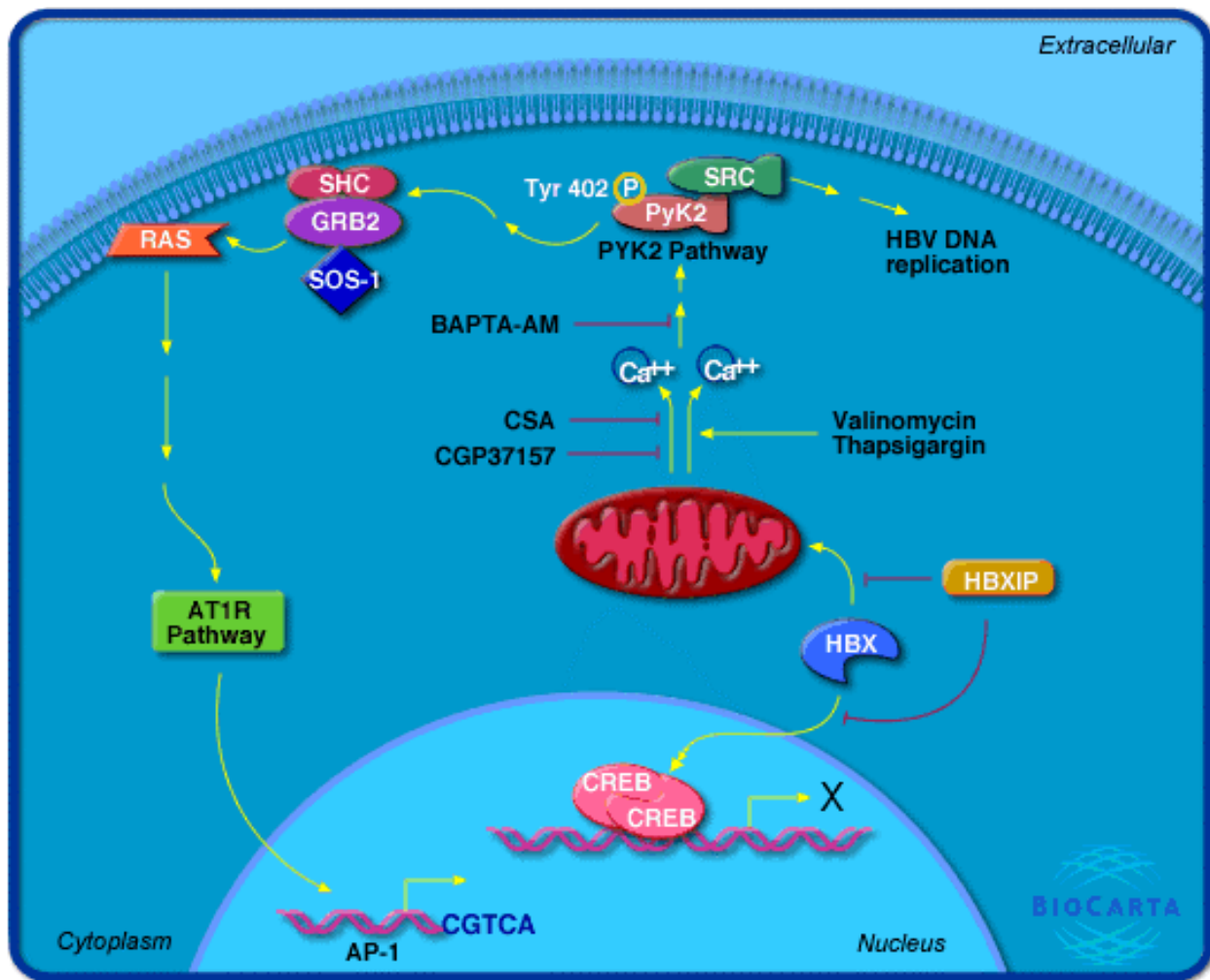


Calcium & Heart Disease



Hepatitis B is a small DNA virus that contains only 4 open reading frames in its genome. Three of these ORFs have been identified as the envelope, capsid and polymerase genes, while the function of the fourth has remained unknown until recently. The fourth reading frame has been called the X gene and produces HBx protein that is essential for viral replication in liver cells and acts broadly to activate a variety of transcription factors. One hypothesis of HBx activity has been that it enters the nucleus to act as a transcriptional regulator. One piece of evidence supporting this mechanism of HBx action is that HBx interacts with the transcription factor CREB and increases its DNA-binding activity. This mechanism does not explain all of the effects of HBx however. Another hypothesis for the HBx mechanism of action is that HBx increases calcium release into the cytoplasm. This mechanism of action is consistent with the variety of transcription factors and kinases affected by HBx since calcium signaling affects many different signaling pathways. HBx does not appear to interact directly with Ras or protein kinases but does appear to activate the calcium activate protein

kinase Pyk2. A dominant negative form of Pyk2 blocks HBx activity and the involvement of calcium in HBx activation of Pyk2 is indicated by the action of several molecular probes that alter cytosolic calcium signaling. BAPTA-AM chelates cytosolic and blocks HBx action. Cyclosporin A blocks mitochondrial calcium signaling and also blocked HBx signaling. CGP37157 is a compound that blocks the mitochondrial sodium calcium pump and also blocks hepatitis B viral replication, indicating that mitochondrial calcium signaling is the target of HBx function. Compounds that elevate cytoplasmic calcium levels (valinomycin and thapsigargin) increase the rate of replication of viruses that lack HBx, further supporting the role of HBx as an inducer of intracellular calcium signaling. The mechanism by which HBx causes calcium release is not yet known. Src activation appears to induce viral replication while Ras signaling does not, suggesting that the activation of Ras signaling by HBx may play a distinct function, perhaps the induction of cancer.