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Editorial

Opioids, transporters and the blood–brain barrier

Conventional teaching holds that drug transport across physiological barriers such as the membrane of the gut or the blood–brain barrier is primarily determined by molecular weight, degree of ionization and lipophilicity. The blood–brain barrier is a physical and metabolic barrier whose main function is to protect the brain from a wide range of toxins and drugs, i.e. xenobiotics and metabolites. It is formed by the endothelial cells lining the brain capillaries. Complex tight junctions link adjacent cells and result in these capillaries being around 100 times less permeable to hydrophilic molecules than peripheral capillaries. Drugs such as the benzodiazepines, anaesthetic agents, nicotine and alcohol are highly lipophilic and easily penetrate the blood–brain barrier. Recently, brain penetration of a number of less lipophilic substances has been found to be largely dependent on a group of substances known as transporters. These are a diverse group of proteins which play a crucial role in drug transport and modulate drug absorption, excretion and redistribution [1–3].

Transporters are complex molecules that span the lipid bilayer of cell membranes. They may be of two basic types, passive, such as the glucose transporter and ion channels or active, requiring an energy source such as adenosine triphosphate (ATP). One particular class of ATP-powered transport proteins is larger and more diverse than the other classes and is referred to as the ATP-binding cassette, a superfamily of more than one hundred proteins that are found in organisms ranging from bacteria to human beings. These ATP-binding cassettes are found in numerous locations in the human body and have been found to exert a key role in a wide range of conditions including Alzheimer's disease [4], cystic fibrosis [5], stress/depression [6], gastrointestinal disease [7] and Parkinson's disease [8]. Recently, connections have been found with breast cancer [9] and the immune system [10].

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The ATP-binding cassette is grouped into families designated by a letter and further subdivided into subfamilies identified by a number. Subtype B1 (also known as P-glycoprotein), which is found mainly in liver, gut and kidney, and which is encrypted by the multidrug-resistant gene-1 (MDR-1) (the mouse orthologue is designated mdr-1), was the first ATP-binding cassette transporter to be cloned and to be functionally investigated. This transporter was initially studied in the context of cancer chemotherapy because of its ability to confer multidrug resistance to cancer cells [11].

Transporters may assist either in the uptake or the excretion of drugs. P-glycoprotein is one of the main efflux transporters and is therefore responsible for the active extrusion of drugs across membranes, i.e. its main effect is to limit the net uptake from the gut or into the central nervous system. Of significance to anaesthetists is the fact that P-glycoprotein is present in the blood–brain barrier and some opiate analgesics including morphine and fentanyl are among its substrates. The implications of these are far reaching. For example, this hitherto unrecognized mechanism may underlie the inter-individual differences in response to analgesics which is well recognized by anaesthetists. Secondly, it may be possible to modulate this system by a number of commonly used medications thus altering the response to analgesics.

The ease with which opiates penetrate the central nervous system will determine their effects. For example, the opiate loperamide used in the treatment of diarrhoeal illnesses does not have any central effects. This is now recognized to be mainly due to the active extrusion of the drug from the central nervous system by the efflux transporter P-glycoprotein. If this transporter is blocked by specific inhibitors then central effects such as respiratory depression ensue [12]. This beneficial effect of P-glycoprotein is also seen with the second generation antihistamine citerizine, which unlike other sedating antihistamines is actively extruded from the central nervous system [13]. In rodents, the brain concentrations of morphine are significantly increased if a P-glycoprotein inhibitor is administered beforehand [14]. If morphine is administered to mice which are selectively

bred to be deficient in P-glycoprotein (i.e. gene knockout mice) they have an increased response to the drug [15,16]. In human beings, the plasma concentration of orally administered morphine can be increased by simultaneous administration of P-glycoprotein inhibitors [17]. Similarly, the absorption of fentanyl both at the blood–brain barrier and from the gut has been shown to be dependent on a tranporter-mediated system. The main efflux transporter is P-glycoprotein which can be similarly modulated with blockers [18]. Although not widely used by anaesthetists, methadone is an opiate which is widely used in the treatment of opiate addiction. Both plasma and brain concentrations are increased up to sixfold if P-glycoprotein inhibitors are given simultaneously [19].

The implications for the anaesthetist of drug interaction at the level of P-glycoprotein are now quite clear. Fortuitous or unintentional blocking of P-glycoprotein transport may result in unexpectedly high plasma or brain levels of opiates with a concomitant improved analgesia in some, or the occurrence of side-effects in others. A wide range of commonly used medications is now known to be active inhibitors of P-glycoprotein. These include the anti-arrhythmics verapamil [20] and quinidine, antifungals such as ketoconazole, immunosuppressives such as cyclosporine [16], the antidepressives fluvoxamine and paroxetine [21], and the lipid-lowering agent simvastatin [22].

In addition to the recognition of P-glycoprotein blocking effects of certain drugs a further interesting aspect of transporter activity is their capacity to be induced in much the same way as hepatic enzymes. For example, drug-resistant epilepsy may be caused by an overexpression of P-glycoprotein induced by antiepileptic drugs [23]. Similarly, in rats P-glycoprotein activity can be increased by chronic administration of morphine, suggesting an important role for this mechanism in the development of tolerance to opiates [24]. Interestingly, there is probably co-expression of the cytochrome P450 enzyme CYP3A4 and P-glycoprotein in the brush border of the small intestine as both proteins have similar substrates and are both modulated by similar induction agents [25]. Finally, P-glycoprotein has become the recent focus of attention of those researchers studying the human genome for clues as to the basis of the subtle but important inter-individual differences in response to medications (pharmacogenomics). For example, not only do the plasma levels of protease inhibitors in human immunodeficiency virus (HIV) patients correlate with the P-glycoprotein genotype [26], but it is also now known that variations in the P-glycoprotein (MDR) gene in patients are related to outcome, as reflected in a corresponding CD4 cell count [27]. It is possible, therefore, that similar variations in response to opiates may be caused by variations in the gene encrypting P-glycoprotein.

In summary, therefore, the ATP-binding cassette transporter family is an important class of membrane proteins which translocate a wide variety of substrates across membranes such as the gut and blood–brain barrier. Genetic variation in these genes has implications for the disposition of a number of important drugs, including morphine and may partially explain inter-individual responses to opiates. The blood–brain barrier can no longer be considered as an inert, lipid barrier, but rather it should be considered to be a functional, dynamic interface with highly organized influx and efflux mechanisms. Knowledge of the ATP-binding cassette family continues to expand with regular characterization of new members [28]. A number of inhibitors of P-glycoprotein are frequently encountered in clinical practice and may interfere with drug transport. Deliberate pharmacological modulation of these transporters is now possible. Fuller understanding of the role of transporters at the blood–brain barrier will help clarify the nature of central nervous system complications of some drugs and be utilized to increase the brain concentration of others. The recognition of the importance of the role of transporters at the blood–brain barrier has catalysed innovative and exciting approaches to the therapy of central nervous system disorders such as drug-resistant epilepsy and has opened up revolutionary avenues of drug discovery.

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