Growth-Depressing Effects of 5-*n*-Pentadecylresorcinol: A Model for Cereal Alkylresorcinols

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ABSTRACT

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Tests were performed on male weanling rats to determine whether 5-pentadecylresorcinol (PDR) causes appetite depression, which, in turn, depresses growth, or if some effect apart from palatability is responsible for the observed growth depression. Two experiments were performed to assess effects on food intake and body weights in a pair-feeding experiment, using diets with three levels of added PDR, and effects on food intake and body weights in a pair-fed experiment when PDR was force-fed at two levels. Generally, PDR depressed growth through a depression of food intake, and this was observed with both modes of administration. Approximately 70% of the growth depression was attributed to decreased food intake, and 30% was due to a toxic effect of PDR. Histopathological evaluations of internal tissues of rats did not show any abnormalities.

The alkylresorcinols in cereal grains have become of interest only recently. These compounds previously were associated with rye and were thought to be a problem only in animal nutrition.

Feeding rye in large amounts to cattle, sheep, horses, pigs, and poultry causes slower growth than feeding of other cereal grains (Friend and MacIntyre 1969, Friend 1970, Smith and MacIntyre 1970, Fernandez et al 1973). Rye is also less palatable to chicks than is wheat, corn, or barley. In experiments with chicks, Misir and Marquardt (1978) identified two detrimental factors in rye: an appetite-depressing factor and a growth and feed efficiency depressing factor. The former was located primarily in the bran fraction, which contained the highest concentration of alkylresorcinols. The latter was associated with water-soluble pentosans.

The diminished growth rate was caused primarily by a decrease of feed intake, which some researchers blamed on the bitter taste of rye. But the question remained whether the feed intake was lower because of this bitter or disagreeable taste or whether an unknown physiological effect on the animal body was involved.

The growth-inhibiting effect of rye has often been ascribed to ergot (*Claviceps purpurea*) contamination. Rations with toxic levels of ergot exceeding 1% are so unpalatable, however, that most animals refuse to eat them (Lorenz 1974). The effect of ergot, therefore, must not be mistaken for the effect of rye itself.

Wieringa (1967) identified the harmful substances in rye as a mixture of 5-*n*-alkylresorcinols with odd-numbered side chains of 15–23 carbon atoms and of smaller amounts of 5-alkenylresorcinols. These compounds were primarily concentrated in the pericarp of rye kernels. Wenkert et al (1964) found 5-*n*-alkylresorcinols in wheat bran. The nuclear magnetic resonance spectrum pointed to resorcinol derivatives with a side chain of 17, 19, 21, 23, and 25 carbon atoms.

Since the work of Wenkert et al (1964) and Wieringa (1967), alkylresorcinols have been detected in wheat, rye, and triticale by many other researchers (Evans et al 1973, Verdeal and Lorenz 1977, Tluscik 1978, Musehold 1978, Salek 1978). Evans et al (1973) showed differences in alkylresorcinol content between varieties of wheat and rye. Generally, rye contains much higher amounts of alkylresorcinols than wheat. There have been indications that soil type, fertilization, and weather influence the amounts of alkylresorcinols.

Milling of wheats produces bran fractions with rather high amounts of alkylresorcinol (Verdeal and Lorenz 1977), which might be used in high-fiber products because of the alleged benefits of higher levels of this nutrient in the diet of man. Thus, alkylresorcinol intake could increase through certain high-fiber foods. There are no established toxicity levels for these compounds.

Wieringa (1967) fed rats and pigs diets that were supplemented with alkylresorcinols isolated from cereals or from synthetic sources. He observed a depressed rate of growth and concluded that the alkylresorcinols were toxic; however, a classic pair-feeding experiment to control for the depressed food intake was not conducted. From Misir and Marquardt's (1978) findings, the toxic factor, defined as causing growth- and feed efficiency-depression, can be separated from the appetite-depressing factor. The aim of our experiments was to use pair-feeding and force-feeding protocols to quantify the degree to which depressed food intake contributes to depressed growth.

MATERIALS AND METHODS

Animal Care and Diet

Sprague-Dawley male weanling rats (Charles River Laboratories, Wilmington, MA) were used to assess growth and food consumption when fed synthetic 5-pentadecylresorcinol (Aldrich Chemical Co., Milwaukee, WI). Weights of each rat were taken twice a week between 8:00 A.M. and 9:00 A.M. All animals were carefully observed.

Each rat was housed in a suspended stainless steel cage. The animal room was maintained at 21–23°C and at 30–50% rh. Lights were regulated by an automatic timer to provide light from 6:00 A.M. to 6:00 P.M. and darkness from 6:00 P.M. to 6:00 A.M. All rats were fed rat chow on the day of arrival. Fresh tap water was provided twice weekly.

Composition of the basal diet is shown in Table I. The concentration of PDR was 0.13% of the basal diet and multiples thereof. This level was based on that found in whole rye by Verdeal and Lorenz (1977).

Experimental Design

In the first experiment the effects of three levels of added 5-pentadecylresorcinol on food intake and rate of growth of rats were assessed in a pair-feeding experiment. All animals were fed the basal diet ad libitum for one week to allow them to become large enough to withstand meal-feeding (Ozelci et al 1978). Rats were then trained for a week to consume their diets between 9:00 A.M.

TABLE I
Composition of the Basal Diet

Ingredients	Amount (%)
Lactalbumin	20
Sugar	25
Starch	25
Cellulose	5
Beef tallow	9
Corn oil	9
Salt mix[a]	5
Vitamin mix[a]	2

[a] See Fine et al 1981, for composition.

and 5:00 P.M. Seventy rats were divided randomly into seven groups, with 10 rats in each group. The design was as follows: control (basal diet), 0.13, 0.26, or 0.65% PDR, and respective pair-fed controls that were fed the basal diet. Food intake and body weight of the animals were assessed over the next six weeks.

In the second experiment, PDR was force-fed at two levels and the effects of this compound on food intake and rate of growth of rats were assessed in a pair-feeding experiment. Thirty rats were fed the basal diet ad libitum for two weeks to allow the animals to become large enough to withstand the meal- and force-feeding regimens. Beginning with the third week, all rats were fed the basal diet between 9:00 A.M. and 5:00 P.M. In addition, a slurry of diet and water (1:1) was tube-fed between 7:00 A.M. and 9:00 A.M. at the rate of 1 ml/100 g of body weight through infant feeding tubes (no. 10 Bard) by plastic syringes. The dosage of PDR in the slurry was 13 or 65 mg/100 g of body weight and approximated the amount consumed in the first experiment. Three control groups were tube-fed an equivalent amount of basal diet; one group was meal-fed and two groups served as pair-fed controls. Food intake and body weight were assessed for the next five weeks. Liver, lung, intestines, pancreas, kidney, heart, spleen, brain, and adrenal from six rats receiving higher level PDR and three pair-fed controls were submitted to the Department of Veterinary Pathology, Colorado State University for routine histopathological evaluation using hematoxylin and eosin staining procedures.

TABLE II
Effect of 5-Pentadecylresorcinol (PDR) on Food Intake and Body Weights of Meal-fed Rats

Week	Control	PDR 0.13%	PDR 0.26%	PDR 0.65%
	Average Daily Food Intake (g)[a]			
4	9.3 ± 1.65[b]	8.2 ± 0.44	7.6 ± 0.63	6.2 ± 0.75
6	12.4 ± 1.06	7.5 ± 0.81	7.8 ± 0.73	7.5 ± 0.71
8	13.0 ± 1.08	7.9 ± 0.60	8.5 ± 1.10	7.3 ± 0.98
	Average Body Weight (g)[a]			
4	95 ± 11.21[c]	92 ± 7.20	87 ± 7.18	79 ± 10.21
6	161 ± 12.02	123[d] ± 10.10	121 ± 9.82	116[d] ± 9.35
8	218 ± 12.56	147[d] ± 10.51	151[d] ± 14.69	142[d] ± 12.24
	Average Body Weight of Pair-fed Control Groups (g)			
4	···	93 ± 8.50[c]	85 ± 5.42	84 ± 11.25
6	···	132 ± 11.73	123 ± 10.97	124 ± 14.43
8	···	168 ± 14.79	165 ± 16.78	156 ± 11.29

[a] One-way analyses of variance was $P < 0.01$ for all observations.
[b] Mean ± SE ($N = 9$ or 10).
[c] Mean ± SD ($N = 9$ or 10).
[d] Significantly ($P < 0.05$) different from pair-fed control by paired t-test.

TABLE III
Effect of Force-Feeding 5-Pentadecylresorcinol (PDR) to Meal-fed Rats

Week	Control	13 mg PDR (per 100 g of body weight)	65 mg PDR (per 100 g of body weight)
	Average Food Intake (g/day)[a]		
3	9.6 ± 1.05[b]	8.9 ± 0.88	7.6 ± 1.14
5	13.0 ± 0.80	12.4 ± 0.57	10.3 ± 1.06
7	12.9 ±0.81	13.0 ± 0.78	10.2 ± 1.00
	Average Body Weight (g)[a]		
3	111 ± 8.79[c]	108 ± 9.75	100 ± 15.56
5	182 ± 16.88	183[d] ± 15.47	156 ± 16.39
7	247 ± 24.49	253[d] ± 12.73	202 ± 24.36
	Average Body Weight of Pair-fed Control Groups (g)		
3	···	104 ± 6.09[c]	102 ± 14.58
5	···	161 ± 8.64	155 ± 12.69
7	···	224 ± 15.20	207 ± 18.28

[a] One-way analysis of variance was $P < 0.05$ for all observations except body weight at week 3.
[b] Mean ± SE ($N = 6$).
[c] Mean ± SD ($N = 6$).
[d] Significantly ($P < 0.05$) different from pair-fed control by paired t-test.

Statistical Analyses

The effects of PDR were tested statistically by two methods using a computerized software package (Hewlett-Packard, Loveland, CO). All treatment groups were compared to the control by one-way analyses of variance. A second comparison was made against the pair-fed control by a paired t-test.

RESULTS

The effect of PDR on food intakes and body weights of meal-fed rats in the first experiment is shown for weeks 4, 6, and 8 in Table II. The feeding of PDR was started at the beginning of week 3, and a depression in food intake and body weight was apparent ($P < 0.01$) at the end of week 4. There was no dose response associated with this depression. The body weights of the rats consuming PDR did not become statistically different ($P < 0.05$) from their pair-fed controls until week 6 or 8. One can estimate from these results that approximately 70% of the growth depression can be attributed to decreased food intake, whereas 30% is due to a toxic effect of PDR.

The results of the second experiment in which tube-feeding was utilized to eliminate any possible unpalatability of PDR are reported in Table III. Force-feeding PDR depressed ($P < 0.05$) food intake during the first week of administration (ie, week 3), but body weights were not decreased. Food intake continued to be depressed by the higher PDR dosage and resulted in 16% depression ($P < 0.05$) of body weights of the rats. The body weights of their pair-fed controls were not significantly different; thus, one can conclude that the depressed growth due to force-feeding PDR is due solely to depressed food intake. The pair-fed controls for the lower dose PDR-treated rats grew significantly less ($P < 0.05$). This could possibly be explained by the observation that they did not consume all the diet offered during the 8-hr meal. This does not weaken the above conclusion. No indication of abnormal organs were found histopathologically, except for the usual chronic respiratory disease found in our colony and one hepatic mineralized granuloma.

CONCLUSIONS

The observed decrease in food intake independent of taste as a result of alkylresorcinol consumption correlates with and extends the findings reported by Wieringa (1967). Almost all of the depression of growth observed in our experiments was the result of a depression in food intake. Evidence from these experiments indicate that the chemical does exert some toxic effect which decreases food intake without the consideration of palatability.

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