Some Metabolic Effects of Substituted Alkanesulfonamidophenethanolamines in Rats (36526)

D. A. RIGGILO, W. T. COMER, AND H. R. ROTH
(Introduced by W. A. Zygmunt)
Mead Johnson Research Center, Evansville, Indiana 47721

The alkanesulfonamidophenethanolamines were introduced by Larsen and Lish (1) as a series of compounds displaying the pharmacologic properties of hydroxy phenethanolamines. The chemistry and general structure–activity relationships for both a monosubstituted (2) and disubstituted (3) series have been described.

The disubstituted compounds are analogs of the catecholamines (epinephrine, norepinephrine, isoproterenol, etc.), and consist of 2 isomeric series, *meta* and *para* (3). Compounds in the *meta* series have an alkanesulfonamido group *meta* and a hydroxy group *para* to the ethanolamine side chain. In the *para* series, these groups are reversed. Compounds in the *meta* series cause potent adrenergic responses on typical physiological systems, while similar compounds of the *para* series are considerably less active.

In the present study, structurally modified catecholamine analogs were assessed for hyperglycemic and hyperlacticacidemic effects in fasted rats.

Materials and Methods. Harlan male rats[1] (165–270 g, fasted for 18 hr) were anesthetized with sodium pentobarbital (30 mg/kg ip) 30 min prior to the start of the study. Blood samples were obtained by means of retro-orbital puncture immediately prior to intraperitoneal injection of a catecholamine analog and again 1 hr later (previously determined time of peak effect). Test compounds were administered in fourfold dose increments from 3.125–800.0 μg/kg. When possible, dose–response data were subjected to linear regression analysis. D_{G20} and D_{L20} values (doses of test drug required to induce a 20 mg/100 ml rise in glucose and lactate, respectively) were interpolated or extrapolated from the regression lines and potency ratings determined. Five to 10 animals were used for each of one to five dose levels employed per compound.

Blood glucose was estimated in an AutoAnalyzer utilizing the ferricyanide procedure (4). Blood lactate was determined enzymatically in an AutoAnalyzer without a dialyzer according to the method of Hochella and Weinhouse (5).

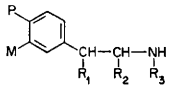
Doses of all test agents refer to the free base and were administered as saline solutions of the HCl salts in a volume of 2 ml/kg.

Results. Six alkanesulfonamidophenethanolamines elicited dose-related hyperglycemic and hyperlacticacidemic responses, while the remaining nine were inactive or lethal at the doses tested. The maximal blood glucose rise observed with any compound at any dose was 45 mg/100 ml, while blood lactic acid levels continued to increase with the dose. The structural characteristics and metabolic potencies (relative to isoproterenol) of the compounds evaluated in this study are listed in Table I.

In the *meta* series, compounds 2 and 3 (analogs of epinephrine and norepinephrine) were active at low doses but lethal at higher levels precluding any potency estimates. Compound 4 (isoproterenol analog) when compared at the D_{G20} and D_{L20} levels of activity, had 5.2× and 3.1×, respectively, the hyperglycemic and hyperlacticacidemic effects of isoproterenol. On this basis, howev-

[1] The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

TABLE I. Hyperglycemic and Hyperlacticacidemic Activity of Substituted Alkanesulfonamidophenethanolamines.

Compound no.	 P	M	R_1	R_2	R_3	Glucose D_{G20} (μg/kg ip)	Glucose Potency rating	Lactate D_{L20} (μg/kg ip)	Lactate Potency rating
1[a]	OH	OH	OH	H	$(CH_3)_2CH$	170	1.0	330	1.0
2	OH	MSA[b]	OH	H	CH_3	—	Lethal @ 200 μg/kg	—	Lethal @ 200 μg/kg
3	OH	MSA	OH	H	H	—	Lethal @ 200 μg/kg	—	Lethal @ 200 μg/kg
4[c]	OH	MSA	OH	H	$(CH_3)_2CH$	33	5.2	105	3.1
5	OH	MSA	OH	CH_3	$(CH_3)_2CH$	> 800	Inactive	> 800	Inactive
6	OH	MSA	OH	C_2H_5	$(CH_3)_2CH$	220	0.8	2300	0.1
7	OH	MSA	OH	H	$(CH_3)_3C$	12	14.2	78	4.2
8	OH	MSA	OH	H	3,4-$(CH_2O_2)C_6H_3CH_2CH(CH_3)$	12	14.2	30	11.0
9[d]	OH	MSA	OH	H	$C_6H_5CH_2C(CH_3)_2$	16	10.6	44	7.5
10	OH	MSA	OH	CH_3	4-$CH_3SO_2NHC_6H_4CH_2CH_2$	> 800	Inactive	> 800	Inactive
11[e]	OH	MSA	H	CH_3	4-$CH_3OC_6H_4CH_2CH_2$	> 800	Inactive	> 800	Inactive
12	OH	MSA	OH	C_2H_5	4-$CH_3OC_6H_4CH_2CH_2$	310	0.5	1000	0.3
13	OH	MSA	OH	C_2H_5	$C_6H_5OCH_2CH(CH_3)$	> 800	Inactive	> 800	Inactive
14	MSA	OH	OH	H	CH_3	> 800	Inactive	> 800	Inactive
15	MSA	OH	OH	H	H	> 800	Inactive	> 800	Inactive
16	MSA	OH	OH	H	$(CH_3)_2CH$	> 800	Inactive	> 800	Inactive

[a] Isoproterenol HCl.

[b] MSA = methanesulfonamido (CH_3SO_2NH–).

[c] Soterenol HCl (MJ 1992).

[d] Prepared according to scheme I of Ref. (3); analytically pure as the HCl salt, corr. mp 206–207° dec, designated MJ 9184-1.

[e] Prepared by converting the corresponding arylethanolamine, mesuprine [compound 60 in Ref. (3)], to the chloroethylamine with thionyl chloride, followed by reductive dechlorination with $NaBH_4$; analytically pure as the HCl salt, corr. mp 197.5–200.5°, designated MJ 9089-1.

er, compounds 7–9 were the most active agents studied, having 10.6–14.2× the hyperglycemic and 4.2–11.0× the hyperlacticacidemic effects of isoproterenol. Compounds 6 and 12 possess only marginal activity while compounds 5, 10, 11, and 13 were inactive.

Three compounds of the *para* series were tested, compounds 14, 15, and 16 (analogs of epinephrine, norepinephrine and isoproterenol), and were found to be devoid of activity at 800 μg/kg.

Discussion. Whereas catecholamine-induced hepatic glycogenolysis in the rat cannot be classified as either an α or β response (6, 8), both α- and β-adrenergic agents exert a characteristic effect depending on the prandial state of the animals (9–11). Thus, epinephrine induces hyperglycemia in both fed and fasted animals. Norepinephrine elicits hyperglycemia in fed, but not in fasted, rats; while the reverse is true for isoproterenol. Furthermore, the glycemic response to β stimulants is fairly well defined—moderate hyperglycemia characterized by a maximal increase of 40–50 mg/100 ml (10–12).

On the other hand, catecholamine-induced muscle glycogenolysis (skeletal and cardiac) is considered to be a relatively pure β-adrenergic response in the rat as well as other species (6, 7). Moreover, the hyperlacticacidemic response to β-adrenergic agents is quite prominent and not influenced by the prandial state (10).

In the present investigation, some methanesulfonamido analogs of catecholamines elicited prominent hyperlacticacidemia and moderate hyperglycemia which did not exceed 45 mg/100 ml. These metabolic responses are quite similar to those previously described for isoproterenol and soterenol (9, 12), and are characteristic of β-receptor agonists in fasted rats. Furthermore, the metabolic potencies correlate, in general, with those obtained on the isolated guinea pig trachea and isolated rat uterus (3), and thus provide additional evidence for the β-adrenergic nature of these particular compounds.

With respect to structure–activity relationships, the following observations can be made. Replacement of the *meta* hydroxyl of isoproterenol with the MSA group (cpd 4) enhances metabolic activity. When the MSA group is *para* and the hydroxyl group is *meta* (relative to the ethanolamine side chain) (cpds 14–16) activity is markedly diminished. A methyl or ethyl substituent on the α carbon of the ethanolamine side chain (cpds 5 and 6) decreases metabolic potency. Bulky substituents attached to the ethanolamine nitrogen, such as *t*-butyl (cpd 7) and sterically hindered aralkyl groups (cpds 8 and 9), increase metabolic activity compared to the isopropyl group of isoproterenol and soterenol, whereas less bulky aralkyl groups (cpds 11–13) are associated with a decrease in metabolic effectiveness.

Summary. The hyperglycemic and hyperlacticacidemic effects of two isomeric series of substituted alkanesulfonamidophenethanolamines were determined in fasted rats. The metabolic responses to these agents are characteristic of β-adrenergic stimulation and correlate with their adrenergic effects on isolated tissue. Structure–activity relationships are discussed.

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