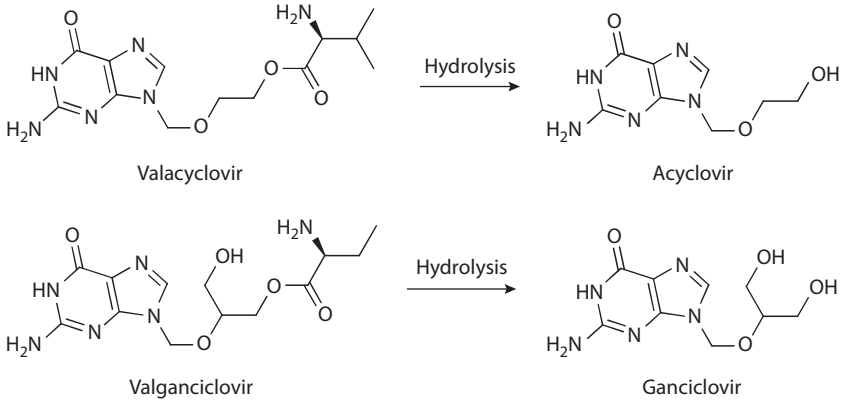


**FIGURE 10.11** Hydrolysis of valacyclovir and valganciclovir to their parent drugs.

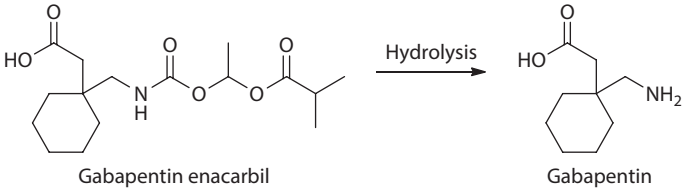


**FIGURE 10.12** Structure and hydrolysis of gabapentin enacarbil to the active gabapentin.

including monocarboxylate transporter 1 (MCT-1) and sodium-dependent multivitamin transporter (SMVT). Prodrug modification produced an extended release of gabapentin with twofold improved, more predictable, and dose-proportional oral bioavailability in humans. During and after its absorption, gabapentin enacarbil is efficiently hydrolyzed by nonspecific esterases to yield gabapentin (Figure 10.12). Currently, gabapentin enacarbil is commercially available for the treatment of restless legs syndrome and post-herpetic neuralgia of adults.

Other examples of prodrugs with improved transporter-mediated permeability include midodrine and enalapril.

### 10.5.4 Improved Targeting

Targeting drug action into specific organs, tissues, or cells is an attractive strategy for more effective therapeutics with less adverse effects. In a prodrug approach, the targeted drug action can be achieved either by site-directed drug delivery or site-specific drug bioactivation. In site-directed drug delivery, intact prodrug is selectively transported to its site of action, and thus constitutes a very challenging task after oral or systemic administration. In site-specific bioactivation, a prodrug can be widely distributed throughout the body, but undergoes bioactivation and exerts pharmacological action only at the desired site. The site-specific bioactivation of prodrugs can be achieved either by: (1) exploiting endogenous transporters, enzymes or physiological conditions of target tissue, such as pH or hypoxia, (2) delivering genes that encode prodrug-activating enzyme into target tissue (e.g., virus-directed enzyme prodrug therapy [VDEPT] and gene-directed enzyme prodrug therapy [GDEPT]), or (3) delivering prodrug-activating enzyme into target tissue via monoclonal antibodies (e.g., antibody-directed enzyme prodrug therapy [ADEPT]). In this chapter, only examples of prodrugs, which exploit physiological differences between target and other tissues, are discussed, but it should be noted that some ADEPT and GDEPT systems are currently under clinical investigation.