Growth-Promoting Potential and Toxicity of Spermidine, a Polyamine and Biogenic Amine Found in Foods and Feedstuffs

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Experiments were conducted to determine the relative growth-promoting potential and toxicity of dietary spermidine, a biogenic amine and polyamine. Week-old chicks were fed purified diets containing 0.0, 0.2, 0.4, 0.6, 0.8, or 1.0% supplemental spermidine for 2 weeks. As little as 0.4% supplemental spermidine depressed growth and hepatic ornithine decarboxylase activity, while hepatic concentrations of putrescine, spermidine, and N^1-acetylspermidine increased. In a second experiment, 0.00, 0.05, 0.10, 0.20, and 0.60% supplemental spermidine were fed. Low levels of supplemental spermidine tended to increase relative weights of the duodenum and pancreas. The temporal response to 0.00, 0.05, and 0.60% supplemental spermidine was determined in a third experiment when measurements were taken following 1, 2, 4, and 8 days of feeding. Chicks fed diets containing 0.05% supplemental spermidine had increased growth after only 1 day of feeding. Enlargement of the duodenum and pancreas was subsequently seen, although these changes became less obvious with time. It was concluded that the toxicity of polyamines increases with molecular weight and charge and, although some growth promotion is possible, the biogenic amine content of suspect feedstuffs should be determined before feeding with caution.

Keywords: *Spermidine; polyamine; growth; toxicity*

INTRODUCTION

The biogenic amines are a group of biologically active compounds synthesized from amino acids and are commonly found in foods and animal feeds. Food-borne biogenic amines are considered to be potential toxins and are often produced by spoilage microorganisms (Eggum et al., 1989). Included in the biogenic amines are the mammalian polyamines: putrescine, spermidine, and spermine (Figure 1). The polyamines are essential for cell growth and have been correlated with many anabolic processes including synthesis of DNA, RNA, and protein (Seiler, 1992). Bardocz et al. (1993) have recently suggested that the consumption of foods rich in polyamines may promote growth and health.

The feeding of 0.2% putrescine, the least cationic of the polyamines, has been shown to promote the growth of chicks fed purified diets, but 0.8% and higher levels proved to be toxic (Smith, 1990). Dietary spermine, the most cationic of the polyamines, has been shown to be much more toxic than putrescine, although growth-promoting potential was seen at very low levels (Sousadias and Smith, 1995). In light of these observations, the growth-promoting potential and relative toxicity of dietary spermidine, the mammalian polyamine intermediate in molecular weight and charge, were determined.

MATERIALS AND METHODS

Experimental Animals and Diets. Leghorn cockerel chicks, approximately 1 week old (Shaver Poultry Breeding Farms, Cambridge, ON), housed in thermostatically controlled, electrically heated cages with raised wire floors were used in all experiments (initial body weight approximately 75 g).

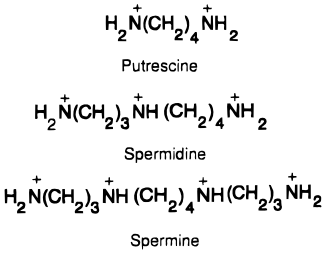

Figure 1. Chemical structures of the mammalian polyamines.

Lighting was continuous, and feed and water were supplied ad libitum. Purified crystalline amino acid diets (Calvert et al., 1982) were fed for 2 weeks (experiments 1 and 2), during which time growth and feed consumption were measured (all experiments). Spermidine (Sigma Chemical Co., St. Louis, MO) was added to diets at the expense of cellulose. In experiment 1, a total of 96 chicks were fed diets containing 0.0, 0.2, 0.4, 0.6, 0.8, or 1.0% supplemental spermidine with four birds per pen and four pens per diet. Liver and breast muscle samples were taken immediately after killing, frozen in liquid nitrogen, and stored at −80 °C until analyzed for ornithine decarboxylase (ODC, liver), *S*-adenosylmethionine decarboxylase (AdoMetDC, liver), and polyamines and metabolites (liver and muscle). In the second experiment, a total of 120 chicks were fed diets containing 0.00, 0.05, 0.10, 0.15, 0.20, or 0.60% supplemental spermidine (five birds per pen, four pens per diet). At the conclusion of the study, all animals were killed, and livers, kidneys, a sample of breast muscle, duodenum (intestinal tissue distal to the pylorus and surrounding the pancreas), and pancreas were excised, weighed, frozen in liquid nitrogen, and stored at −80 °C until analyzed for ODC and AdoMetDC. In experiment 3, the temporal effects of supplementary dietary spermidine were determined using a total of 240 birds with spermidine supplements made at 0.00, 0.05, and 0.60% of the diet. Sixty birds (four pens of five birds per diet) were killed after 1, 2, 4, and 8 days of feeding supplemental spermidine. The same tissues were removed and weighed as for experiment 2 and analyzed for activities of ODC and AdoMetDC.

Enzyme Assays. Tissue activities of ODC (EC 4.2.2.17) and AdoMetDC (EC 4.1.1.50) were measured by quantification of the release of $^{14}CO_2$ from [1-^{14}C]ornithine and [1-^{14}C]-*S*-

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Table 1. Effect of Supplemental Dietary Spermidine on Chick Growth Parameters and Activities of Hepatic Polyamine Synthetic Enzymes (Experiment 1)

supplemental spermidine (%)	body wt gain[a]	feed consumed[b]	feed efficiency[c]	ODC activity[d]	AdoMetDC activity[d]
0	121.1	854.7	0.58	675	106
0.2	113.2	908.1	0.50	264**	113
0.4	85.6**	712.8*	0.48*	95**	93
0.6	75.4**	653.2**	0.47*	444*	102
0.8	66.1**	568.2**	0.47*	234**	92
1.0	63.5**	595.1**	0.43**	129**	91
pooled SE	2.4	21.8	0.01	24	3

[a] g/chick/14 days, $n = 16$. [b] g/pen/14 days, $n = 4$. [c] Weight gain/feed consumed, $n = 4$. [d] Ornithine decarboxylase activity, pmol of $^{14}CO_2$ produced/min/g of protein, $n = 5$. [e] *S*-Adenosylmethionine decarboxylase activity, pmol of ^{14}CO produced/min/g of protein, $n = 5$. *,** Significantly different from controls, $P < 0.05$, 0.01, respectively.

adenosylmethionine, respectively (Eloranta et al., 1976). Values were corrected for soluble protein concentration (Lowry et al., 1951).

Analysis of Polyamines and Metabolites. Liver and breast muscle samples (experiment 1) were analyzed for concentrations of polyamines, their precursor amino acids, and their metabolites as *N*-heptafluorobutyrylisobutyl derivatives (Lindqvist and Mäenpää, 1982) using a modification (Smith, 1990) of the electron capture detection capillary gas−liquid chromatographic technique of Bedford et al. (1987).

Statistical Analyses. Data were analyzed by analysis of variance appropriate for a completely randomized design (Steel and Torrie, 1980). Treatments were compared to controls using orthogonal contrasts (Ostle and Mensing, 1975). Differences between means were considered significant when $P < 0.05$.

RESULTS AND DISCUSSION

The effect of feeding up to 1.0% supplemental spermidine on chick growth and feed consumption is given in Table 1. As little as 0.4% supplemental spermidine depressed chick growth with no indication of growth promotion at any level tested. Feed consumption and feed/weight gain both declined with increasing supplemental spermidine. Hepatic ODC activity fell compared to controls in all birds fed diets containing supplemental spermidine, but AdoMetDC activity was not affected by diet. Hepatic concentrations of putrescine and spermidine tended to increase with spermidine feeding, particularly when 0.6 and 1.0% supplemental spermidine were fed, respectively (Table 2). More obvious increases were observed in hepatic concentrations of N^1-acetylspermidine. Hepatic concentrations of arginine, ornithine, spermine, and N^1-acetylspermine were largely unaffected by diet.

Muscle arginine and putrescine concentrations fell when 0.4% or greater supplemental spermidine was fed. Spermidine concentrations also fell, although this fall was significant only when 1.0% supplemental spermidine was fed. Other polyamines and metabolites in this tissue were not affected by diet.

The effect of feeding low amounts of supplemental spermidine on chick growth and organ development is given in Table 3. Feed consumption was reduced when 0.20 or 0.60% supplemental spermidine was fed, and growth tended to also decline. Birds fed the control diet and the diet containing 0.20% supplemental spermidine grew more rapidly in experiment 1 than in experiment 2. This was likely due to small differences in initial body weights of birds used in the two studies. When the more toxic diet containing 0.60% spermidine was fed, however, no differences were seen in chick growth by comparing the two experiments. Relative and absolute pancreatic and duodenal weights tended to increase with supplemental spermidine but differences were not significant. The activities of polyamine synthetic enyzmes were affected by diet, although the effects varied according to tissue (Table 4). ODC activities fell with increasing supplemental spermidine in duodenum, liver, and kidney, while pancreas and muscle were not affected. AdoMetDC activities were

Table 2. Effect of Supplemental Dietary Spermidine on Hepatic and Muscle Concentrations of Precursor Amino Acids, Polyamines, and Metabolites (Experiment 1)

	supplemental sperimidine (%)						pooled
compound[a]	0	0.2	0.4	0.6	0.8	1.0	SE
				Liver			
arginine	6.66[b]	5.76	8.61	9.10	14.81	8.84	0.46
ornithine	7.31	12.37	2.64	5.23	38.26	1.02	1.21
putrescine	1.04	1.04	1.39	1.43*	0.69	1.34	0.07
spermidine	0.49	0.45	0.65	0.54	0.53	0.84**	0.03
N^1-spd[c]	0.18	0.23	0.57**	0.47	1.19**	0.19	0.04
spermine	0.34	0.47	0.20	0.21	0.35	0.17	0.02
N^1-spm[d]	0.09	0.07	0.12	0.10	0.05*	0.15**	0.01
				Muscle			
arginine	4.89	3.79	1.84**	1.91**	1.99**	1.59**	0.21
ornithine	0.70	0.55	0.48	0.49	0.38	0.27	0.05
putrescine	0.83	0.76	0.50**	0.46**	0.44**	0.45**	0.03
spermidine	0.30	0.35	0.17	0.18	0.21	0.16*	0.02
N^1-spd[c]	0.15	0.11	0.07	0.13	0.09	0.07	0.01
spermine	0.08	0.07	0.09	0.10	0.04	0.07	0.01
N^1-spm[d]	1.23	1.62	2.13	2.22	2.02	1.58	0.14

[a] μmol/g of wet tissue. [b] Values are means, $n = 10$. [c] N^1-Acetylspermidine. [d] N^1-Acetylspermine. *,**Significantly different from controls, $P < 0.05$, 0.01, respectively.

Table 3. Effect of Supplemental Dietary Spermidine on Chick Growth Parameters and Digestive Organ Enlargement (Experiment 2)

supplemental spermidine (%)	body wt gain[a]	feed consumed[b]	feed efficiency[c]	pancreas wt[d]	duodenal wt[d]
0	89.5	1190	0.38	0.30	1.44
0.05	90.0	1158	0.39	0.31	1.49
0.10	86.7	1174	0.37	0.32	1.57
0.15	87.1	1105	0.39	0.33	1.57
0.20	83.3	1079*	0.39	0.34	1.51
0.60	76.4	963**	0.40	0.34	1.59
pooled SE	1.6	14.5	0.02	0.01	0.03

[a] g/chick/14 days, $n = 20$. [b] g/pen/14 days, $n = 4$. [c] Weight gain/feed consumed. [d] Percentage of body weight. *,** Significantly different from controls, $P < 0.05$, 0.01, respectively.

Table 4. Effect of Supplemental Dietary Spermidine on Tissue Activities of Polyamine Synthetic Enzymes (Experiment 2)

	supplemental spermidine (%)						
organ	0	0.05	0.10	0.15	0.20	0.60	SE[a]
duodenum							
ODC[b]	4606	522**	563**	544**	473**	623**	204
AdoMetDC[c]	2028	1221**	1400*	1205**	1147**	1466*	75
pancreas							
ODC	283	349	218	280	206	173	22
AdoMetDC	3488	3350	4070	3477	3122	3708	644
liver							
ODC	645	227**	200**	163**	208**	153**	25
AdoMetDC	1076	1225	1193	1071	1046	1218	31
kidney							
ODC	1978	439**	285**	262**	286**	217**	103
AdoMetDC	1782	1482	1357	1605	1488	1766	112
muscle							
ODC	267	293	309	265	286	259	14
AdoMetDC	869	1010	1221	1183	1153	869	96

[a] Pooled SE. [b] Ornithine decarboxylase activity, pmol of $^{14}CO_2$ produced/min/g of protein, $n = 6$. [c] *S*-Adenosylmethionine decarboxylase activity, pmol of $^{14}CO_2$ produced/min/g of protein, $n = 6$. *,** Significantly different from controls, $P < 0.05$, 0.01, respectively.

Table 5. Temporal Effects of Supplemental Dietary Spermidine on Chick Growth Parameters and Digestive Organ Development (Experiment 3)

supplemental spermidine (%)	body wt gain[a]	feed consumed[b]	feed efficiency[c]	pancreas wt[d]	duodenal wt[d]
		1 Day of Feeding			
0	8.0	72	0.56	0.47	1.31
0.05	9.8*	79	0.62	0.47	1.34
0.60	5.4**	70	0.39*	0.47	1.40
pooled SE	0.4	1.8	0.03	0.01	0.02
		2 Days of Feeding			
0	12.9	134	0.49	0.39	1.47
0.05	13.0	130	0.50	0.40	1.55
0.60	8.7**	119	0.37*	0.43*	1.49
pooled SE	0.3	3.2	0.01	0.01	0.02
		4 Days of Feeding			
0	25.6	266	0.48	0.35	1.33
0.05	25.7	281	0.47	0.36	1.37
0.60	22.1	247	0.45	0.40**	1.59**
pooled SE	0.7	10.0	0.02	0.01	0.03
		8 Days of Feeding			
0	56.6	644	0.44	0.34	1.46
0.05	55.6	602	0.46	0.32	1.39
0.60	52.2	577	0.45	0.33	1.49
pooled SE	1.4	11.8	0.01	0.01	0.03

[a] g/chick, $n = 20$. [b] g/pen, $n = 4$. [c] Weight gain/feed consumed. [d] Percentage of body weight. *,** Significantly different from controls, $P < 0.05, 0.01$, respectively.

Table 6. Temporal Effects of Supplemental Dietary Spermidine on Tissue Ornithine Decarboxylase Activities (Experiment 3)

	ODC activity[a]			
supplemental spermidine (%)	liver	kidney	pancreas	duodenum
	1 Day of Feeding			
0	1107	3787	242	23160
0.05	355*	1396	324	1047**
0.60	90**	349**	238	727**
pooled SE	140	490	33	2901
	2 Days of Feeding			
0	1938	2708	221	10128
0.05	313**	864**	226	400**
0.60	23**	201**	142	522**
pooled SE	242	251	33	832
	4 Days of Feeding			
0	727	1937	314	6807
0.05	242**	933*	297	1094**
0.60	212**	308**	202	840**
pooled SE	67	142	27	322
	8 Days of Feeding			
0	394	2178	325	2712
0.05	299	572**	264	487**
0.60	193	267**	250	426**
pooled SE	51	108	19	258

[a] Ornithine decarboxylase activity, pmol of $^{14}CO_2$ produced/min/g of protein, $n = 6$. *,** Significantly different from controls, $P < 0.05, 0.01$, respectively.

Table 7. Temporal Effects of Supplemental Dietary Spermidine on Tissue *S*-Adenosylmethionine Decarboxylase Activities (Experiment 3)

	AdoMetDC activity[a]			
supplemental spermidine (%)	liver	kidney	pancreas	duodenum
	1 Day of Feeding			
0	1481	2032	5064	3775
0.05	1542	1688	3914	2189**
0.60	653**	1339	2781**	2249**
pooled SE	62	112	256	122
	2 Days of Feeding			
0	1438	1844	4554	2914
0.05	1250	1409	3772	1898**
0.60	555**	1281	2663**	2120*
pooled SE	56	107	185	101
	4 Days of Feeding			
0	1318	1684	3206	2906
0.05	1079	1510	3535	2280*
0.60	948	1668	3058	1980**
pooled SE	275	117	219	100
	8 Days of Feeding			
0	1029	2029	3464	205
0.05	940	1326	3889	148
0.60	977	1739	2775	140
pooled SE	36	203	221	12

[a] *S*-Adenosylmethionine decarboxylase activity, pmol of $^{14}CO_2$ produced/min/g of protein, $n = 6$. *,** Significantly different from controls, $P < 0.05, 0.01$, respectively.

less affected by diet but did decline in the duodenum when supplemental spermidine was fed.

The temporal effect of supplemental dietary spermidine on chick growth and organ development is given in Table 5. After 1 day of feeding, but not subsequently, chicks fed 0.05% supplemental spermidine grew more than controls. The feeding of 0.60% supplemental spermidine proved to be toxic and reduced both growth and feed efficiency. This toxicity persisted after 2 days of feeding, after which time birds fed the highest level of supplemental spermidine also developed enlarged pancreases. Birds fed this diet continued to exhibit pancreatic enlargement after 4 days of feeding but not after 8 days. Duodenal enlargement was seen after 4 days of feeding, while growth parameters only tended to be depressed. Diet had no effect on growth or organ enlargement after 8 days of feeding.

Liver, kidney, and duodenal ODC activities fell when as little as 0.05% supplemental spermidine was fed, while ODC activities in pancreas were not affected by diet (Table 6). Differences tended to decrease with increasing duration of feeding. Tissue AdoMetDC activities were less affected by diet (Table 7). Activities in liver, pancreas, and duodenum initially fell with supplemental spermidine, but there was no effect of diet after 8 days of feeding.

It was observed that excesses of dietary spermidine are intermediate in toxicity between putrescine and spermine. Growth was depressed when 0.4% supplemental spermidine was fed. Putrescine has been shown to be toxic to chicks when added to a purified diet at 0.8% (Smith, 1990), while spermine proved to be toxic when only 0.2% was fed (Sousadias and Smith, 1995). Toxicity of exogenous polyamines to chicks tends to increase, therefore, with increasing molecular weight and increasing cationic charge.

The rate-limiting steps in polyamine synthesis are reactions catalyzed by ODC, which regulates synthesis of putrescine from ornithine, and by AdoMetDC, which provides substrate for synthesis of spermidine and spermine (Seiler, 1992). The activities of both ODC and AdoMetDC are highly regulated, and both enzymes are subject to feedback inhibition from reaction products (Holm et al., 1989; Persson et al., 1989). The decrease in hepatic ODC activity in the first experiment was obvious at even the lowest levels of supplemental spermidine feeding. This could not be explained by an accumulation of putrescine causing enzyme inhibition since putrescine concentrations increased only when higher levels of spermidine were fed. Hepatic spermidine concentrations rose only slowly with supplemental spermidine feeding, and this would seem to be because spermidine was being metabolized to N^1-acetylspermidine to increase water solubility and promote excretion (Seiler, 1991). Acetylated metabolites also tended to accumulate in liver when excesses of spermine were fed, and it was suggested that the energetic costs of in-

creased polyamine metabolism might contribute to spermine toxicity (Sousadias and Smith, 1995). Spermidine accumulation was not adequate to inhibit hepatic AdoMetDC activity.

Concentrations of polyamines and metabolites were also determined in muscle since this peripheral tissue might be more influenced by overall organismal growth than the metabolically more active liver. The decline in muscle putrescine and spermidine concentrations as increasingly toxic levels of spermidine were being fed indicates that supplemental dietary spermidine was metabolized and excreted before reaching peripheral tissues such as muscle. Any growth-promoting effect of dietary spermidine, therefore, would unlikely be due to a direct effect on target tissues. Such an effect would be more likely indirect and due to enhanced nutrient uptake from the intestinal tract, as has been indicated in studies of the effect of dietary putrescine in preruminant calves (Grant et al., 1989) and neonatal pigs (Grant et al., 1990).

The second experiment was undertaken to determine if small amounts of supplemental spermidine could promote growth as previously seen with the feeding of putrescine (Smith, 1990) and, to a much lesser extent, with spermine (Sousadias and Smith, 1995). Although growth was not affected by diet, there was a trend toward increased pancreatic and duodenal weights. Duodenal ODC activity was inhibited by even the lowest level of supplemental spermidine, indicating that this tissue is particularly sensitive to flooding doses of exogenous spermidine. The short half-life of ODC results in very rapid responses of enzyme activities to external stimuli, and the experimental design of the first two experiments would not allow rapid responses to diet to be determined. The third experiment was designed, therefore, to monitor the adaptation to supplemental dietary spermidine over time. Under these conditions, it was possible to observe growth promotion with the feeding of small amounts of supplemental spermidine, although this effect did not persist beyond the first day. The growth effect preceded enlargement of the duodenum and pancreas, indicating that supplemental dietary spermidine may have been influencing digestive function.

Duodenal ODC activities were observed to decline over time in birds fed the control diet, perhaps indicating that intestinal cell growth and division are most rapid in the neonate. The large inhibition of duodenal ODC and AdoMetDC activities when even 0.05% supplemental spermidine was fed would indicate that any increase in intestinal growth and nutrient absorptive capacity would not be due to endogenous polyamine synthesis.

It can be concluded that dietary spermidine has lower toxicity and, when fed at low levels, greater potential to promote growth and alter digestive function than has been reported for spermine (Sousadias and Smith, 1995). The benefits seen, however, were smaller than those reported for putrescine (Smith, 1990). The concentrations of spermidine in foods as reported by Bardocz et al. (1993) are much lower than the supplemental spermidine shown to depress growth in experiment 1. They do approximate, however, the diet containing 0.05% spermidine, which lowered ODC activities in duodenum and liver when fed to chicks in experiments 2 and 3. Feedstuffs are likely to be of lower quality than foods and may include by products that have undergone some degree of spoilage. Larger concentrations of spermidine may, therefore, be expected. The biogenic amine content of foods and feedstuffs should be determined, and those rich in spermidine should be fed with caution.

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