SB431542

SB431542 is a selective and potent inhibitor of the TGF-β/Activin/NODAL pathway that inhibits ALK5 (IC_{50} = 94 nM), ALK4 (IC_{50} = 140 nM), and ALK7, but does not inhibit the BMP type I receptors ALK2, ALK3, and ALK6.

While dopamine agonists are a primary method of therapeutic treatment for Lactotroph adenoma, the rate of resistance to these drugs continues to increase each year. During previous long-term clinical investigations, Hu et al., from Department of Neurosurgery and Pituitary Tumor Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, found that partial resistant prolactinomas exhibited significantly more fibrosis than did sensitive adenomas, suggesting a role of fibrosis in their drug resistance. Furthermore, resistant adenomas with extensive fibrosis mainly express type I and type III collagens. Since TGF-β1 is the key factor in the initiation and development of tissue fibrosis, including in the pituitary, in this study, they aimed to determine whether TGF-β1 mediated fibrosis in prolactinomas and whether fibrosis was related to prolactinoma drug resistance. Using immunochemistry and western blotting, they found that the TGF-β1/Smad3 signaling pathway-related proteins were elevated in resistant prolactinoma specimens with high degrees of fibrosis compared to levels in sensitive samples, suggesting that this pathway may play a role in prolactinoma fibrosis. In vitro, TGF-β1 stimulation promoted collagen expression in normal HS27 fibroblasts. Furthermore, the sensitivity of rat prolactinoma MMQ cells to bromocriptine decreased when they were co-cultured with HS27 cells treated with TGF-β1. The TGF-β1/Smad3 signaling-specific inhibitor SB431542 counteracted these effects, indicating that TGF-β1/Smad3-mediated fibrosis was involved in the drug-resistant mechanisms of prolactinomas. These results indicate that SB431542 may serve as a promising novel treatment for preventing fibrosis and further improving the drug resistance of prolactinomas [1].

1)
Hu B, Mao Z, Jiang X, He D, Wang Z, Wang X, Zhu Y, Wang H. Role of TGF-β1/Smad3-mediated fibrosis in drug resistance mechanism of prolactinoma. Brain Res. 2018 Jul 26. pii: S0006-8993(18)30408-6. doi: 10.1016/j.brainres.2018.07.024. [Epub ahead of print] PubMed PMID: 30055965.