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Morphine and the blood-brain barrier: diffusion, uptake, or efflux?

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In order to balance a strictly regulated microenvironment, the central nervous system (CNS) is separated from the blood by three barriers: the blood-brain barrier, the blood-cerebrospinal fluid barrier, and the arachnoid barrier.[1] As the primary transfer interface between blood and the CNS, the blood-brain barrier maintains a tightly regulated milieu to permit undisturbed signalling between the cells of the CNS. Substances arriving at the blood-brain barrier, be they toxic or therapeutic, face three distinct mechanisms that regulate barrier function: first, a *physical barrier* made up of the tight junctions between endothelial cells; second, a *transport barrier* made up of specific membrane-bound transport proteins on both the luminal and abluminal side of the membrane; and third, a *metabolic barrier* consisting of intra- and extracellular enzymes (Figure).[2] The transport proteins form a biochemically selective barrier that relies on the dynamic integration of neuronal, glial, and vascular components, thus comprising a neurovascular unit.[3,4] Altered blood-brain barrier function in the setting of pathologic states can lead to increased exposure of the brain to various neurotoxins.

Animal models have provided the basis for much of our understanding of the changes induced in blood-brain barrier function during the perioperative period. Most rigorously, the blood-brain barrier has been studied in the context of stroke and neuroinflammatory disorders. Membrane proteins of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter family protect the CNS against potentially toxic exogenous substances by actively removing them from the brain. In so doing, they control drug and metabolite transport to and from the brain. The ABC transporters are distinctly regulated in CNS models of ischemia and inflammation and include, among others, the efflux transporters P-glycoprotein (PGP), multidrug resistance proteins (MRPs), and breast cancer resistance protein (BCRP).[4,5] In addition to these efflux transporters, it is also evident that uptake transporters, such as organic anion–transporting polypeptides (e.g., OATP1A2) and organic cation transporters (e.g., OCT1) are expressed at the blood-brain barrier.[6,7] Net movement of substances into the CNS reflects a product of active uptake and efflux across the blood-brain barrier. Genetic variants of both OCT1 and MRP3 have been associated with altered

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postoperative effects of morphine in humans. Such changes are readily explainable by systemic (non-blood-brain barrier) effects, as expression of these transport proteins is not limited only to the brain.[8,9]

The clinical relevance for the discovery of specific substrates for human blood-brain barrier transporters is their potentially variable compartment concentrations based on genetically variable expression of their respective transport proteins. To date, the lack of specific inhibitors approved for such use in humans remains a major challenge for clinical studies examining precise roles of individual ABC transporters. Nonetheless, the effects of morphine in human volunteers were enhanced by the co-administration of the PGP inhibitor cyclosporine.[10] Still, functional evidence for physiologically altered levels of PGP expression in humans remains uncertain.

While results within different models vary,[11] it appears that, following short-term exposure to inflammatory stimuli, such as tumor necrosis factor (TNF)-α PGP undergoes down-regulation mediated by activation of inducible nitric oxide synthase and up-regulation with long-term exposure to TNF-α.[12] The PGP and BCRP expression levels also increase after ischemia/reperfusion injury in rats, and peak expression correlates with behavioural recuperation.[13] Paracellular permeability increases in response to hypoxia, an effect that is attenuated during reperfusion by increased expression of tight junction protein and up-regulation of luminal and abluminal transport proteins.[14]

In this issue of the *Journal*, Wang *et al.* report the results of a study examining the pharmacokinetics of morphine and its metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in plasma and cerebrospinal fluid.[15] Elegantly, the authors chose to study patients undergoing major open or endovascular thoracic aortic aneurysm repair, which enabled simultaneous measurement of morphine (and its metabolites) as well as pro-inflammatory cytokines and albumin in both cerebrospinal fluid (CSF) and plasma. Parsimoniously including open *vs* endovascular performed aortic repairs allowed the authors access to two very different levels of perioperatively induced inflammation. Indeed, a differential pro-inflammatory effect was detected from the cytokine responses. The CSF/plasma area under the curve (AUC) ratios for morphine were not correlated with levels of the pro-inflammatory cytokine interlukin-6 (IL-6). Although a moderate positive correlation was detected between the M3G AUC CSF/plasma ratio and CSF IL-6, a surgery-specific effect of PGP on blood-brain barrier morphine efflux transport was not ascertained.

The authors should be congratulated on their ambitious work, which comprises one of the first attempts to quantify changes in transport barrier effects during a surgical stimulus. The authors' achievement is not diminished by the limitations of their work. For example, because of the potential differential expression of ABC transporters at the different compartments of the blood-brain barrier,[12] their substrate specificity, as well as other unknown regulatory effects, their study results should be seen as specific for the chosen inflammatory stimulus and for opioid excretion into the CSF. Their observations probably represent the net effect of complex regulatory processes, which are likely impossible to decipher fully in human subjects. There are examples of ABC transport studies suggesting that *in vitro* and animal studies may overestimate the clinical relevance of ABC transport

activity in humans.[16–18] In light of known genetic variability of many ABC transporters in humans, the "negative" results reported in this issue of the *Journal* may, therefore, reassure clinicians. Nevertheless, tissue concentrations and opioid effects were not studied in this setting, even though morphine dosages were recorded.

Studying such performance in a real-world scenario—i.e., the three components of blood-brain barrier function (i.e., physical, transport, and metabolic) and the differential effects of blood-brain *vs* blood-CSF barrier contributions—will always be subject to the inherent limitations of research in human subjects. Nevertheless, the active efflux and uptake of exogenous and endogenous substances play a critical role in maintaining CNS hemostasis in the face of a relatively preserved physical barrier. Therefore, further clinical studies to advance our understanding of perioperative alterations in select drug *and* toxin permeability across the blood-brain barrier should be encouraged.

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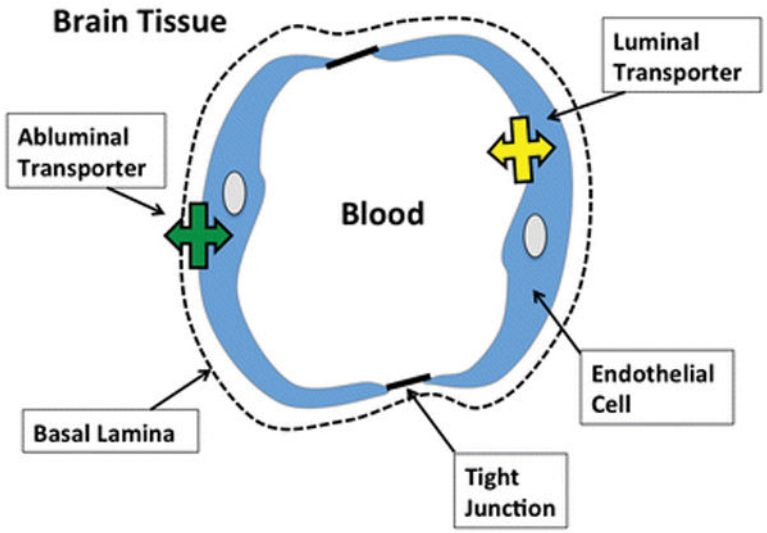

FIGURE.

Select mechanisms of blood-brain barrier function

Endothelial cells (blue) are enclosed by a basal lamina (dashed line) and connected via tight junction proteins to form a physical barrier between blood and brain tissue. Proteins performing active efflux or uptake of substances from or into the brain are embedded in the luminal (yellow) and abluminal (green) side of the endothelium and comprise the transport barrier.[2]