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KHWANCHIT TANPHICHAI : STIMULATORY EFFECT AND MECHANISMS OF ACETOPHENONES ON BILE SECRETION IN RATS. THESIS ADVISORS: PAWINEE PIYACHATURAWAT, Ph.D., PRAYAD KOMARATAT, Ph.D., APICHART SUKSAMRARN, Ph.D. WISUDA SUVITAYAWAT, Ph.D. 157 p. ISBN 974-664-858-6

A previous screening for choleretic activity in phloracetophenone analogs and derivatives indicated that the hydroxylated acetophenone analogs were effective in inducing choleresis, with a wide variation of activities. The purpose of this study was to extend the previous finding by investigating in more detail, the effect and mechanisms of action of six hydroxylated acetophenone analogs which vary in number and position of hydroxy substituents on the benzene nucleus. These included 2-mono, 4-mono, 2,4-di, 2,6-di, 2,3,4-tri and 2,4,6-trihydroxyacetophenone (2-MHA, 4-MHA, 2,4-DHA, 2,6-DHA, 2,3,4-THA, and 2,4,6-THA). In this study, the hydroxyacetophenone analogs were intraduodenally administered to adult male Wistar rats at various doses (100-1000 μmol/kg BW) and bile samples were collected via a bile fistula for analysis of bile flow rate and biliary concentration and output of bile acids, cholesterol and phospholipid. All analogs induced the dose-related effects on bile flow rate and bile acid excretion. The activities were dependent on the number and position of hydroxy groups on the benzene nucleus. The hydroxy group at 4-position was essential for induction of high bile flow rate. The number and position of hydroxy group(s) also directly related to the hydrophilic-hydrophobic properties of the compounds which inversely related to their choleretic activity. However, there was no obvious relation between the number of hydroxy groups on benzene ring of hydroxyacetophenone and the concentration and output of biliary cholesterol and phospholipid. Among hydroxylated acetophenone analogs used in this study, only 4-MHA, 2,4-DHA, and 2,4,6-THA were the potent hydrocholeretic agents generating high bile flow rate with low lithogenic index. Changes of bile flow rate by the hydroxyacetophenones, to some extent, related to an enhancement of bile-acid dependent flow (BADF). Meanwhile, most of these compounds, except for 2,6-DHA, induced an increase in bile flow rate by elevating bile acid-independent flow (BAIF). Among the hydroxyactophenones used, 4-MHA, which induced the highest BAIF, was evaluated for its non-bile acid metabolite and 4-hydroxyacetophenone-4-*O*-glucuronide was identified as the major metabolite. The excretion of this metabolite was linearly correlated with the increment in bile flow. The choleretic effect of 4-MHA was partly due to its osmotic effect of the conjugate eliminated in bile. This mechanism might also account for choleretic activities of other hydroxyacetophenone analogs which particularly contain a hydroxy group at 4-position.

These analysis of secretory fraction of bile and the identification of the metabolite may provide a significant information, at least, for understanding the choleretic mechanism of hydroxyactophenone. It is suggested that analogs with a hydroxy group at the 4-position including 4-MHA, 2,4-DHA, and 2,4,6-THA might have therapeutic potential for use as cholelytic agents.