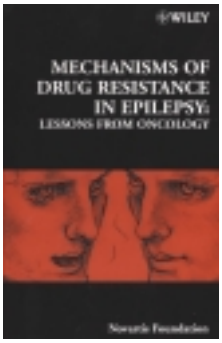

Mechanisms of Drug Resistance in Epilepsy: Lessons from Oncology

Novartis Foundation Symposium, Wiley 2002, £75.00, 254 pages in hardback, ISBN: 0-470-84146-X

Optimal current anticonvulsant drug (ACD) therapy results in freedom from seizures in approximately two-thirds of patients with epilepsy. Why do the other third of patients fail ACDs? Last year's Novartis Foundation (http://www.foundation.novartis.com) symposium in London, UK (13–15 March, 2001), convened investigators from the fields of multidrug resistance and epilepsy to attack the question: Are there parallels between drug resistance in oncology and in epilepsy? Their contributions and discussion resulted in the book *Mechanisms of Drug Resistance in Epilepsy: Lessons from Oncology*.

The multidrug-resistant (MDR) phenotype is defined as resistance of cancer cells to a broad range of structurally unrelated cytotoxic agents. Victor Ling and colleagues (BC Cancer Agency; http://www.bccancer.bc.ca) first identified P-glycoprotein (Pgp) as an overexpressed protein in clones of cells that were resistant to multiple chemotherapeutic agents. They were able to transfect naïve cells with Pgp and transfer the MDR phenotype. Drug binding to Pgp is followed by an ATP-dependent conformational change in Pgp, coupled to extrusion of the drug across the membrane, thus resulting in drug 'resistance'.

The idea that MDR molecules such as Pgp could be involved in epilepsy drug resistance arose from the observation that Pgp is overexpressed in epileptic glia. Further studies demonstrated that phenytoin and carbamazepine, common anticonvulsants, could be Pgp substrates. Immunohistochemical studies have demonstrated immunoreactivity for Pgp and MRP1, a distinct MDR molecule, in human epilepsy tissue specimens.

There are attractive aspects to the hypothesis that MDR molecules might contribute to drug resistance in epilepsy. First, the MDR phenotype is similar to pharmacoresistant epilepsy in that, if one type of drug fails, another structurally unrelated drug is also likely to fail. Second, if drug-resistance molecules, such as Pgp, are overexpressed in the epileptic focus and actively extrude otherwise effective anticonvulsant drugs, then MDR inhibitors could theoretically restore ACD penetration and efficacy. Third, MDR inhibitors would constitute an entirely new and different type of pharmacotherapy for drug-resistant epilepsy.

Despite the attractiveness of the hypothesis, little direct evidence supports it. First, it is not clear which, if any, ACDs other than phenytoin and carbamazepine are substrates for MDRs. Second, it is not clear whether MDRs are altered in the epileptic focus, and if so whether this alters ACD concentration locally. On this point, Annamaria Vezzani and colleagues (Istituto di Richerche Farmacologiche Mario Negri, Milano, Italy) have recently shown that seizures upregulate *Mdr1* mRNA, and mice lacking Pgp protein display higher brain ACD concentrations following injection. However, to date, studies have not demonstrated any change in whole-tissue levels of ACDs in epileptic tissue. Third, raising ACD concentration via MDR inhibition might not restore ACD efficacy. Instead, side effects could arise along with the overall increase in brain concentration, and 'resistance' could be unrelated to focal ACD concentration.

Furthermore, there are important differences between cancer and epilepsy. Cancer is based on cells accumulating mutations that make them progressively resistant to multiple cytotoxic drugs. In epilepsy, distributed neural networks achieve pathologic levels of hyperexcitability and could be resistant to ACDs even on initial treatment. Thus, both the 'unit' of pathology as well as the mechanism and progression of resistance could be unique. As Brian Meldrum (GKT School of Biomedical Sciences, Guy's Campus; http://www.kcl.ac.uk) points out, if drug-resistant epilepsy is a network phenomenon, then MDR approaches will fail.

Among the most useful chapters in the book are those defining the clinical problem of the drug-resistant epilepsies (by J.W. Sander) and the description of *Animal Models of Drug Resistant Epilepsy* (by W. Löscher). Löscher's work gets to the heart of the issue in defining a subset of epileptic rats that are resistant to phenytoin. Review-type descriptions of the drug-resistance molecules are provided in several chapters with the drawback of significant redundancy because at least eight chapters introduce similar material.

For an entire book based on an unproven hypothesis, the discussion from the dynamic participants is excellent. Ultimately, however, observations from animal and human studies of the effects of genotype (pharmacogenomics of drug-resistant epilepsy) and phenotype (disease-specific factors contributing to drug resistance) will be necessary to unravel the biology of pharmacoresistant epilepsy.

Devin K. Binder
M779 Moffitt Hospital
Box 0112
Department of Neurological Surgery
University of California
San Francisco
CA 94143-0112, USA
e-mail: dbinder@itsa.ucsf.edu

 PII: S1359-6446(02)02441-8