Polyamines in the Initiation of Pancreatic Growth

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The role played by polyamines in mediating the pancreatic growth and secretory responses to hormonal stimulation is uncertain. The effect of an inhibitor of ornithine decarboxylase (ODC), α -di-fluoromethylornithine (DFMO), on the rat pancreatic growth and protein secretion and synthesis in response to hormonal stimulation was therefore studied. Attempts were also made to elucidate the time course of events leading to pancreatic growth. Anesthetized rats with the pancreatic duct cannulated were given an intravenous injection of DFMO (50, 100 or 150 mg/kg), followed by a 7-hour continuous infusion (15, 25 or 35 mg/kg/h, respectively). After a basal 1-hour period an intravenous infusion of 2.5 μ g/kg/h of the cholecystokinin-like peptide Thr²⁸Nle³¹CCK²⁵⁻³³ (CCK-LP) was added and continued for 6 h. The control rats received CCK-LP only. In other experiments conscious rats were given a continuous intravenous infusion of 2.5 μ g/kg/h of CCK-LP for 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 96 h, with or without DFMO at 8, 24 and 48 h (100 mg/kg as an injection initially and thereafter 25 mg/kg/h). The pancreas was quickly removed, and analyzed for variables indicating synthesis and accumulation of DNA, RNA and polyamines. The ODC activity in the pancreas of anesthetized rats was markedly reduced by DFMO, but DFMO did not affect pancreatic juice volume or protein output. The ODC activity and the putrescine concentration in the pancreas of conscious rats were significantly reduced by DFMO at 8 and 24 h, but not at 48 h. DFMO also significantly reduced the activities of RNA polymerase, DNA polymerease and thy-midine kinase at 24 h, but not at 48 h. CCK-LP increased the activity of RNA polymerase already after 1 h, whereas an increase in the activity of ODC and the level of putrescine was seen at 4 h. Spermi-dine was increased after 12 h. The activities of DNA polymerase and thymidine kinase were increased at 12 and 24 h, respectively, whereas the total contents of DNA and RNA were first increased at 48 h. The present study indicates that polyamines play an important role in the initiation of the growth response to hormonal stimulation, but does not support a similar dependency for early pancreatic protein synthetic and secretory responses. Both the increased ODC activity and the accumulation of polyamines are early and sensitive determinants of the trophic effect of CCK on the pancreas.