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EDITORIAL

Transporters are an under-developed therapeutic target. Discuss

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The title of this editorial would make a challenging and discriminative final-year pharmacology examination question.

On the one hand, particular examples of transporters have been very well exploited in pharmacotherapy. Of the P-type ATPases, both the Na^+/K^+-ATPase and the H^+/K^+-ATPase are blocked by very useful, and widely used, medicinal agents (cardiac glycosides and proton pump inhibitors, respectively). For the solute carrier family, inhibitors of the catecholamine transporters (SLC6A family members) and Na-K-Cl or Na-Cl symporters (SLC12A family members) are also hugely prescribed as antidepressants and diuretics, respectively. Beyond those examples, however, there is a rapid downward slope in the number of drugs targeting transporters for therapeutic gain. Given the number of targets available, this paucity of drugs is slightly surprising. Thus, analysis of the human genome yields over 370 members of the solute carrier (SLC) transporter superfamily, while the ATP-binding cassette family (ABC transporters) number over 40 functional entities. These numbers compare favourably with the number of 'druggable' G protein-coupled receptors (approximately 316) in the human genome. However, GPCR represent a significant proportion of therapeutic drug targets – at least one-quarter (Overington *et al.*, 2006). Why then are transporters targeted by only approximately one-tenth of that number?

That is not a straightforward question to answer. Many reasons probably contribute to this: the high proportion of orphan transporters; the physiological (rather than pathological) function of many members; a lack of knowledge of the role of particular transporters in pathological states; and a concentration of focus on the toxicological influences of transporters on therapeutic drugs. While it would be a major work to produce reviews that cover all of the 50 plus families of transporters, a summary of the available pharmacology and nomenclature for P-type, V-type and F-type ATPases, ABC transporters and the SLC superfamily of transporters is available in the fifth edition of the *Guide to Receptors and Channels* (Alexander *et al.*, 2011), as well as online at the related website (http://www.GuideToPharmacology.org).

Members of the ABC superfamily of transporters, particularly of the ABCB and ABCC families, are crucially important in the extrusion of xenobiotics from the cell and underlie many examples of therapeutic drug resistance. P-glycoprotein, also known as multi-drug resistance protein 1, is possibly the best known member of the ABC transporter superfamily, as the product of the gene *ABCB1*. Although not an acknowledged target for therapeutic exploitation, the many substrates for this transporter include antibiotics and anticancer agents. In this themed section, two of the less recognizable families of ABC transporters have been addressed. Peroxisomal ABCD transporters perform vital cellular functions in terms of delivery of fatty acids for oxidation or transformation. Stephan Kemp and colleagues (Kemp *et al.*, 2011) have summarized the current knowledge about these transporters, including their topology, distribution, physiological substrates, pathology and regulation. Ian Kerr and colleagues (Kerr *et al.*, 2011) complete a similar task for the ABCG family, which primarily regulate lipid flow across plasma membranes, particularly of sterols and their metabolites. The ABCG2 transporter is unusual in the family, as functionally, it resembles members of the ABCB or ABCC family, in that it influences pharmacotherapy by altering the disposition of a variety of drugs. The authors also point out the therapeutic potential of ABCG1 in the area of lipid transport in obesity and atherosclerosis.

Members of the SLC superfamily subserve a huge variety of roles in cells, allowing the movement of neurotransmitters, nutrients, amino acids and short peptides, lipid derivatives, nucleosides and nucleotides, cations and anions, as well as diverse metabolites, both on the cell surface and on intracellular organelles. James May describes the SLC23 family of

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vitamin C transporters, which help to regulate the cellular accumulation of this important regulator of cellular redox potential (May, 2011). Gavin Stewart describes the SLC14 family of facilitative urea transporters, which allow for the concentration of urine and illustrate some fascinating influences of splice variation (Stewart, 2011). David Thwaites and Catriona Anderson look at the disposition of amino acids regulated by the proton-coupled transporter family SLC36, which function in the intestine and kidney (Thwaites and Anderson, 2011). Atsushi Yonezawa and Ken-ichi Inui describe one of the newest families of SLC transporters, the SLC47 multidrug and toxin extrusion proteins, which allow for the extrusion of organic cations, including endogenous metabolites and xenobiotics into the urine (Yonezawa and Inui, 2011). The SLC47 family perform a similar function to SLCO and SLC22 families of transporters, also known as organic anion transport proteins, organic anion transporters and organic cation transporters. Bruno Hagenbuch and colleagues (Roth *et al.*, 2011) summarize information on these organic anion and cation transporters, which also have a major influence on the disposition of many drugs in clinical usage.

It is hoped that these reviews stimulate a greater awareness of, and interest in, transporters as alternative drug targets, as well as reminding pharmacologists of the dominant role of transporters in influencing the efficacy of medicinal agents by altering their biodistribution.

Conflict of interest

The author declares no conflict of interest.

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