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Computer modeling of epilepsy: opportunities for drug discovery

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Analysis of the brain as a dynamical system can assist drug development for dynamical diseases such as epilepsy. The pathological trajectories that make up a seizure differ significantly from the physiological trajectories of normal brain function. These trajectories depend on parameters – conductances and time constants of ion channels and synapses – that can be modified by drugs. Drug development will benefit by taking account of the way in which multiple parameters – multiple drug targets – produce trajectory alterations. This may lead us to reconsider potential benefits of multi-target polypharmacy, of drug cocktails, and of so-called ‘dirty drugs’ (drugs with activity at multiple locations).

Introduction

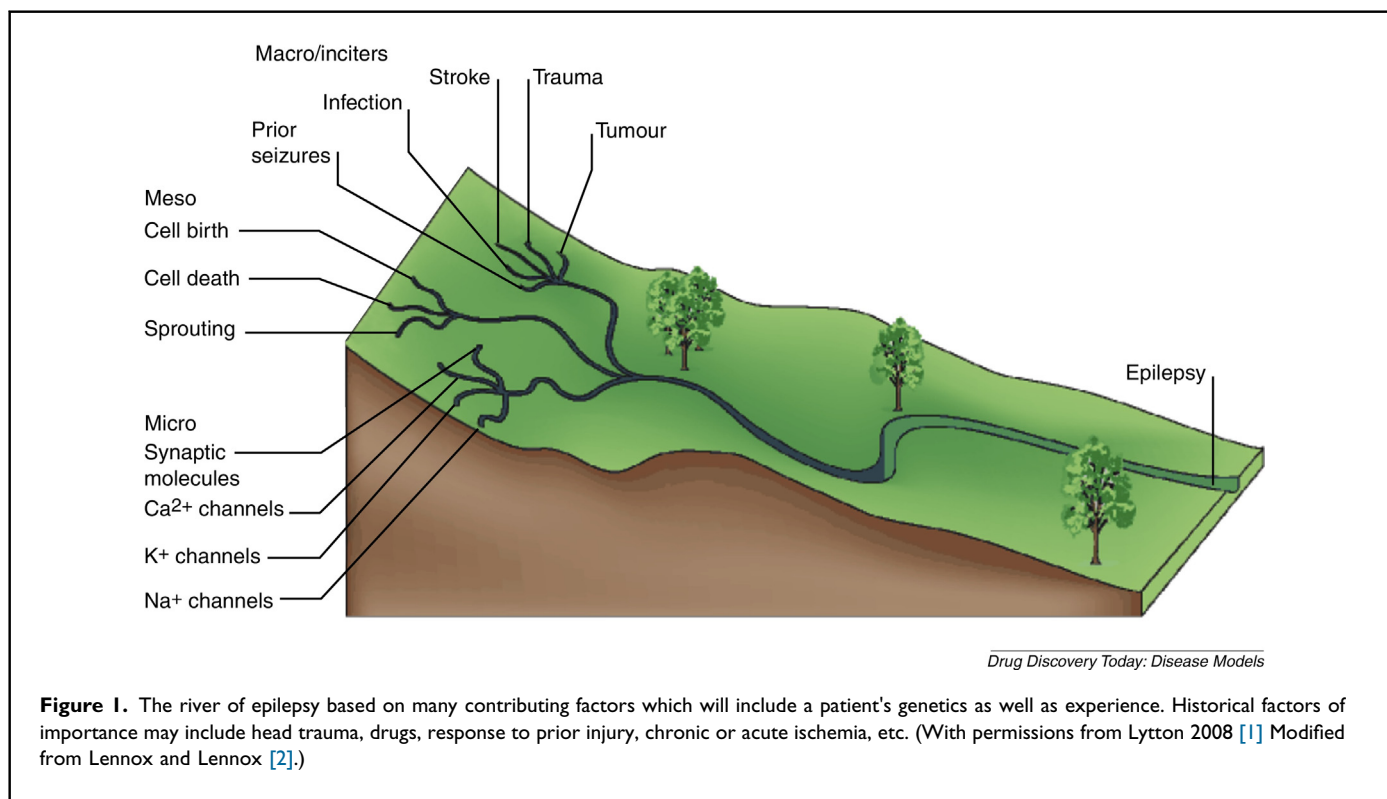
Multi-target pharmacological treatment through polypharmacy is used empirically for brain disease without good understanding of the interrelated effects of drug combinations. These limitations reflect the difficulties in understanding interactions in the brain, a complex nonstationary organ where both physiological and pathophysiological interactions span orders of magnitude both in space and in time. Multiscale computer modeling represents an effort to begin to master this complexity through simulation. Epilepsy is

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complex in both cause and manifestation, having multiple disease subtypes. Traditional evidence-based medicine (EBM) can only take us so far, since EBM works best when dealing with a clearly defined unitary disease where one or a few medications are being considered that act at only one or two sites. In epilepsy, the combinatorics of multiple drugs being used variously against multiple sites for multiple disease subtypes at many different stages of pathological developments provides a combinatorial explosion of situations to be studied.

The notion of a ‘river of epilepsy’ (Fig. 1) dates back to the work of Lennox and others from the mid-19th century. This concept was used to distinguish epilepsy from the prevailing notions and hopes that most diseases would follow the single-hit model seen with infections. In infectious disease, Koch’s influential *postulates* focused on this one-hit notion of disease. If the causative infectious agent, typically a bacterial strain, was present, the patient would develop the disease. If that specific agent was not present, the disease could not develop. What Lennox noted was that epilepsy was not at all like that – patients developed the disease based on a confluence of factors. No one factor, no one agent, could be identi-

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fied as being *the* critical causal factor. Ironically, the solution of the human genome only reinforced Lennox's interpretation for epilepsy, as well as for other brain diseases. Only rarely can a single mutation be identified as the single major causal factor. Instead many complex diseases are polygenic, a result that was not anticipated when the human genome project was initially projected as having the potential to identify disease carriers who could then be subject to prophylactic treatment to prevent development of full pathological manifestations.

Epilepsy is polygenic, polycasual and polyscale and can best be studied using the multiscale, multifactorial techniques available by applying mechanistic multiscale modeling to data obtained from a variety of *in vivo* and *in vitro* epilepsy models, as well as from clinical material. Factors that should be taken into account in such models would include various types of brain plasticity, alterations in ion channel composition of cells based on both genetics and on varying phosphorylation states determined by neuromodulators, changes in synaptic connectivity, damage to subpopulations in response to brain trauma, and other factors [1]. The clinician, and the drug developer, must consider how this mix of factors produces disease and what combination of countervailing factors could prevent seizures. Given the many causes, treatment may in many cases require drug cocktails which would ideally be precisely worked out in a way to provide complementary interventions for prophylaxis, for prevention of exacerbation, as well as for prevention of seizures.

Epilepsy is a dynamical disorder. Dynamical study can connect the kinetics of activations of onset, offset and metabolism of drugs with the set of dynamical tools that can be used to simulate electrophysiology and chemophysiology in the brain. A dynamical system, originally referring to physical motion, now refers to the many systems that evolve in time – weather, climate, physiology, etc. For the brain, the *state variables* which change over time would be neural membrane voltages at various locations, ion concentrations and states and concentrations of signaling proteins. Significantly, this includes ion channels and synaptic receptors that are affected by anti-convulsant drugs. By analogy with the dynamics of planets, the change in state variables can be described as trajectories, which can then be identified as either physiological or pathological trajectories, which are associated with different *parameter* settings in the models. These parameter settings can be modified by application of drugs that server to set up a system that is consistent with physiological trajectories. However, note that many dynamical systems, including the brain, can show bistability. In a bistable system, two different trajectories are consistent with the same parameters so that a system can jump between physiological and pathological due to the application of noise to the system [9].

Dynamics can also be described in terms of interlocking systems of positive feedback and negative feedback loops. Multiple feedback loops in the brain produce outcomes that are non-intuitive. Some feedback loops end up being partially compensatory and reduce disability, but others may end up

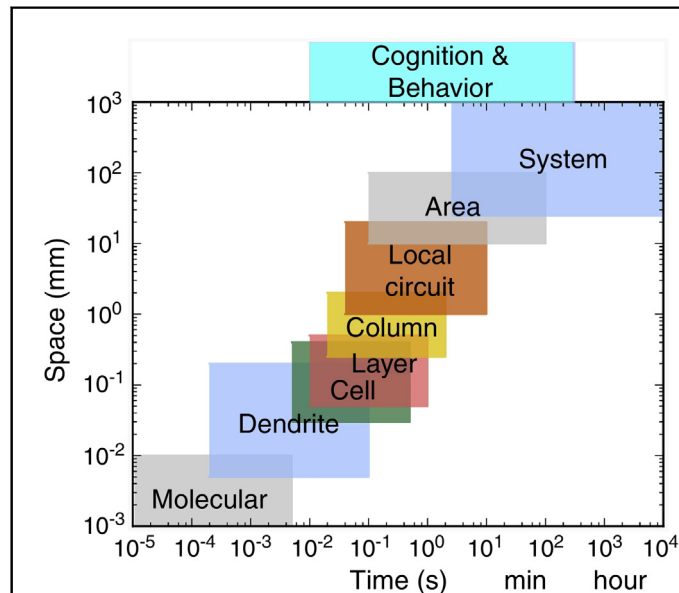
worsening the pathology. Similarly some drugs that are useful in particular kinds of epilepsies can exacerbate other types. For example, benzodiazepines increase inhibition and are used as ancillary or acute treatment in several epilepsies. However, in absence epilepsy, this increased inhibition can facilitate firing through mechanisms involving the T calcium channel, a calcium channels that is deinactivated by hyperpolarization, thereby producing increased cell firing and exacerbating seizures [10–12].

The many causes and many manifestations that characterize epilepsy can be organized in terms of the spatial and temporal scales of organization of the brain (Fig. 2). Brain function is prone to disruption at these many scales and such disruptions and reactions to the disruptions will interact both within and across scales. Temporally, relevant scales range from the millisecond scale of neural spike signaling to the multi-year scale of brain development and, later, degeneration. Spatially, a fundamental scale is the molecular scale where neuropharmacological agents act. These agents can then make changes that are expressed across scales. Chemical signaling via second messengers will elaborate many of these pharmacological signals and spread their influence throughout the cell, while other pharmacological agents will act on

membrane channels and thereby rapidly spread their influence through effects on electrophysiological properties. From there, effects will be propagated upward as alterations of cell firing influences local, areal, and brain-wide network properties; and thence propagated back downwards as these changes alter synaptic efficacy, network and cell firing patterns and cell chemical signaling through adaptive, plastic changes at all these levels.

Targeted drug discovery, and rational pharmacotherapeutics, has thus far primarily referred to methods for designing ligands to target specific receptors identified by prior therapeutic experience or experiment. The next level of drug discovery through rational exploration will add the use of these mechanistic multiscale computer models to identify receptors or other proteins to be targeted. It has been suggested that ‘The application of [computational] systems biology to medical practice is the future of medicine.’ [3] Compared to other brain diseases, epilepsy is the ideal disease substrate for these advances: (1) biomarkers are available – seizures can be identified by EEG; (2) many of the known drugs for epilepsy act on voltage- or ligand-sensitive ion channels, thereby providing an pre-identified set of parameters to consider as drug targets (3) polypharmacy and multi-target pharmacy from multitarget drugs are common in epilepsy and provide a level of complexity that cannot be understood without explicit computational models (4) seizures were the first disease manifestation that were described with explicit multiscale simulation, having been studied in this way for 40 years [4,5]. (5) Recent advances in biological measurement and in computational methods make possible ever larger and more accurate simulations.

The multifactorial causation of epilepsy, exemplified in the river metaphor, can best be approached by computer models that are able to encapsulate the many conspiring and counteracting causes and mitigating or exacerbating influences [1]. Though it is possible to experimentally determine and then conceptualize how a single mutation could produce seizures, modeling is required in order to understand how 2, 5 or 10 such mutations could lead to seizures where none would alone. This complexity also extends to the therapeutic domain, where many drugs are noted to have multiple binding sites and multiple effects. This complexity has traditionally been downplayed by calling the drugs ‘dirty drugs,’ in presumption that the additional binding is likely to be a cause of undesirable side effects while a single primary binding site is responsible for the therapeutic effect. This leads pharmacologists to attempt to achieve ever-greater ligand specificity in an effort to avoid these multiple effects. However, in some cases, this ‘dirtiness’ – the binding and activation across multiple different receptors, may be a critical aspect of the drug’s efficacy [6–8]. Development of anticonvulsant drugs will benefit from an understanding of how these multiple effects can be synergistic. Perversely, there may be cases



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Figure 2. Treatment of epilepsy occurs at the molecular level of pharmacological intervention. Measures of the consequences of epilepsy, the seizure, can be made at the level of single brain area through electrocorticography or of multiple brain areas through the spatial filtering due to the intervening skull, scalp and skin when doing electroencephalography [13]. Above that is the clinical manifestation of alterations of behavior seen in convulsions as well as the more subtle alterations of cognition that are noted in the interictal state [14].

where modern highly-selective drugs might then best be used in combination with other highly-selective drugs, to recreate the multi-target effect that had been so carefully eliminated from individual agents.

Conclusion

Computational modeling of the brain is the best way to get a handle on the complexities of the use of multi-target poly-pharmacy as well as the complexities of current single drugs that affect multiple sites. One current confusion in the pharmacology of anti-epileptic drugs arises from the effort to identify one drug effect as primary and the other drug effects as either irrelevant or actively harmful through causing side effects. Modeling will enable us to see how and when these effects may be synergistic, contributing together to the reduction of seizures. This perspective seems reasonable when one considers that most and likely all physiological signaling agents are active at different receptor subtypes with different effects.

Conflict of interest

The author has no conflict of interest to declare.

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References

- [1] Lytton W. Computer modelling of epilepsy. *Nat Rev Neurosci* 2008;9:626–37.
- [2] Lennox W, Lennox M. *Epilepsy and related disorders*. NY: Little Brown; 1960.
- [3] Kitano H. Computational systems biology. *Nature* 2002;420:206–10.
- [4] Traub R, Llinas R. Hippocampal pyramidal cells: significance of dendritic ionic conductances for neuronal function and epileptogenesis. *J Neurophysiol* 1979;42:476–96.
- [5] Traub R. Neocortical pyramidal cells: a model with dendritic calcium conductance reproduces repetitive firing and epileptic behavior. *Brain Res* 1979;173:243–57.
- [6] Rogawski M, Loscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nat Med* 2004;10:685–92.
- [7] Rogawski M. Molecular targets versus models for new antiepileptic drug discovery. *Epilepsy Res* 2006;68:22–8.
- [8] Rogawski M. Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res* 2006;69:273–94.
- [9] Lopes da Silva F, Blanes W, Kalitzin S, Parra J, Suffczynski P, Velis D. Dynamical diseases of brain systems: different routes to epileptic seizures. *IEEE Trans Biomed Eng* 2003;50:540–8.
- [10] Thomas E, Lytton W. Computer model of antiepileptic effects mediated by alterations in GABA_A mediated inhibition. *Neuroreport* 1998;9:691–6.
- [11] Lytton W. A computer model of clonazepam's effect in a thalamic slice model of absence epilepsy. *Neuroreport* 1997;8:3339–43.
- [12] Deyo S, Lytton W. Inhibition can disrupt hypersynchrony in model neuronal networks. *Prog Neuro-Psychopharmacol Biol Psychiatry* 1997.
- [13] Nunez P, Silberstein R, Cadusch P, Wijesinghe R, Westdorp A, Srinivasan R. A theoretical and experimental study of high resolution EEG based on surface Laplacians and cortical imaging. *Electroencephalogr Clin Neurophysiol* 1994;90:40–57.
- [14] Gaitatzis A, Trimble M, Sander J. The psychiatric comorbidity of epilepsy. *Acta Neurol Scand* 2004;110:207–20.