THE CANNABINOID WIN 55212 INHIBITS PANCREATIC AMYLASE SECRETION VIA CHOLINERGIC SUPPRESSION

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INTRODUCTION. In the digestive tract there is evidence of the presence of high amounts of endocannabinoids and of mechanisms for cannabinoids metabolism and uptake (1). Several studies have shown that cannabinoids inhibit excitatory transmission and peristalsis in the isolate guinea pig ileum and intestinal motility in the mouse (2). The mechanism by which cannabinoids depress the elettrically-evoked contraction of the longitudinal muscle of the small intestine is mediated by presynaptic inhibition of acethylcholine release. There are few reports on the action of cannabinoids on the exocrine pancreas and the presence of cannanbinoid receptors has not been reported in the pancreas. This study evaluates the hypothesis that WIN55212, a synthetic cannabinoid, influences amylase release from pancreatic lobules of guinea pig and from pancreatic acini of the rat. METHODS. Amylase secretion from lobules stimulated by KCl and from isolated acini was studied in the presence of WIN55212 and expressed as percent of total content in the tissue. RESULTS. Depolarization by KCl, that is known to release Ach from nerve fibers, resulted in a 4-fold increase of amylase release over basal. Addition of WIN55212 (10^{-9} M to 10^{-6} M) inhibited KCl stimulated amylase release in a dose–related fashion. The effect of WIN55212 was antagonized by SR141716A, a selective cannabinoid CB1-receptor antagonist. The cannabinoid did not modify basal unstimulated amylase release. In isolated acini, WIN55212 at concentrations ranging from 10^{-9} M to10^{-7} M did not affect basal amylase, but 10^{-5} M concentration stimulated enzyme release from 5.8+0.6% to 19.4+3%. DISCUSSION. These data indicate that the cannabinoid WIN55212 inhibits enzyme secretion from lobules via Ach release suppression. The inhibitory effect observed in lobules, that contain intrapancreatic neurons, taken togheter with the antagonism displayed by the CB1-receptor selective antagonist, suggest the presence of cannabinoid receptors on nerve fibers in the lobules. As non-specific binding sites for cannabinoids have been found in peripheral tissues of the rat and in the pancreas (3), membrane effects of WIN55212 at sites where cannabinoids are sequestered non-specifically cannot be excluded. Immunofluorescence studies with anti-CB1-receptor antibody will clarify the effective presence of cannabinoid receptors on nerve fibers in lobules and in acinar cells.

1) Pinto l., et al., Prostaglandins Leukot Essent Fatty Acids, 2002,66, 333-41.
2) Pertwee R.G., Gut, 2001,48,859-867.
3) Lynn A.B., Herkenham M., J.Pharmacol.Exp Ther., 1994,268,1612-23.