Oleic acid stimulated the net output (μmoles/g liver/4 hours) of triglyceride (3.03 $\pm$ 0.23 vs 8.49 $\pm$ 0.46), free cholesterol (0.96 $\pm$ 0.04 vs 1.15 $\pm$ 0.05), and cholesteryl esters (0.24 $\pm$ 0.04 vs 0.53 $\pm$ 0.08) ($2p < .05$ in all cases). The rate of synthesis (μmoles/g liver/hour) of triglyceride-glycerol (4.36 $\pm$ 0.75 vs 8.73 $\pm$ 0.19), free cholesterol (0.12 $\pm$ 0.02 vs 0.26 $\pm$ 0.03), and cholesteryl esters (0.01 $\pm$ 0.001 vs 0.07 $\pm$ 0.001) ($2p < .005$ in all cases) was also stimulated by oleate whereas the rate of synthesis of fatty acid was depressed (1.53 $\pm$ 0.27 vs 0.37 $\pm$ 0.05) ($2p < .02$). The high relative specific activity of triglyceride-glycerol, free cholesterol and esterified cholesterol in the microsomal fraction of the liver suggests that it is the most active site of synthesis for these lipids.

The data reported in this dissertation led us to suggest that biosynthesis of free cholesterol by the perfused liver is controlled by a mechanism which is similar to a direct endproduct (free cholesterol) inhibition. It is proposed that the removal of free cholesterol from the site of synthesis (primarily in microsomes) could be the pathway through which cholesterogenesis is modified in the isolated rat liver perfused in the absence or presence of oleic acid. Free cholesterol is a necessary component of the water soluble triglyceride-rich particles. The assembly of these particles resulted in the removal of free cholesterol from the site of synthesis. The need for cholesterol in the formation and subsequent secretion of these particles into the perfusate as the VLDL, and/or the dispersion of these particles within the cytoplasm of the cell may constitute a functional pathway by which free cholesterol biosynthesis in the perfused liver is modulated. An alternative pathway, molecular in nature, for the removal of free cholesterol from the site of synthesis is the esterification of free cholesterol by fatty acid. The removal of free cholesterol by these pathways could be the primary modulator for the direct endproduct inhibition on hepatic cholesterogenesis.

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THE EFFECTS OF PHENCYCLIDINE ON THE PERIPHERAL NERVOUS SYSTEM

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Phencyclidine (PCP) is an anesthetic agent which in low doses produces psychotomimetic effects. PCP has previously been shown to produce a pressor response and to potentiate the pressor effects of the catecholamines. Experiments were designed to determine the site and mechanism of action of PCP on the peripheral nervous system in an attempt to elucidate a mechanism of action which could be related to the psychotomimetic effects. In vitro on the isolated guinea-pig vas deferens preparation, PCP (5×10^{-5}M) was found to significantly potentiate norepinephrine (NE) ED_{30} induced contractions 338 $\pm$ 65 percent over control ($p > 0.005$) while completely blocking acetylcholine (ACH) ED_{30} induced contractions. In comparison, mescaline (5×10^{-5}M) and LSD-25 (3×10^{-7}M) also potentiated NE (ED_{30}) induced contractions ($p > 0.05$). Mescaline partially blocked ACH (ED_{30}) induced contractions ($p > 0.05$) while LSD significantly potentiated ACH (ED_{30}) induced contractions ($p > 0.05$). In vivo, on the cat nictitating membrane preparation, PCP potentiated both epinephrine (EPI) ($p > 0.005$) and electrically induced contractions ($p > 0.20$) which were also not blocked by hexamethonium. After denervation of the nictitating membrane, the potentiation of EPI induced contractions by PCP were significantly reduced ($p > 0.001$) when compared to EPI induced contractions by PCP in normally innervated nictitating membranes. In the frog sciatic-gastrocnemius preparation, PCP 10 mg/ml increased the amplitude of muscle contractions by 36 $\pm$ 12 percent in nerves which were submaximally stimulated. In nerves which were stimulated supramaximally, PCP 10 mg/ml significantly decreased ($p > 0.05$) the time necessary for muscle contractions to respond to nerve stimulation after inhibition of sciatic nerve conduction by lidocaine 10 mg/ml when compared to nerves treated only with lidocaine. Pretreatment with PCP before lidocaine, more than doubled the time necessary for lidocaine to inhibit muscle contractions compared to nerves treated only with lidocaine. In the compound action potentials of the frog sciatic nerve, PCP 10^{-3}M in Ringer solution facilitated nerve conduction by increasing the amplitude of the action potentials. At 10^{-2}M, PCP produced significant local anesthetic activity ($p > 0.05$) compared to untreated nerves. The local anesthetic effects were increased by hypocalcemic Ringer solution and antagonized by hypernatremic Ringer solution. PCP appears to have indirect sympathomimetic effects and to also have dose-dependent direct effects on nerve membranes to affect conduction. In the CNS, the effect of PCP to increase adrenergic activity, facilitate nerve transmission or produce local anesthetic effects would be a significant factor in the development of psychotomimetic effects.

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DETERMINATION OF THE APPROXIMATE LOCI OF ACTION OF DIAZOXIDE, NITROGLYCERIN, PAPAVERINE AND TETRACAINE

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The approximate loci of action of diazoxide, nitroglycerin, papaverine and tetracaine were determined through the employment of concepts derived from a theoretical construct. This construct was based on the assumptions: (1) that the introduction of norepinephrine into the immediate environment of rabbit aortic muscle initiates a sequence of cellular processes that are arranged in a sequential fashion and (2) that the cellular processes induced are interrelated in a linear or hyperbolic fashion. The initial process is believed to be a rapid, reversible association of the norepinephrine molecules with specific receptors in the muscle membrane to form the norepinephrine-receptor complex. A direct or indirect consequence of this interaction is the activation of a transport system by which calcium ions enter the cytoplasm. The calcium ions are thought to enter the cytoplasm by first interacting with active sites of the transport system to form the calcium-transport receptor complex. The divalent ions are then ferried to the cytoplasm as the complex. It is postulated that the calcium ions in the cytoplasm interact with active centers of the contractile mechanism to form the calcium-contractile mechanism complex. The consequence of this interaction is shortening of the smooth muscle fibers producing a contractile response. Further insight as to the approximate loci of action of diazoxide, nitroglycerin, papaverine and tetracaine was gained by determining the specificity of action of these agents. The specificity of action of the spasmolytic agents diazoxide, nitroglycerin, papaverine and tetracaine was determined by comparing the effects of these agents upon norepinephrine-induced and potassium-induced contractions of rabbit aortic muscle. The assumption underlying this portion of this study was the postulate that the immersion of rabbit aortic muscle in an isotonic KCl medium initiates a sequence of cellular processes within the muscle that is independent of an agonist-receptor interaction. The initial process induced when the muscle is immersed in the isotonic KCl medium is