Circulating Protein Adducts in Diclofenac Patients

Covalent protein modifications by electrophilic acyl glucuronide (AG) metabolites are hypothetical causes of hypersensitivity reactions associated with certain carboxylate drugs. The complex rearrangements and reactivities of drug AG have been defined in great detail, and protein adducts of carboxylate drugs, such as diclofenac, have been found in the liver and plasma of animals and humans. This study targeted mass spectrometric analyses of human serum albumin (HSA) isolated from diclofenac patients to characterize drug-derived structures, and thereby have deconstructed conclusively the pathways of adduct formation from a drug AG and its isomeric rearrangement products in vivo. Results demonstrate that HSA modifications by diclofenac in vivo are complicated and variable; that at least a fraction of the modifications are derived from the drug’s AG metabolite; and that albumin adduction is not inevitably a causation of hypersensitivity to carboxylate drugs or a coincidental association.


PHPB Attenuates Symptoms in a Mouse Model of Alzheimer’s Disease

PHPB [potassium 2-(1-hydroxypentyl)-benzoate] has been shown to have neuroprotective effects in animal models by inhibiting oxidative injury, neuronal apoptosis, and glial activation. The aim of the present study was to examine the effect of PHPB on learning and memory in amyloid precursor protein and presenilin 1 double-transgenic Alzheimer’s disease (AD) mouse models (APP/PS1). Twelve-month-old APP/PS1 mice were given 30 mg/kg PHPB by oral gavage for 3 months. PHPB treatment significantly improved the spatial learning and memory deficits compared to the vehicle-treated mice and reduced τ hyperphosphorylation at Ser199, Thr205, and Ser396 sites. In addition, the expressions of cyclin-dependent kinase and glycogen synthase kinase 3β, important kinases involved in τ phosphorylation, were markedly decreased. These data raised the possibility that PHPB might be a promising multitarget neuronal protective agent for the treatment of AD.


Casein Kinase II Regulates Synaptic Plasticity in Neuropathic Pain

This study shows that peripheral nerve injury induces a large GluN2A-mediated increase in N-methyl-d-aspartate receptor (NMDAR) activity in spinal lamina II, but not lamina I, neurons. However, NMDAR currents in spinal dorsal horn neurons are not altered in rat models of diabetic neuropathic pain and resiniferatoxin-induced painful neuropathy. Casein kinase II (CK2) inhibitors normalize increased NMDAR currents of dorsal horn neurons in nerve-injured rats. Furthermore, nerve injury significantly increases CK2α and CK2β protein levels in the spinal cord, and inhibition of CK2 or CK2β knockdown at the spinal level substantially reverses pain hypersensitivity induced by nerve injury. These results indicate that neuropathic pain conditions with different etiologies do not share the same mechanisms, and increased spinal NMDAR activity is distinctly associated with traumatic nerve injury.


Structure and Pharmacodynamics of an Adnectin PCSK9 Inhibitor

Proprotein convertase subtilisin kexin-9 (PCSK9) is an important pharmacological target for decreasing low density lipoprotein (LDL); however, it is seemingly inaccessible to small molecule approaches. Compared with therapeutic IgG antibodies, targeting circulating PCSK9 with smaller molecular scaffolds could offer different profiles and reduced dose burdens. This inspired genesis of PCSK9-binding Adnectins, a protein family derived from human fibronectin-10th-type III-domain and engineered for high-affinity target binding. BMS-962476, an ∼11-kDa polypeptide conjugated to polyethylene glycol to enhance pharmacokinetics, binds with subnanomolar affinity to human. Treatment of cynomolgus monkeys with BMS-962476 rapidly suppressed free PCSK9 >99% and LDL-cholesterol ∼55% with subsequent 6-fold increase in total PCSK9, suggesting reduced clearance of circulating complex. Liver sterol response genes were consequently downregulated, following which LDL and total PCSK9 returned to baseline.