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Rapid Communication

Design and Hypoglycemic Activities of 2-Alkylglycidate Possessing Aryloxyalkyl Residue

Kyung Hoon Min, So Young Baek, Ra Ok Jeon, Hyun Ju Park, Won Ki Kim#, Seung Hoon Cheon[1] and Young Ger Suh*

College of Pharmacy, Seoul National University, Seoul 151-742, Korea, #College of Medicine, Medical Research Center, Ewha Womans University, Seoul 158-056, Korea and [1]College of Pharmacy, Chonnam National University, Kwang-Ju 500-757, Korea

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Diabetes mellitus is a chronic disease and its characteristics include defects in the metabolism or utilization of insulin, carbohydrate, fat and protein. Excessive free fatty acid oxidation might be a key factor underlying the decreased tolerance to glucose in diabetes (Randle, *et al.*, 1966). One of the promising approach to the treatment of diabetes mellitus would be to devise agents that would inhibit the abnormally high rate of fatty acid oxidation. It was predicted from the concept of glucose/fatty acid cycle that inhibiting fatty acid oxidation would increase utilization of glucose and lower blood glucose concentration. In the cellular mechanism of fatty acid oxidation (Ponde, 1975, Hoppel, 1976, Murthy, *et al*, 1987) short- and long-chain fatty acids enter the cell from the bloodstream where they are esterified immediately to coenzyme A (CoA) esters by fatty acyl CoA synthetase. The CoA esters of long chain fatty acids (C12-C20) cannot enter the mitochondria directly where oxidation takes place. They must first be transesterified to their carnitine palmitoyltransferase I (CPT-I) which is bound to the outer membrane. The carnitine ester is shuttled across the inner mitochondrial membrane by translocase present on the inner membrane. The carnitine esters are retransesterified by carnitine palmitoyl transferase II (CPT-II) to form acyl CoA esters. The resulting fatty acyl-CoA esters then enter into the normal β-oxidative pathway. (Fig. 1)

However, the short-chain fatty acids(shorter than nonanoic) can enter the mitochondria directly without conversion to their carnitine esters. Thus the transport of

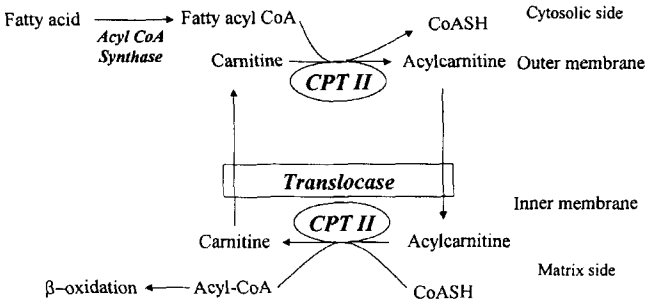


Fig. 1. A schematic representation of the mitochondrial CPT system

long-chain acids into the mitochondria via their carnitine esters provides a locus of selective interference for long-chain fatty acids.

The coenzyme A(CoA) esters of the substituted oxirane-2-carboxylic acids such as palmoxirate have been reported to be powerfully hypoglycemic drugs by irreversible, active site-directed inactivation of CPT-1 (Chase, et *al*, 1972) The lowering of blood glucose by palmoxirate results from both inhibition of hepatic gluconeogenesis and stimulation of peripheral glucose utilization (Tutwiler, et *al*, 1979). Accordingly, a number of its analogues have been developed and etomoxir which has aryloxyalkyl moiety among them exhibits the most effective hypoglycemic effects. In addition, it was very recently proposed that the bound fatty acid is present in a bent conformation in the interior of fatty acid binding proteins (VeerKamp, *et al*, 1991)

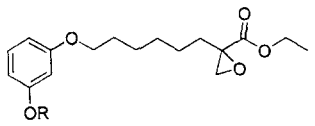
In conjunction with investigation of the conformational effects of aryloxyalkyl residue of the 2-alkylglycidate on hypoglycemic effects, we have recently been working on syntheses of a series of ethyl 2-(alkoxyaryloxy) alkylglycidates. Particularly, the bent conformation of these compounds was designed on the basis of the reported fatty acid-binding proteins. Thus, we expected that the enzyme preferentially binds the designed compound that has a proper pocket fit. We herein report the preliminary structure-activity relationship of the aryloxyalkyl residue based on biological results of the designed and synthesized variants of aryloxyalkylglycidates.

The compounds listed in Table I were efficiently synthesized by the procedure developed in our laboratory (Suh, *et al*, 1998) The bent conformation of aryloxyalkyl residue was maintained by introducing resorcinol moiety which provides both aromatic character of etomoxir and the requisite geometry of the aryloxyakyl residue. The synthesized compounds were evaluated for their ability to lower glucose levels in diabetic rat induced by streptozotocin and the results are summerized in Table II.

All the synthesized compounds efffectively reduced the

Correspondence to: Professor Young Ger Suh, College of Pharmacy, Seoul National University, Seoul 151-742, Korea
E-mail: ygsuh@plaza.snu.ac.kr

Table I. Synthesized molecules



compound	R
1	H
2	CH_3
3	$CH_2CH{:}CH_2$
4	$COCH_3$
5	$CH_2OCH_2CH_2OCH_3$
6	$CH_2OCH_2(CH_2)_6CH_3$
7	CH_2OCH_3

Table II. Effects of the synthesized compounds on plasma glucose concentration in diabetic rat induced by streptozotocin.
Plasma glucose concentrations are expressed as the mean ± S.D. of 3-5 animals. *indicates a significant difference between the value of plasma glucose concentration before and after p.o. application of each synthesized compound. (*:P< 0.01)

compounds	Reduction % of Plasma Glucose Concentration (mg/dl)
	3 h after treatment
control	-
1	3.0
2	9.1
3	19.7*
4	9.1
5	10.4
6	17.8*
7	27.5*

plasma glucose concentration. In particular, compound 3, 6 and 7 were found to be relatively more effective hypoglycemic although their potency are still unsatisfactory. It seems that moderate liphophilicity of the aliphatic side chains as well as the bent conformation of aryloxyalkyl residue are beneficial for the higher potency.

In summary, the synthesized compounds designed based on the morphology of the fatty acid binding proteins didn't show the satisfactory hypoglycemic activity. However, this present study has partly provided more information to support the proposal that CPT-I would be preferentially bound to the bent conformational glycidate.

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