TABLE 16.8
Specific Delivery to Systems or Organs by Targeting Enzymes

Organ or System	References
Cancer	Niculescu-Duvaz et al. (1998); de Groot et al. (2003); Bagshawe et al. (2004); Sharma et al. (2004); Dachs et al. (2005); Rautio et al. (2008); Huttunen and Rautio (2011); Zawilska et al. (2013)
Central nervous system	Anderson (1996); Rautio et al. (2008); Huttunen and Rautio (2011); Zawilska et al. (2013)
Colon	Friend and Chang (1985); McLeod et al. (1993, 1994); Sinha and Kumria (2001); Rautio et al. (2008); Huttunen and Rautio (2011)
Eye	Järvinen and Järvinen (1996); Rautio et al. (2008)
Kidney	Wilk et al. (1978); Orlowski et al. (1979); Hwang and Elfarra (1989); Huttunen and Rautio (2011); Zhou et al. (2014)
Liver	Erion et al. (2004, 2005, 2006); Kumpulainen et al. (2006); Rautio et al. (2008); Huttunen and Rautio (2011); Guo et al. (2015)
Skin	Sloan and Wasdo (2003); Majumdar and Sloan (2006); Sloan et al. (2006); Rautio et al. (2008)
Transporters in the intestinal wall	Han and Amidon (2000); Heimbach et al. (2003); Rautio et al. (2008); Zawilska et al. (2013)

process was not surprising since the prodrugs are amphiphilic, surfactant-like chemicals. Increasing the chain length lowered the critical micelle concentration, and also improved their stability. The major advantage of the micellar prodrug approach is that slightly soluble degradation products, including the poorly soluble parent drug, are solubilized. The core of the micelles, formed by the surfactant-like prodrugs, should behave as an ideal environment for the parent drug since it utilizes the parent drug as the more hydrophobic portion of the molecule. Anderson (1985) also notes that since *in vivo* hydrolysis would destroy the surfactant properties of the micellar prodrugs, they should be better tolerated than the more stable commercial surfactants.

Due to the importance of enzyme systems in the biodegradation of prodrugs, Liederer and Borchardt (2006) have presented a compilation of enzymes that can be targeted to accomplish metabolism of ester prodrugs to their parent drugs. The design of prodrugs by considering the target enzyme system has been discussed in detail (Sinkula and Yalkowsky, 1975; Amidon et al., 1977; Radhakrishnan, 1977; Banerjee and Amidon, 1985; Fleisher et al., 1985; Liederer and Borchardt, 2006; Rautio et al., 2008; Huttunen and Rautio, 2011; Bai et al., 2014). In addition, there are descriptions of enzymes that might be generally useful to facilitate targeting cancer, the central nervous system, the colon, the eye, the kidney, the liver, the skin, or the transporters in the intestinal wall, and to serve as catalysts for reconversion of prodrugs to parent drugs (Table 16.8). In addition, it has been recommended that the kinetic and binding specificity of the enzyme system, the type of reaction to be catalyzed, the enzyme distribution and concentration, and the role of the enzyme in cellular biochemistry should be known (Notari, 1973, 1985).

FURTHER READING

A number of reviews and discussions of prodrugs exist in the literature (Harper, 1959, 1962; Albert, 1964; Ariens, 1966; Digenis and Swintowsky, 1975; Sinkula, 1975; Stella, 1975; Sinkula, 1977; Anderson, 1980; Ettmayer et al., 2004; Huttunen et al., 2011), along with several books that have been cited earlier. The reader will discover that these reviewers approach the prodrug topic from different viewpoints, although some discussion overlap does exist. Reviews have been offered dealing with esters and amides as prodrug types (Digenis and Swintowsky, 1975; Huttunen and Rautio, 2011), antibiotic prodrugs (Notari, 1973), or nucleotide prodrugs (Jones and Bischofberger, 1995),