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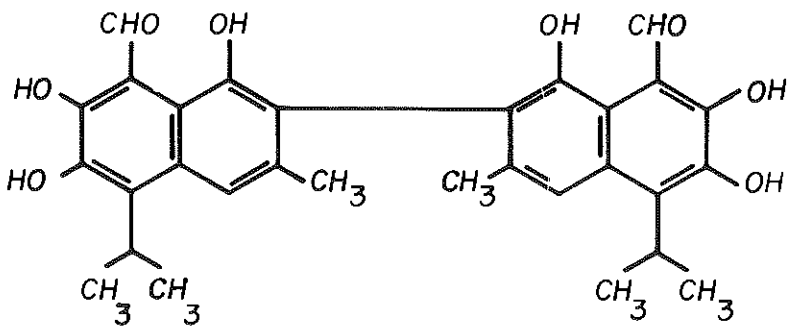
SHORT COMMUNICATION

EFFECTS OF GOSSYPOL ON FOOD INTAKE AND BODY WEIGHT

Muckda Chitcharoenthum
Department of Pharmacology, Khon Kaen University

Gossypol is a compound extracted from cotton seeds. Its structure is composed of many aldehyde and hydroxyl groups which can bind with amino, carbonyl and hydroxyl constituents in cell membrane, amino acids, proteins and enzymes. The compound exerts a variety of biological effects which may be of medical usefulness, for example, as contraceptive and topical spermicide, antiviral agent, anticancer agent and in the treatment of abdominal pain and bleeding in endometriosis.

Chemical structure of Gossypol



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Many investigators have reported the depressant effects of gossypol on food intake (FI) and body weight (BW) during the study of its antifertility effect. Moreover, Sotelo in 1982 and Beaudoin in 1985 pointed out that the effect of this compound on BW was relatively irreversible compared to its antifertility effect. Therefore, it is of interest to study the mechanism of action of gossypol on FI and BW to see whether the effects are useful or adverse. We began the investigation of how gossypol decreases FI and BW in young rats. In the first experiment we studied dose-response of FI and BW to subcutaneously injected gossypol acetic acid (GAA) in Sprague-Dawley rats.

Figure 1 Effects of subcutaneously injected gossypol acetic (GAA) on body of young male rats.

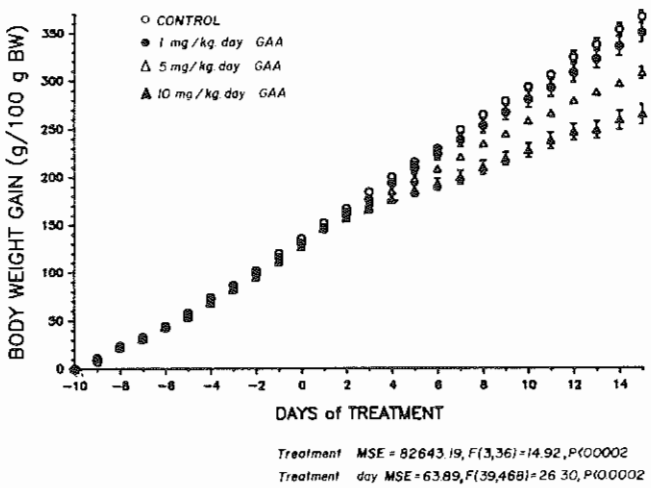


Figure 1 shows percentage of BW-gain from the age of 24 days in 4 groups of 10 rats. During 10 pre-treatment days, there is no significant difference in growth among these groups of rats. Gossypol treatment at 1, 5, or 10 mg daily per 100 g BW began at

day zero, when the rats were 34 days old, and was given for 14 days. During the treatment period, the control group maintained their growth linearly and similar to its pre-treatment rate. On the other hand, the group treated with 1 mg dose of gossypol exhibited a nonsignificant decrease in growth rate by 7% below that of the control; that of the group receiving the 5 mg dose decreased significantly by 20 % and the 10 mg dose produced a significant 40 % decrease in rate. The effect on growth seems to appear within 2 or 4 days of treatment.

Table 1 Effects of gossypol acetic acid (GAA, s.c.) on food intake of young male rats.

Days of treatment	Daily Food Intake (g/100 g BW±S.E)		
	3	6	14
Treatments (6 observations/group)			
Control	14.0±0.24	12.8±0.24[c]	11.0±0.16[c]
GAA			
1 mg/kg.day	13.8±0.16	13.0±0.24[c]	10.7±0.16[c]
5 mg/kg.day	13.5±0.20	11.8±0.33[a]	9.8±0.12[a]
10 mg/kg.day	12.9±0.41	10.5±0.24[b]	8.8±0.29[b]

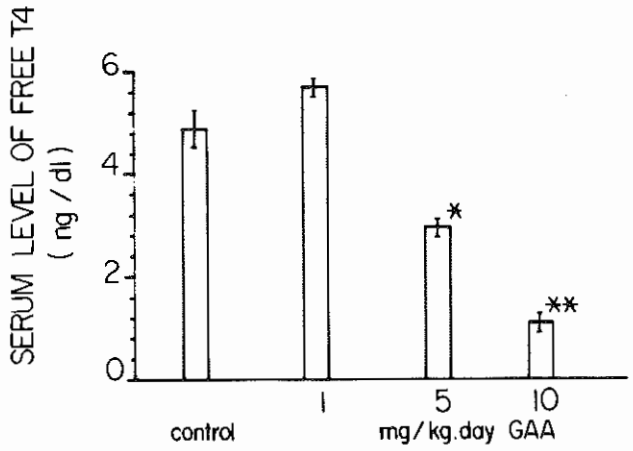
Means are compared using the Student-Newman-Keul test at $p<0.05$

Means with the same letter are not significantly different

Daily food intake of these rats (Table 1) was also depressed by this compound in a dose related manner. The amount of food eaten daily per 100 g BW of these 4 groups of rats was similar before the treatment and up to day 6 of treatment when significant depressant effects of the 5 and 10 mg doses of gossypol appeared. This effect persisted to the end of 14 days of treatment. Rats treated with 5 mg gossypol ate less than the control by 10% and those treated with 10 mg gossypol ate 20% less than controls.

At the end of treatment, trunk blood was collected. Serum samples from 2 rats each were assayed for free T4 and total T3 by radioimmunoassay using commercial kits from Amersham and Serono Diagnostics. Figure 2 shows a dose-dependent effect of

Figure 2 Effects of gossypol acetic acid (GAA) on free thyroxine (fT_4) level. Dunnett's test * $p<0.005$, ** $p<0.01$



gossypol on serum free T4. Gossypol at 1 mg dose has no significant effect on T4 level while the 5 mg dose significantly decreased the hormone level by 30% and at 10 mg dose by 75%. Similarly, the serum level of T3 (Fig 3), an active metabolite of T4, is affected by gossypol.

The hormone levels are decreased 20%, and significantly decreased 35 % and 45 % by 1 mg, 5 and 10 mg dose of gossypol, respectively.

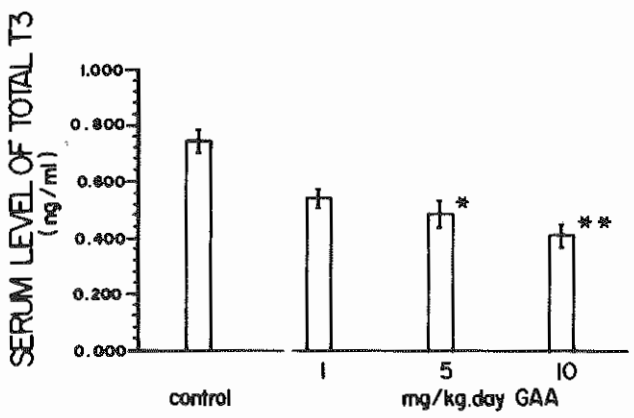
Table 2 shows the result from carcass analysis of 5 rats treated with 10 mg dose of gossypol compared controls. At the end of 14 days of treatment both control and gossypol treated rats have similar BW and wet carcass weight which is the BW of rats

Table 2 Effects of 14-days treatment with gossypol acetic acid (GAA) (10 mg/kg.day,s.c.) on body composition of young male rats.

	# rats	BW (g±se)	wet carcass weight (g±se)	Body Composition (mean±se) water (g/rat)	fat (g/rat)	protein (g/rat)
Treatment						
Control	5	136.2±8.4	102.4±7.3	72.6±4.8	6.0±0.6	8.7±0.7
GAA	5	121.1±8.2	92.2±5.8	68.0±4.6	1.7±0.4	8.8±0.6
t(8)		0.75	1.09	0.69	6.53	0.10
p		>0.20	>0.20	>0.50	<0.001	>0.50

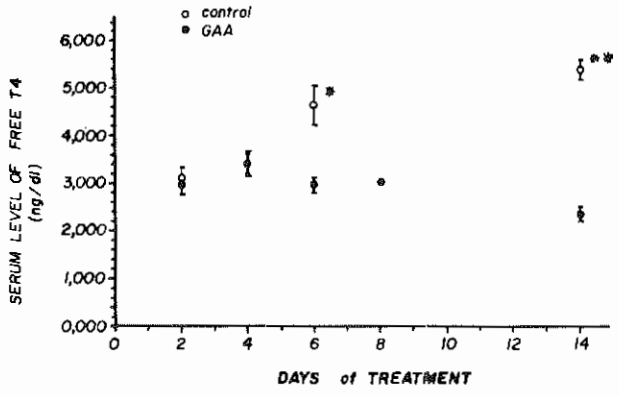
minus head,tail,blood and GI-contents. Fat is the only compartment in gossypol treated rats that is significantly decreased regardless of whether the body composition is expressed in absolute term as show here or relative to BW.

Figure 3 Effects of gossypol acetic acid (GAA) on serum triiodothyronine (T_3) level. Dunnett's test * $p<0.05$, ** $p<0.01$



In the next experiment, we studied the time-course of effect of gossypol on serum free T4 in groups of 5 rats treated for 2, 4, 6, 8 and 14 days.

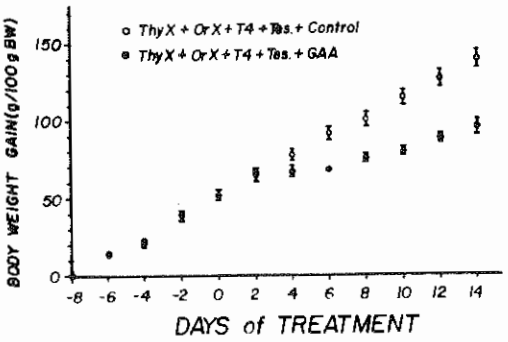
Figure 4 Time course of effects of gossypol acetic acid (GAA) on serum thyroxine (Free T_4) level. t-test * $p<0.03$, ** $p<0.001$)



The results (Fig.4) show that whereas the serum level of T4 increased in control rats from 34 to 48 days of age, gossypol treated rats have a constant level of free T4 after day 2 or 4 of treatment. The time course of the effect on T4 is similar to that on BW. This suggests that the effect of gossypol on BW may be mediated through its effect on T4. We also found that the time course of gossypol's effects on serum testosterone is similar to that on T4. Thus the effects on these two hormones may influence the effect on BW and FI.

The results of experiment designed to assess the participation of thyroid hormone and testosterone in the effects of gossypol on BW using hormone supplementation are shown in figure 5.

Figure 5 effects of gossypol acetic acid (GAA,10 mg/kg.day,s.c.) on body weight of orchidectomized (OrX) and thyroidectomized (ThyX) rats supplemented with testosterone (Tes.5 mg/rat) or thyroxine (T_4,800 ng/100 gBW).



Effects of gossypol on BW were compared with the control treatment in 2 groups of 9 orchidectomized and thyroidectomized young rats receiving testosterone implants and daily subcutaneous injection of T4 for 14 days. The doses used had been found to be optimal for maintaining BW in orchidectomized and thyroidectomized rats. The depressant effect of gossypol on growth rate by 50% is still observable and appears by day 2 or 4 of treatment. Similarly, FI of these rats as shown in table 3 is still significantly depressed by gossypol from day 4 to the end of 12 days of treatment.

These results suggest that the effect of gossypol on FI and BW may be from action sites other than the thyroid and testes.

Table 4 shows results from carcass analysis of these hormone supplemented rats. After 14 days of treatment gossypol treated rats have significantly lower BW and wet carcass weight

Table 3 Effects of gossypol acetic acid (GAA,10 mg/kg. day,s.c.) on food intake of orchidectomized (OrX) and thyroidectomized (ThyX) rats supplemented with testosterone (Tes.) and thyroxine (T_4).

Daily Food Intake (g/100 g BW±S.E)				
Days of treatment		2	4	12
Treatments	#rats			
ThyX+OrX+T4+Tes.				
+control	9	15.2±0.2	15.4±0.7	12.8±0.5
+GAA	8	14.4±0.4	11.8±0.7	10.8±0.3
t(14)		1.79	3.60	3.43
p		>0.2	<0.005	<0.005

than the controls. Although absolute weight of water, fat and protein of gossypol treated carcass are significantly lower than the controls, only fat content is significantly lower than the

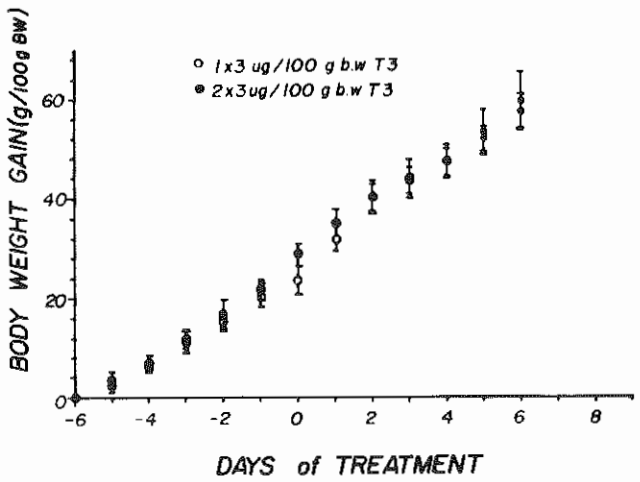
Table 4 Effects of gossypol acetic acid (GAA) (10 mg/kg.day) on body composition of the thyroidectomized (ThyX) and orchidectomized (OrX) rats supplemented with testosterone (Tes.) and thyroxine (T_4).

	# rats	BW (g±se)	wet carcass weight (g±se)	Body Composition (mean±se) water	fat (g/rat)	protein
Treatment						
ThyX+OrX+T4+Tes.						
+ Control	8	155.7±5.3	118.2±3.6	80.4±2.7	7.6±0.5	11.1±0.4
+ GAA	6	132.6±4.5	95.3±4.3	68.8±3.0	2.9±0.5	9.3±0.6
t(11)		8.76	4.08	2.87	6.65	2.50
p		<0.0005	<0.005	<0.05	<0.0005	<0.05

controls when body composition is expressed relative to BW. These results suggest that gossypol may interfere with fat metabolism to affect FI and BW.

In the last experiment we examined gossypol's effects in rats in which almost all carcass fat had been eliminated. Two groups of 7 young male rats were treated with 3 and 6 mcg of T3 for 7 days before BW was recorded. Growth rates of these two groups of rats during 7 days of gossypol treatment were similar to rates before the treatment (Fig.6)

Figure 6 Effects of gossypol acetic acid on body weight of young rats when body fat has been removed by high dose of triiodothyronine (T_3).



Thus elimination of body fat can prevent the effects of gossypol on BW. Our observations also tentatively suggest that the depression of FI is prevented as well. In conclusion, gossypol may affect both BW and FI through actions on fat metabolism.