in general, it is fairly obvious that genetic factors might significantly contribute to the large variability of the response to ASDs among epileptic patients, some of them being subjects to DRE. Thus, the response to ASD treatment conceivably depends on genetic variation of genes influencing drug pharmacokinetics and pharmacodynamics, such as the genes that encode enzymes that metabolize ASDs and ion channel proteins that are ASDs targets, but also genes involved in causing epileptic pathology itself.^{10,22,39} The number of genes that could influence seizure susceptibility when appropriately mutated might be quite vast since *i*) epilepsy, as a diagnosis, covers a few dozen clinical syndromes having in common recurrent, spontaneous seizures, and *ii*) the basic mechanisms of the epilepsies involve a substantial fraction of the neural processes active in a normal brain.

Genetic studies in epilepsy achieved success chiefly in the case of some rare monogenic syndromes, with mutations of large effect, while lesser progress has been achieved for most of the common epilepsy syndromes encountered in clinical practice, which are polygenic or complex disorders, influenced by the effect of variation of multiple genes and likely by environmental factors.⁴⁰ This is convincingly illustrated by the long list of publications reporting variations in the genes

associated with epileptic pathology,⁴¹ a large proportion of them addressing aspects of drug resistance. The most common type of genetic variation reportedly associated with DRE is single nucleotide polymorphism (SNP), variation at the level of a single nucleotide occurring in a larger percentage, e.g. more than 5% of the entire population. SNPs are probably the most consequential form of genetic variation in the human genome.⁴² As a genetic effect mediated by SNPs, the DRE likely arises by way of sum of effects of several genetic variants and environmental factors that individually might have only relatively minor contributions.⁴² But, one has to notice that in spite of the wealth of genetic studies in epilepsy, robust findings with established evidence are quite rare, while most of them remain controversial, beset by methodological deficiencies and lack of replication. Such is the case of many association studies on variation in genes for transporter systems and ASDs targets.^{10,22,39}

Because the genotype-phenotype correlations for the mutated DNA sequences in genes encoding for ion channels or neurotransmitter receptors identified in hereditary focal or generalized epilepsies are poor, additional factors likely contribute to the effect of a genetic predisposition.⁴³ Indeed, beyond the genome, there are other possible sources of endogenous variation that might contribute to differences in disease risks among people. Of obvious interest is the *epigenome*, the ensemble of molecules such as histones and noncoding RNAs, (small interfering RNAs and micro RNAs), which regulate gene expression by post-transcriptional changes in expression levels of proteins, without altering the DNA sequence. Recurrent seizures may change DNA methylation, deacetylation of histones and the expression of micro RNAs, as occasionally detected in patients with DRE, and the ASDs themselves can induce such epigenetic changes, as suggested by some studies.⁴³⁻⁴⁶ But, a troubling central problem in studying the epigenome in humans is to

disentangle cause from effect and relevance from epiphenomena, as it was rightly noticed.¹⁰

2.2.3. Numerous hypotheses, scarce answers

Beyond the putative mechanisms evoked in the above mentioned hypotheses on DRE, other molecular and cellular changes in the epileptic brain, associated with resistance to ASDs have been described, particularly neuro-inflammation leading to BBB dysfunction. The brain was traditionally considered an immunologically privileged site, in view of the presence of BBB and the lack of a conventional lymphatic drainage. That view became obsolete, after it was shown that the brain has an inflammatory response consisting in activation of its resident macrophages (the microglia), local invasion of circulating immune cells and production of cytokines and other immune factors.⁴⁷ The glial cells of brain's own immune system engage in inflammatory processes that normally protect the brain from pathogens and help it to recover from stress and injury. But, the response to some injuries can result in a more severe and chronic neuro-inflammatory cycle that promotes neurodegeneration and epilepsy. Thus, in rodent models of epilepsy, the seizures trigger a prominent inflammatory response in brain areas engaged in the onset and propagation of epileptic activity, and induce a pattern of inflammatory mediators in the brain largely similar to that occurring after the endotoxemia provoked by administration of lipopolysaccharide.⁴⁸ This, together with reports that anti-inflammatory drugs have anticonvulsant activity in some cases of DREs, suggests that chronic inflammation in the brain may be implicated in the pathogenesis of seizures and the associated long-term events, such as the increase in multidrug transport proteins in the BBB, thereby contributing to resistance to some ASDs.¹⁰ Conceivably then, anti-inflammatory strategies might contribute to counteracting DRE. There are, indeed, reports that add-on anti-inflammatory therapy with dexamethasone reduced seizure frequency

or interrupted SE in a majority of pediatric patients affected by DRE pathologies and also significantly decreased the status epilepticus induced in rats by pilocarpine.⁴⁹

The conspicuous gliosis observed in sclerotic hippocampi resected from patients with drug-resistant TLE and in brain tissue of rat models of TLE is, however, associated not only with inflammatory processes but also with alterations in astrocytic properties, including an unusual amplification of glutamatergic activity and functional alterations of specific glial membrane channels, receptors, and transporters.^{50,51} These multiple changes credibly point to a significant involvement of glia in DRE, beyond the mere

inflammation.^{52,53} Likewise, the account of functional changes appearing in the brains affected by DRE might continue with chloride transport-associated changes in neuronal excitability, neurotransmission, and neuromodulation,⁵³ still extending the already long list of mechanistic hypotheses about the origins of DRE. Table 1 gives a synoptic overview of the presumed origins and mechanisms of DRE, discussed in this section. Unfortunately, the abundance of hypotheses is contrasted by the scarcity of solutions to this stringent medical need, justifying the lucid recognition that “antiepileptic drug development has failed to deliver”.⁵⁴

Table 1: Simplified synopsis of current views on the origins and mechanisms of DRE

Essential features		Short titles of the hypotheses	Prototype references
Environmental origins	Foremost hypotheses	Transporter hypothesis	25
		Target hypothesis	28
		Intrinsic severity hypothesis	31, 32
		Pharmacokinetic hypothesis	34
		Neural network hypothesis	35
Endogenous origins		Genetic variation, mainly SNPs	42
		Epigenetic post-transcriptional variation	43, 44
DRE-associated changes in epileptic brains		Neuroinflammation & BBB dysfunction	48
		Astrocytic alterations afar inflammation	50, 52
		Changes in neuronal excitability, neurotransmission & neuromodulation	53 (review)

3. Non-Pharmacological Approaches of Intractable Epilepsy

Drug intractability of a significant number of epileptic patients has long led to several non-pharmacological options. Among these, of foremost importance is *neurosurgery* therapy, practiced since late 19th century and consisting now in a spectrum of surgical procedures, with

different potential to alleviate or even cure various syndromes of intractable epilepsy. Further on, several other approaches evolved,⁵⁵ chiefly relying on developments in the emergent technical domain of neuroengineering.⁵⁶

3.1. Resective and disconnective neurosurgery

Surgical resection of a localized epileptic focus responsible for initiating the seizures in mesial TLE (the lesionectomy) is the only therapeutic intervention that offers more than symptomatic treatment of the seizures, in fact a consistent chance to *cure* epilepsy. Temporal lobectomy completely controls complex partial and generalized seizures in a very significant number of cases, more than half of patients being seizure-free at 1–2 years follow-up. Meta-analyses of long-term outcomes of temporal lobe surgery indicated that 14% of patients reached long-term (≥ 5 years) ASD interruption and 50% achieved monotherapy,⁵⁷ epilepsy surgery offering the chance of seizure remission for up to 40% of patients with focal DRE.⁵⁸

A more recent alternative to resection, much less invasive than craniotomy surgery is the *gamma knife radiosurgery* that allows destruction, in a single session, of chosen target structures, without significant concomitant or late damage to adjacent tissues. The “gamma knife” is represented by some two-hundred discrete ⁶⁰Co gamma ray sources, placed within a helmet-like configuration, the gamma beams of all sources crossing at a common point in space, chosen to coincide with the targeted structure within the head.⁵⁹

When the focus is not resectable or destructible because of proximity to eloquent brain areas, or when epilepsy is multi-focal, *disconnection* surgical procedures are chosen. They do not stop the seizures, but limit the clinical expression of severe seizures, affording a more normal lifestyle.

3.2. Brain stimulation

Many intractable patients are not candidates for brain surgery because of intolerable neurologic risk. Moreover, among those having undergone surgery, some continue to have seizures. For such situations, useful palliation can be obtained with different forms of *brain stimulation*. These can inhibit

the seizures, presumably upon disrupting the pathologic hyper-synchrony, which is a truly basic feature of epileptic seizures, though virtually ignored in ASD pharmacology.⁶⁰

The observation that brain stimulation can stop seizures can be traced back to Greek antiquity, where the discharges of the electric fish (genus *Torpedo*) were used to treat seizures. Also, at the infancy time of electrophysiology in the 18th century, Leyden jars were used for the same purpose.⁶¹ More recently, the idea of brain stimulation therapy for epilepsy was prompted by the achievements of deep brain stimulation for movement disorders and of pacemakers and automatic implantable cardiac defibrillators.⁵⁶ Brain stimulation can be realized either by invasive procedures, with electrodes and electronic devices surgically implanted in the patient’s body, such as the vagus nerve stimulation (VNS) and the “responsive” neurostimulation (RNS), or without any surgery, by external transcranial magnetic stimulation (TMS).^{62,63} The mechanistic bases of the anti-seizure activity of various forms of brain stimulation remain by now at best loose if not purely obscure, but some effects are perceptible, such as the effect in DRE of deep brain stimulation of the anterior nucleus of the thalamus.⁶⁴ Anyhow, with respect to the resections and the disconnecting interventions, brain stimulation has the clear advantage of being reversible and adjustable.

The VNS consists in electrical stimulation of the left vagus nerve by a pulse generator implanted under the left clavicle, through a contact wrapped around the nerve trunk in the neck, so that it is a procedure really invasive, similar to cardiac pacemakers. VNS is accepted as an adjunctive therapy in DRE, the vagus nerve stimulator of Cyberonics Inc. (now LivaNova) having been approved since 1997 by the FDA for adjunctive therapy in drug-resistant partial epilepsy. Clinical trials have indicated that VNS is comparable with ASD therapy, in the sense that the proportion of patients with $\geq 50\%$ reduction in seizures is

similar to that in the trials of new ASDs and serious complications are rare. In the trials leading to market approval, the median reduction of the number of seizures was up to 30 %, but only less than 2% of patients become seizure-free at 1 year.

The VNS device is of “open-loop” type, since no direct feed-back modulates the therapy, the stimulation parameters being programmed by the physician at implantation and it being manually triggered in response to an epileptic aura. But, the success of deep brain stimulation for the treatment of movement disorders, together with relevant observations of abnormal electro-cortical activity before clinically evident epileptic seizures, led to consider a potential treatment option for epilepsy via a “closed-loop” system of brain stimulation.⁶⁵ Analogous to the feed-back control in implantable automatic cardiac defibrillators, the closed-loop devices actively record EEG signals, process these signals in real time to detect evidence of imminent seizure onset, then trigger an intervention. Thus, *responsive* neuro-stimulation (RNS) delivers therapeutic cortical stimulation upon the detection of precursor signals to potentially halt epileptic seizure activity. In 2013, the FDA approved NeuroPace RNS system (NeuroPace, Inc.) for the treatment of severe DRE, clinical experience indicating the safety and efficacy of RNS to provide relief to those who experience debilitating seizures.^{63,65} A newer generation of such systems of epilepsy management integrates the implanted device with local handheld and distributed cloud-computing devices, wirelessly coupled.⁶⁶

The non-invasive transcranial magnetic stimulation (TMS) is a procedure of non-contact stimulation of the cerebral cortex by weak electric currents, induced in the tissue by changing magnetic fields. The current flowing briefly in a magnetic coil, held on the scalp of the patient, generates a powerful changing extracranial magnetic field that induces an intracranial electric current in the nearby cerebral cortex that allows to assess and

modulate focal cortical excitability.⁶⁷ Associated with electromyography and/or electroencephalography, TMS enables a convenient measurement of the cortical excitation/inhibition ratio, which is pathologically shifted towards excitability in epileptic patients. The diagnostic potential in epilepsy of TMS-derived biomarkers was stated in noteworthy publications,^{67,68} but the actual relevance for cracking the DRE is really meagre.

3.3. Focal treatments for DRE

Epilepsy treatment is primarily via systemic administration of ASDs, most often by standard oral intake of these, or by alternative systemic intravenous, subcutaneous, nasal spray or rectal delivery, for acute seizure management, such as to interrupt status epilepticus. As in most cases the ASDs have to be taken longtime, often life-long, the peripheral organs and the non-epileptic brain regions are unduly exposed to the drug, causing systemic and neurological side effects. Thus, the lack of ASDs to control seizures might likely derive in the case of some patients from pharmacokinetic factors relating to therapeutic/toxic ratio, since systemic drug delivery is inevitably limited by the potential for the unwanted effects. Moreover, as discussed in the section 2.2.1 above, a core suggested mechanism for DRE is the transporter hypothesis of alterations of ASDs uptake in the brain due to over-activity and/or over-expression of MDT proteins in the endothelial cells of the BBB. Also, another pharmacokinetic hypothesis assigns the insufficient arrival of ASDs in brain neurons to overexpression of efflux transporters in the peripheral organs. Thus, for targeting either the seizure focus or key propagation pathways, focal treatments of epilepsy upon bypassing the BBB by local drug delivery and neuronal stem cell grafting have been tackled since decades,⁶⁹ and were actively pursued.⁷⁰

The delivery of ASDs directly to the regions of the brain involved in seizures is

meant to include the seizure-stimulated drug release from an implanted pump or an external reservoir, based on the “closed-loop” principle presented above. The fact that focal pharmacological manipulations in the brain, triggered by seizure detection can actually suppress seizure activity was confirmed in animal models,⁷¹ in which ASDs have been successfully delivered to seizure foci in the brain by programmed infusion pumps, acting in response to computer EEG seizure detection. In human patients many practical aspects are not yet settled, but a recent first-in-man clinical study reported the successful long-term infusion of the ASD valproate, from a subcutaneously implanted microinfusion pump, via a catheter into the brain ventricle of patients with DRE.⁷²

An additional domain of focal treatments for DRE, that of cell and gene therapies emerged since more than two decades,^{69,73,74} and looked highly promising to offer several pluses. With respect to conventional systemic pharmacotherapy, it could have the advantage of focal delivery, meant to avoid side effects and to specifically aim the epileptogenic networks. Beyond this, with respect to focal delivery of ASDs, the cell and gene grafting might offer, by rational design, specificity to underlying pathogenetic mechanisms of DRE.⁷⁵ Noting the legitimate doubt⁷⁶ and skepticism⁷⁷ expressed by valued professionals, one has to observe that cell and gene approaches to DRE continued to evolve⁷⁸⁻⁸² and remains an active field, for which the time is not yet ripe to judge the fulfilment of the promises.

3.4. Dietary therapies

As briefly mentioned in the Introduction, the Antique Greece Hippocratic medicine prescribed sustained fasting (a “water diet”) as treatment for epilepsy, this remedy having a two and a half millennia history.⁸³ In 1920, the American endocrinologist H. Rawle Geyelin reported the remarkable effectiveness of a three-week fasting in treating epileptic

patients. Then, after it was noted that acetone and beta-hydroxybutyric acid appear in a normal subject by starvation or by a diet containing too low a proportion of carbohydrate and too high a proportion of fat, R. Wilder proposed in 1921 that the ketosis arising from fasting may explain seizure control, and devised a diet of (fat)/(carbohydrate + protein) ratio of at least 3:1 to mimic the ketosis during fasting.⁸³ A high-fat, low-carbohydrate and low-protein diet based on that ratio is a ketogenic diet (KD). Variations of the KD, more palatable and better tolerated than that used a century ago, particularly the “modified Atkins diet” have been elaborated and shown to be successful.⁸⁴ At least 50% of pediatric patients treated with KD exhibit more than 50% reduction in seizures, making KD therapy to be currently used around the world.⁸⁵

The central feature of KD is the metabolic shift toward fatty acid oxidation, resulting in production by the liver of ketone bodies (acetoacetate, its metabolic byproduct acetone, and β -hydroxy-butyrate) that provide an alternative substrate to glucose for energy utilization. The changes in cellular metabolism induced by the KD are complex, including ketosis, reduced glucose, elevated fatty acid levels, and enhanced energetic reserves. Hence, the neuronal mechanisms by which KD exerts its anti-seizure effect are highly intricate, involving interactions with channels, receptors, and metabolic enzymes. These include modulation of ATP-sensitive potassium channel, enhanced adenosine and GABAergic neurotransmission, inhibition of glutamate receptors, increased expression of brain-derived neurotrophic factor, attenuation of neuroinflammation, and stabilization of the neuronal membrane potential.⁸⁶ KD also has a novel epigenetic mechanism upon affecting DNA methylation, so that it might have the potential to modify the course of the epilepsy, beyond just suppressing seizures.⁸⁷ It remains a valued therapeutic option for patients with DRE,⁸⁸ though KD is associated with severe

side-effects, most often metabolic (hypoglycemia, hyper-lipidemia, acidosis), but also renal (nephrolithiasis), and gastrointestinal. Together with the difficulty of compliance with a sustained KD, the side-effects preclude its larger acceptance as therapy.

Summing up, the interest towards non-pharmacological therapeutic options is fueled by the enduring sizeable fraction of epileptic patients drug-intractable, as the introduction of the numerous new ASDs, some of them with novel mechanisms of action, have not reduced the frequency of DRE,⁸⁹ the placebo-corrected efficacy for refractory epilepsy of the modern ASDs being disappointingly small.⁹⁰ The neurosurgical therapy (the only intervention that offers a chance to cure epilepsy) works in a significant fraction of intractable patients, but many drug-resistant epileptics are not candidate for neurosurgery, the intervention being highly invasive and associated with serious risks. Palliation of intractable seizures can be obtained with different forms of brain stimulation (that presumably disrupts pathologic hyper-synchrony), but the general feature of all types of focal treatments for DRE, including brain stimulation, is also their invasive nature that imposes serious reluctance. The experimental attempts of cell transplantation and gene therapy need much progress before any considering for clinical application. Ketogenic diet (effective particularly in children) is not a benign therapy, being associated with significant side-effects. Hence, in the predictable future, the mainstay of epilepsy therapy will likely remain pharmacological, the solution to DRE asking for advanced truly antiepileptic drugs.

4. How to get innovative drugs for surmounting DRE?

A straightforward way towards such drugs seems logical to pursue upon attempting to pharmacologically counteract the process underlying DRE. But, no such a boulevard seems currently in view, due to the puzzling

multiplicity of mechanistic hypotheses on DRE, discussed in the sections 2.2.1–3 and emphasized in some notable reviews cited there.^{10,15,21-23} Those multiple explanations, each covering a distinct parcel of the complex pathologic realm of DRE, gives the impression of an intricate array of trails, rather than any broad pathway. The various putative mechanisms of DRE are not mutually exclusive, it being likely that several of them underlie the drug refractoriness in every given patient, but not the same combination of causes act in the ensemble of patients, precluding any uniform remedy. Besides, the different mechanisms of DRE are not independent, connections between some of them having been occasionally underlined,²³ and the need for an integrative view overtly stated.^{23,33} The variety of hypotheses about the mechanism of DRE is supplemented by a multitude of molecular changes detected in neurons and glia from the brain tissue resected from patients with DRE,^{19,50,51,53,89} however, without being obvious whether and which of those changes are causes or mere consequences of the pathology.

The ensuing bewildering multiplicity of potential drug targets suggests, at a first sight, that DRE might be overcome mostly in a “case by case” manner, by a *precision medicine* that personalizes the therapy, upon tailoring the medical treatment to patient characteristics, since the efficiency of any drug action heavily depends on multiple factors, primarily the individual genetic background (all genetic variants, comprising the SNPs assessed in genome-wide association studies). Precision medicine does not mean, however, to create drugs unique to an individual patient, but rather to distinguish subpopulations of patients uniformly responding to a specific treatment. The rapid progress in epilepsy gene discovery, the existence of good models (both animal and *in vitro*) allowing the development of medications proper to genetically defined subtypes of epilepsy, and the facility to assess efficacy of projected treatments in cost-

effective, small clinical trials make epilepsy particularly suitable to achieve precision medicine.⁹¹ The understanding of epilepsy genetics advanced rapidly, thanks to genomic technologies that enable genome-wide discovery of both common and rare variants,^{38, 92} the discovery of several hundred genes associated with epilepsy having led to new animal models, more precise diagnoses and, in some cases, targeted therapies.⁸⁹

As precision medicine treats the patients based on the ensemble of their individual characteristics, instead of just on symptom-based disease diagnosis, its conceptual framework is systemic, pertaining to a *systems biology* (SB) approach.^{93,94} SB is an emergent mounting trend in bioscience to focus on complex interactions in biological systems, rather than on distinct molecular components, favoring a holistic view instead of a reductionist approach.⁹⁵ Through quantitative reasoning, computational models and high-throughput experimental technologies, SB connects the molecular components of an organism to its physiological functions and phenotypes. The computational methods used in SB offer insights to apprehend molecular interactions and dynamics at various levels, within cells, tissues, organs and organisms.⁹⁶

Congruent with the integrative holistic view of SB, pathology expresses a disturbed network of interactions,⁹⁷ and the SB-inspired pharmacology, termed either *systems pharmacology* or *network pharmacology*, aims returning to normal the pathology-disturbed network, via a multi-component therapy or, preferably, multi-potent drugs.⁹⁸ Accordingly,

DRE has to be approached by personalized (i.e. precision) medicine aimed at reversal / avoidance of the pathophysiological effects of specific gene mutations.^{98,99} Though relatively young, the systemic approach in pharmacology – hailed from its inception as “the next paradigm in drug discovery”,¹⁰⁰ – quickly became a very active domain, as illustrated by the quantity of publications. A PubMed search of May 19, 2021 indicated for “network pharmacology” 57,053 entries in the last 10 years, of which 34,597 in the last 5 years. But, the fraction of these publications dealing with epilepsy is by now only tiny, eighteen times smaller than of those dealing with cancer.

In view of the essential features of epileptic pathology to be multifactorial, polygenic and dynamic, the SB approach was pinpointed a decade ago as particularly fit and promising for a drug discovery endeavor that would hopefully result in truly *anti-epileptic* drugs⁹⁸ (not merely ASDs), that would overcome the DRE. At practically the same time, it was proposed that functional genomics, proteomics, and metabolomics be undertaken in both human and animal epileptic brain tissues to identify new therapeutic targets for preventing/stopping the epileptogenic process,¹⁰¹ and a landmark paper scrutinizing new avenues for anti-epileptic drug discovery noticed that “single-target treatments that focus exclusively on a single protein or individual biochemical pathway may be less effective than multiple-target treatments that act on different proteins or pathways involved in the network”.¹⁰²

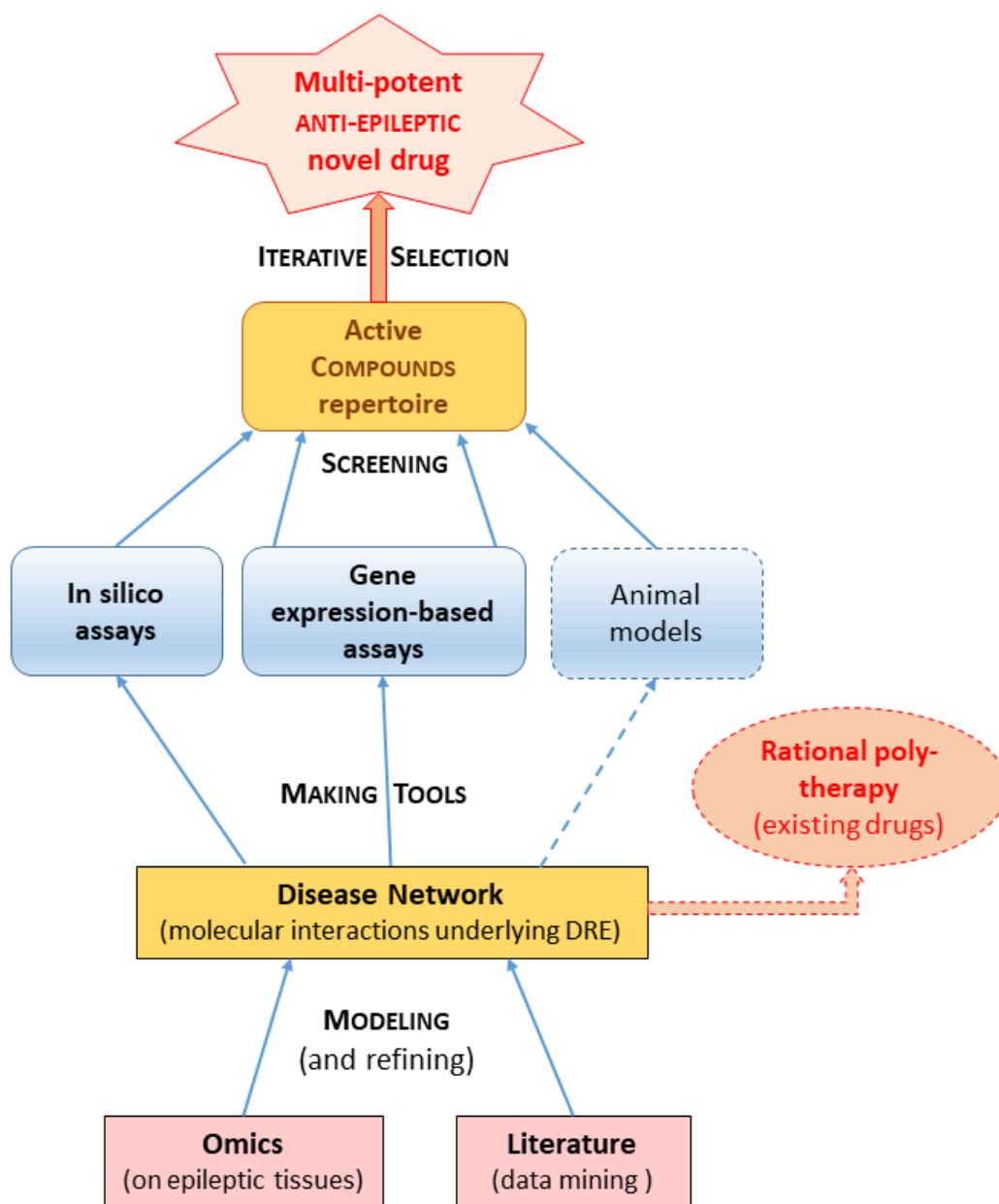


Fig. 1. Presumed succession of main stages of a network pharmacology drug discovery process aimed to invent genuine anti-epileptic drugs able to overcome the DRE, upon acting on the network of molecular interactions that underlie the epileptic state in the patients characterized by the respective omics. Revealing the disease network proper to that subpopulation of patients should, additionally, offer a rational basis for poly-therapy with existing drugs. The scheme is just aimed to illustrate a plausible endeavor, while more definite descriptions are in relevant references.^{105, 106}

A predictable first, though not foremost objective of the systemic approach of DRE is to rationalize polytherapy, upon identifying combinations of existing drugs (ASDs and adjuvants) with efficacy optimized for each seemingly drug-resistant epileptic patient. The goal of a “rational polytherapy” was tracked also apart of the advent of systems pharmacology, but the outcome was only modest,¹⁰³ while the SB approach might impart on multi-drug therapy the long-wanted true rationality. On the other hand, the core objective of systems pharmacology aimed at resolving DRE has to be farer-reaching, namely the design of novel drugs appropriately acting on the ensemble of molecular entities critically involved in a well-defined epileptic pathology, to correct the respective disturbed network of molecular interactions. This would be a real leap forward, part of a purported trend of neuropharmacology to transcend the (still!) prevailing reductionist approach.¹⁰⁴

Such an objective is, however, a task much more complex than the usual single-target strategy. Undeniably, to optimize at once multiple desired activities of a chemical entity, with simultaneous control of undesirable effects and of drug-like properties, appears such a daunting goal that one rightly wonder of its feasibility. Yet, significant bioinformatics and cheminformatics resources and computational methods have been put forward, as previously reviewed either more briefly⁵³ or comprehensively,¹⁰⁵ and they continue to progress. Noteworthy for the subject of this review is the computer-guided design and identification of potentially innovative antiepileptic drugs,¹⁰⁶ beyond less specific advances in multi-target virtual screening and in silico drug discovery.^{107,108} The main steps of a plausible network pharmacology endeavor towards overcoming the DRE, evoked above, are assembled in Fig. 1, for mere visualization.

5. Conclusion

The ASDs are and will likely remain the mainstay of epilepsy therapy, though several useful or at least promising therapeutic approaches do exist. An impressive number of ASDs have been launched, particularly in the last decades, with various ascribed molecular mechanisms of anti-seizure action. However, the resistance to ASDs persistently affects a sizeable part of epileptic patients, in spite of the continuous increase of anti-seizure armamentarium.

The current survey of the subject of DRE highlighted the multiplicity of mechanistic explanations proposed to account for this disturbing unmet medical need, noticing that each explanatory hypothesis suitably covers a larger or narrower domain of the etiopathology of DRE, while none of them is exhaustive. This clearly indicates that the resistance to ASDs is a reality as complex as the epileptic pathology that those drugs are meant to alleviate. Having in mind that epilepsy arises from the confluence of multiple genetic factors and diverse acquired insults, one realizes that DRE expresses a multifactorial, multigenic and dynamic pathology.

Accordingly, the principal conclusion of this review – admittedly reflecting author’s own opinion – is that a real chance to significantly reduce DRE would be brought by the integrative approach of SB, aimed to correct the pathology-disturbed network of molecular interactions in epileptic brains, via multi-component therapies or, preferably, multi-potent drugs. Therefore, a tentative answer to the query from the title might be that the DRE, whose prevalence stubbornly resisted (!) one century of ASDs’ multiplication, might be diminished firstly by informed precision medicine, served by complex SB characterization of individual patient’s epileptic pathology, then – in a longer run – by the advent of innovative multi-potent antiepileptic drugs, generated by the evolving network pharmacology.

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