Activation of ribosomal p70 S6 kinase by selective serotonin $(5\text{-HT})_{2B}$ receptor agonist BW723C86 is mediated by epidermal growth factor/transforming growth factor-α receptor tyrosine kinase in primary cultures of adult rat hepatocytes.

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Serotonin (5-HT) can induce hepatocyte DNA synthesis and proliferation by autocrine secretion of transforming growth factor (TGF)-α through 5-HT_{2B} receptor/phospholipase C (PLC)/Ca^{2+}. In the present study, we investigated whether 5-HT or a selective 5-HT_{2B} receptor agonist BW723C86, would stimulate phosphorylation of TGF-α receptor tyrosine kinase (RTK) and ribosomal p70 S6 kinase (p70 S6K) in primary cultures of adult rat hepatocytes by using Western blotting analysis. Our results showed that 5-HT- or BW723C86-induced phosphorylation of EGF/TGF-α RTK peaked at between 5 and 10 min. On the other hand, 5-HT- or BW723C86 -induced phosphorylation of p70 S6K peaked at about 30 min. Furthermore, a selective 5-HT_{2B} receptor antagonist LY272015, a specific PLC inhibitor U-73122, a membrane-permeable Ca^{2+} chelator BAPTA/AM, an L-type Ca^{2+} channel blocker verapamil, somatostatin, and a specific p70 S6K inhibitor LY2584702 completely abolished the phosphorylation of p70 S6K induced by both 5-HT and BW723C86. These results indicate that phosphorylation of p70 S6K is dependent on the 5-HT_{2B}-receptor-mediated autocrine secretion of TGF-α. In addition, these results demonstrate that the hepatocyte proliferating action of 5-HT and BW723C86 are mediated by phosphorylation of p70 S6K, a downstream element of the EGF/TGF-α RTK signaling pathway.