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STUDIES ON THE METABOLISM OF GLYCOSAMINOGLYCANS UNDER THE INFLUENCE OF NEW HERBAL ANTI-INFLAMMATORY AGENTS

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Abstract—The *in vivo* effect of an herbal based, non-steroidal anti-inflammatory product, salai guggal, prepared from the gum resin exudate of *Boswellia serrata* and its active principle "boswellic acids" on glycosaminoglycan metabolism has been studied in male albino rats. The biosynthesis of sulfated glycosaminoglycans, as evaluated by the uptake of [^{35}S]sulfate, and the content of glycosaminoglycans were measured in specimens of skin, liver, kidney and spleen. Statistical analysis of the data obtained with respect to the boswellic acids and salai guggal were compared with those of ketoprofen. A significant reduction in glycosaminoglycan biosynthesis was observed in rats treated with all of the drugs. Glycosaminoglycan content was found to be decreased in the ketoprofen-treated group, whereas that of the boswellic acids or salai guggal treated groups remained unaltered. The catabolism of glycosaminoglycans was followed by estimating the activities of lysosomal glycohydrolases, namely β-glucuronidase, β-*N*-acetyglucosaminidase, cathepsin B_1, cathepsin B_2 and cathepsin D, in tissues and by estimating the urinary excretion and hexosamine and uronic acid. The degradation of glycosaminoglycans was found to be reduced markedly in all drug-treated animals as compared to controls. The potential significance of boswellic acids and salai guggal was discussed in the light of changes in the metabolism of glycosaminoglycans.

In an attempt to discover herbal-based anti-inflammatory products having beneficial effects on rheumatic diseases without any adverse and undesirable side-effects, the gum resin exudate of *Boswellia serrata*, known as salai guggal, which is used in the Ayurvedic system of medicine for the treatment of rheumatism, obesity and various other disorders [1], has been investigated thoroughly. Singh and Atal [2] demonstrated that salai guggal is very effective against inflammatory disorders, particularly rheumatoid arthritis. The beneficial effects of this new therapeutic agent on glycohydrolases and lysosomal stability in the experimental model of rheumatoid arthritis have been reported [3, 4]. Attention has now been focused towards the effect of anti-inflammatory agents on the formation of carbon chain and sulfonation, which are involved in glycosaminoglycan biosynthesis [5, 6]. However, the concept is not very clear about the beneficial action of salai guggal on glycosaminoglycan metabolism in normal and inflammatory conditions. Since salai guggal has been proven [2] to be non-toxic, it was felt worthwhile to investigate the *in vivo* effects of this new drug on the metabolism of glycosaminoglycans in male albino rats.

The chemical composition of salai guggal has been reported [7] to contain four pentacyclic triterpene acids (boswellic acids) as the main constituents. Therefore, it was also thought essential to study the beneficial effects of purified boswellic acids.

In 1979, Kubota *et al.* [8] demonstrated that the relative potency in the anti-inflammatory action of ketoprofen (benzoyl hydrotropic acid) is greater than that of indomethacin, phenylbutazone or acetylsalicylic acid. In the present investigation, therefore, ketoprofen was used as the standard, and the results obtained with respect to boswellic acids and salai guggal were compared with those of ketoprofen.

MATERIALS AND METHODS

Male albino rats of the Wistar strain, aged 6–8 weeks, having an average body weight of 80 g, were housed in solid polypropylene cages and were fed commercial rat feed (Hindustan Lever, Bombay) and water *ad lib*. The animals were divided into the control group (C), the boswellic acids group (BA), the salai guggal group (SG) and the ketoprofen group (KP). Animals in the BA and SG groups were given orally boswellic acids and salai guggal at a concentration of 10 mg each per day per 100 g body weight. Ketoprofen was administered orally at a concentration of 0.4 mg per day per 100 g body weight to the animals in the KP group. Each group was further divided into three subgroups. One subgroup was used for determining the radioactive [^{35}S]sulfate incorporation, another for the content of glycosaminoglycans, and a third group for the determination of glycohydrolases. Body weights were recorded at weekly intervals throughout the experimental period of 35 days. At the end of every week, urine samples were collected in toluene over a period of 24 hr following gastric loading with 3 ml of saline per 100 g body weight while keeping the animals in individual metabolic cages. One subgroup from each group received intraperitonially 50 μCi of

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$Na_2{}^{35}CO_4$ (BARC, Bombay) per 100 g body weight. All the animals were killed by decapitation 24 hr after the incorporation of radioactive sulfate. Blood samples were collected, and serum was separated by centrifugation.

Measurement of radioactive [^{35}S]*sulfate uptake into the glycosaminoglycans.* Since [^{35}S]sulfate is incorporated into sulfated glycosaminoglycans, its rate of incorporation into tissue has been adopted as a method to study the synthesis of glycosaminoglycans. Labeled tissues were dried, defatted and analyzed for [^{35}S]sulfate incorporation, according to the method of Mahin and Lofberg [9]. The radioactivity was determined in an automated liquid scintillation system (LSS 34, ECIL, Hyderabad). Corrections were made for background and decay. The [^{35}S]-activity was calculated as cpm/100 mg dry defatted tissue sample.

Determination of glycosaminoglycan fraction. Skin, liver, kidney and spleen were removed immediately after the animals were killed. The skins were depilated, fleshed, washed, and pooled together for analysis. All the samples were cut into small pieces and defatted separately at 60° with a methanol–ether mixture (3:1, v/v) and then with a chloroform–methanol mixture (1:1, v/v) using each mixture twice for 2 hr. The defatted tissues obtained from liver, kidney and spleen were treated with 0.5 M NaOH at 4° and kept overnight for neutralization [10]. Proteolytic digestion of all tissue samples was carried out and then analyzed for non-sulfated, mono-sulfated and highly sulfated glycosaminoglycan fractions according to the method of Mier and Wood [11].

Assay of glycohydrolases. Immediately after sacrifice, liver, kidney and spleen were taken from each animal and pooled separately. The pooled tissue sample was homogenized at 4° with 0.25 M sucrose. A portion of the homogenized tissue preparation was used for the determination of the total activity of glycohydrolases [12]. Another portion of the homogenate was centrifuged at 16,000 *g* for 30 min in a refrigerated centrifuge, and the supernatant fraction was analyzed for the free activity of glycohydrolases. All the determinations were made in the presence of Triton X-100 (in a final concentration of 0.2%, v/v). The activity of β-glucuronidase was measured according to the procedure of Kawai and Anno [13] using *p*-nitrophenyl-β-glucuronide as the substrate. β-*N*-Acetylglucosaminidase activity was estimated by the procedure of Moore and Morris [14] using *p*-nitrophenyl-*N*-acetyl-β-glucosaminide as the substrate. The cathepsin B_1 activity was determined by the method of Barrett [15] using *N*-α-benzyl-D-L-arginine-*p*-nitroanilide-HCl (BAPNA) as the substrate. The activity of cathepsin B_2 was assayed according to the method of Otto and Riesenkonig [16] using 4% hemoglobin as the substrate. The cathepsin D activity was estimated by the procedure of Sapolsky *et al.* [17] using 1.5% denatured hemoglobin as the substrate.

Determination of protein content. The concentration of protein in the sample was estimated according to the method of Lowry *et al.* [18] using crystalline bovine serum albumin as the reference standard.

Determination of urinary hexosamine and uronic acid. Urinary hexosamine was estimated according to the method of Elson and Moran [19] as adapted by Rimington [20]. Urinary glycosaminoglycan was isolated and estimated as uronic acid content by the method of Ritchie *et al.* [21]. Creatinine was estimated by the method of Jaffe's reaction [22].

Statistical analysis. Statistical significance was calculated using Student's *t*-test. A P value of less than 0.05 was considered to be statistically significant.

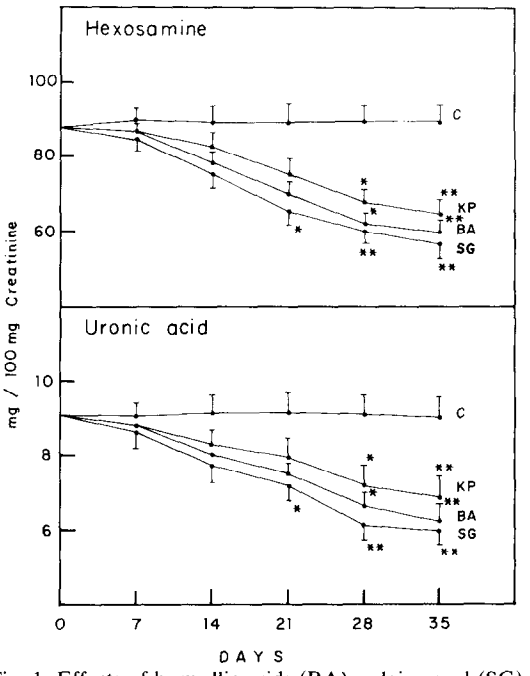

Fig. 1. Effects of boswellic acids (BA), salai guggal (SG), and ketoprofen (KP) on the excretion of hexosamine and uronic acid in urine. Values are means ± SD of six determinations. Each determination was made on a sample pooled from four rats. Key: (*)P < 0.05 and (**)P < 0.01, BA, KP and SG values are compared to C values.

RESULTS

The growth rate of the animals treated with the anti-arthritic drugs was found to be similar to that of controls. The mean body weight of the C, BA, KP and SG groups progressively increased and reached 171, 176, 179 and 186 g, respectively, after 35 days. The urinary excretion of hexosamine and uronic acid in all drug-treated groups was found to be reduced significantly in the later period of the experiment (Fig. 1).

The results obtained with respect to the effects of the drugs on [^{35}S]sulfate uptake after incorporation of radioactive [^{35}S]sulfate in skin, liver, kidney and spleen are presented in Table 1. The [^{35}S]sulfate uptake was reduced significantly in all tissues of drug-treated animals compared to that of controls. No significant alteration was observed in the content of glycosaminoglycan fractions such as non-sulfated, mono-sulfated and highly sulfated glycosaminoglycans in skin, liver, kidney and spleen derived from the BA- or SG-treated group. On the other hand, the KP-treated group was found to show a significant

Table 1. *In vivo* effects of BA, KP and SG on the total uptake of [^{35}S]sulfate and on glycosaminoglycans in various tissues of male albino rats

Tissue	Group	[^{35}S]-Uptake (cpm/100 mg dry wt)	Glycosaminoglycan level (μg glucuronic acid/100 mg dry defatted tissue)			
			Non-sulfated	Mono-sulfated	Highly sulfated	Total
Skin	C	12,800 ± 764	56.64 ± 4.96	60.75 ± 4.89	24.68 ± 2.15	142.07 ± 9.80
	BA	9920 ± 536*	58.35 ± 4.85	63.24 ± 5.08	25.83 ± 2.54	147.42 ± 10.12
	KP	8274 ± 475*	51.86 ± 4.24	52.28 ± 4.63†	20.55 ± 2.08†	124.69 ± 8.75†
	SG	10,190 ± 542*	60.34 ± 5.02	65.25 ± 5.26	26.26 ± 2.62	151.85 ± 11.28
Liver	C	6985 ± 398	28.95 ± 2.84	51.86 ± 4.39	23.43 ± 2.12	104.24 ± 8.04
	BA	5372 ± 282*	27.86 ± 2.48	54.72 ± 4.42	24.86 ± 2.14	107.44 ± 8.16
	KP	4065 ± 245*	24.54 ± 1.85†	45.25 ± 3.92†	19.94 ± 1.93†	89.73 ± 6.40†
	SG	5482 ± 296*	30.82 ± 2.82	55.63 ± 4.65	25.66 ± 2.18	112.11 ± 8.25
Kidney	C	18,760 ± 1095	48.75 ± 4.16	66.88 ± 5.62	36.85 ± 3.24	152.48 ± 10.24
	BA	14,350 ± 925*	51.82 ± 4.24	64.84 ± 5.28	34.89 ± 2.92	151.55 ± 11.35
	KP	12,930 ± 886*	40.32 ± 3.95†	58.62 ± 4.84†	30.56 ± 2.68†	129.50 ± 8.90†
	SG	14,730 ± 938*	55.36 ± 4.76	67.35 ± 5.48	37.34 ± 3.35	160.05 ± 11.95
Spleen	C	16,480 ± 925	44.85 ± 3.88	56.84 ± 4.85	33.75 ± 2.96	135.44 ± 9.52
	BA	12,370 ± 782*	48.72 ± 4.05	55.75 ± 4.62	34.56 ± 3.02	139.03 ± 9.75
	KP	10,960 ± 698*	38.28 ± 3.36†	49.63 ± 3.92†	27.82 ± 2.52†	115.73 ± 8.35*
	SG	12,660 ± 875*	49.24 ± 4.83	60.52 ± 5.04	36.54 ± 3.28	146.30 ± 11.16

Values are means ± SD of six samples. Each determination was made on a sampled pooled from four rats. Abbreviations: C, control group; BA, boswellic acid treated group; KP, ketoprofen treated group; and SG, salai guggal treated group. BA, KP and SG values are compared to C values.

* Significantly different from control group, $P < 0.01$.

† Significantly different from control group, $P < 0.05$.

Table 2. *In vivo* effects of BA, KP and SG on serum glycohydrolases

Group	β-Glucuronidase (μmol *p*-nitrophenol liberated/hr/100 mg protein)	β-*N*-Acetylglucosaminidase (μmol *p*-nitrophenol liberated/hr/100 mg protein)	Cathepsin B_1 (μmol *p*-nitroanilide liberated/hr/100 mg protein)	Cathepsin B_2 (μmol tyrosine liberated/hr/100 mg protein)	Cathepsin D (μmol tyrosine liberated/hr/100 mg protein)
C	2.96 ± 0.26	3.28 ± 0.24	9.62 ± 0.95	5.85 ± 0.44	6.28 ± 0.53
BA	1.98 ± 0.16*	2.50 ± 0.22*	7.82 ± 0.64†	3.32 ± 0.36*	3.64 ± 0.32*
KP	2.45 ± 0.24†	2.78 ± 0.23†	7.96 ± 0.68†	3.68 ± 0.38*	3.80 ± 0.30*
SG	1.82 ± 0.15*	2.05 ± 0.18*	5.95 ± 0.58*	3.14 ± 0.30*	3.02 ± 0.27*

Values are means ± SD of six determinations. Each determination was made on a sample pooled from four rats. Abbreviations: C, control group; BA, boswellic acid treated group; KP, ketoprofen treated group; and SG, salai guggal treated group. BA, KP and SG values are compared to C values.

* Significantly different from control group, $P < 0.01$.

† Significantly different from control group, $P < 0.05$.

decrease in the content of all sulfated and non-sulfated fractions in all tissues except the non-sulfated glucosaminoglycan fraction in the skin sample. The total content of glycosaminoglycan was found to be unaltered in skin, liver, kidney and spleen of the BA- and SG-treated groups. The KP-treated group, however, showed a significant decrease in the total content of glycosaminoglycan in all tissues.

The activities of serum glycohydrolases, viz. β-glucuronidase, β-*N*-acetylglucosaminidase, and cathepsin B_1, B_2 and D were decreased in rats treated with all of the anti-inflammatory drugs (Table 2). The total activities of glycohydrolases in the specimens of liver, kidney and spleen, however, were not found to be altered significantly in the KP-treated group, whereas significant reduction was observed in the SG-treated group (Table 3). In the BA-treated group, total activities of the glycohydrolases were not altered uniformly. The total activities of β-glucuronidase and cathepsin B_1 were found to be decreased significantly, whereas those of β-*N*-acetylglucosaminidase and cathepsin B_2 and D were not found to be altered in the BA-treated group.

The data in Table 4 represent the free activities of glycohydrolases in the drug-treated groups. The free activities of glycohydrolases, namely β-glucuronidase, β-*N*-acetylglucosaminidase and cathepsin B_1, B_2 and D were found to be decreased significantly in the specimens of liver, kidney and spleen in the BA-, SG- and KP-treated groups.

DISCUSSION

In our preceding studies [3, 4, 23], we showed that arthritic rats administered BA or SG orally at a concentration of 10 mg per 100 g body weight per day display prominent anti-arthritic activity with marked inhibition of secondary lesions developed during the process of adjuvant arthritis. In the present investigation, the *in vivo* effects of BA and SG on the metabolism of glycosaminoglycans, using the same therapeutic levels in male albino rats, were analyzed.

In this study, tissue [^{35}S]sulfate activity was taken as a measure of glycosaminoglycan synthesis 24 hr after the intraperitoneal injection of [^{35}S]sulfate into the experimental animals. The [^{35}S]sulfate activity of the tissue was quantitatively present in the glycosaminoglycans as assessed by the counting label technique. The reduction in [^{35}S]sulfate incorporation by BA or SG indicates the inhibitory action of anti-inflammatory drugs on the biosynthesis of glycosaminoglycans. These observations are in agreement with earlier findings [24, 25] that anti-inflammatory drugs, in general, have been shown to inhibit the synthesis of glycosaminoglycans. Watson [26] showed a similar suppression of [^{35}S]sulfate uptake by oral doses of indomethacin to rabbits. It has been reported [27] that non-steroidal anti-inflammatory drugs affect glycosaminoglycan formation by influencing the adenylate cyclase system. However, several reservations to this interpretation are necessary.

The biosynthesis and sulfonation of the sulfated glycosaminoglycans are assumed to take place intracellularly. The use of radioactive sulfate as an indicator of the synthesis of sulfated glycosaminoglycans presupposes, among other things, that the specific radioactivity, i.e. the activity of radioactive sulfate in relation to the amount of unlabeled inorganic sulfate, is identical at the site where the synthesis of glycosaminoglycans takes place [28, 29]. The specific activities of [^{35}S]sulfate in the present study cannot be evaluated as neither the concentration of extra- and intracellular inorganic sulfate nor the inorganic sulfate pool was known.

The decreased uptake of [^{35}S]sulfate following drug treatment may suggest an increase in the synthesis of low sulfated glycosaminoglycans and not necessarily inhibition of the synthesis. It has been reported [30] that cultures of arterial fibroblasts have a lower degree of sulfonation and a faster turnover with respect to the intracellular pool of sulfated glycosaminoglycans. Low sulfated glycosaminoglycans have been isolated from rabbit aorta [31] and granulation tissue of the rat [32].

Most studies on the effects of non-steroidal anti-inflammatory drugs on glycosaminoglycan metabolism have involved the use of indomethacin and salicylic acid. The preponderance of previously reported *in vitro* studies using cartilage explants or isolated chodrocytes derived from various animal species and humans have shown that both indomethacin and salicylates [33–38] consistently suppress glycosaminoglycan synthesis in a dose-dependent manner. It has been suggested that the effects of these drugs on glycosaminoglycan synthesis

Table 3. *In vivo* effects of BA, KP and SG on total activities of glycohydrolases in liver, kidney and spleen of male albino rats

Tissue	Group	β-glucuronidase (μmol *p*-nitrophenol liberated/hr/100 mg protein)	β-*N*-Acetylglucosaminidase (μmol *p*-nitroanilide liberated/hr/100 mg protein)	Cathepsin B_1	Cathepsin B_2 (μmol tyrosine liberated/hr/100 mg protein)	Cathepsin D
Liver	C	52.95 ± 4.98	120.35 ± 9.90	64.82 ± 5.85	41.28 ± 3.96	35.84 ± 3.30
	BA	46.28 ± 4.25*	108.50 ± 8.65	55.90 ± 5.20*	37.90 ± 3.65	31.50 ± 3.15
	KP	48.60 ± 4.70	116.38 ± 8.92	58.96 ± 5.68	39.56 ± 3.80	33.90 ± 3.36
	SG	41.56 ± 3.95†	102.80 ± 8.38*	53.65 ± 4.96*	35.92 ± 3.08*	29.85 ± 2.68*
Kidney	C	28.56 ± 2.74	146.82 ± 12.98	100.25 ± 8.42	61.32 ± 5.92	46.85 ± 4.60
	BA	23.48 ± 2.20*	135.72 ± 10.85	88.96 ± 7.60*	58.86 ± 5.60	41.94 ± 4.06
	KP	25.34 ± 2.48	137.86 ± 11.24	92.56 ± 8.10	59.38 ± 5.70	43.32 ± 4.25
	SG	22.48 ± 2.15†	124.52 ± 9.26*	79.30 ± 6.95†	50.75 ± 4.90*	38.94 ± 3.60*
Spleen	C	43.72 ± 4.20	82.34 ± 7.45	44.82 ± 4.10	38.45 ± 3.65	25.34 ± 2.12
	BA	37.64 ± 3.65*	75.86 ± 6.33	38.96 ± 2.98*	29.56 ± 2.96†	23.48 ± 1.96
	KP	40.38 ± 3.96	77.95 ± 6.95	40.65 ± 3.84	35.84 ± 3.12	24.36 ± 2.08
	SG	34.22 ± 3.28†	69.52 ± 5.96*	37.96 ± 2.92*	26.56 ± 2.44†	16.58 ± 1.72†

Values are means ± SD of six determinations.

Each determination was made on a sample pooled from four rats. Abbreviations: C, control group; BA, boswellic acid treated group; KP, ketoprofen treated group; and SG, salai guggal treated group. BA, KP and SG values are compared to C values.

* Significantly different from control group, $P < 0.05$.

† Significantly different from control group, $P < 0.01$.

Table 4. *In vivo* effects of BA, KP and SG on free activities of glycohydrolases in liver, kidney and spleen

Tissue	Group	β-Glucuronidase (μmol *p*-nitrophenol liberated/hr/100 mg protein)	β-*N*-Acetylglucosaminidase	Cathepsin B_1 (μmol *p*-nitroanilide liberated/hr/100 mg protein)	Cathepsin B_2 (μmol tyrosine liberated/hr/100 mg protein)	Cathepsin D
Liver	C	17.48 ± 1.84	38.26 ± 3.55	24.46 ± 2.35	21.28 ± 1.98	18.54 ± 1.90
	BA	12.20 ± 1.25*	31.85 ± 3.16*	19.85 ± 1.96†	15.20 ± 1.55†	12.62 ± 1.30†
	KP	13.96 ± 1.45*	32.95 ± 3.28*	20.65 ± 2.08*	17.80 ± 1.76*	14.85 ± 1.65*
	SG	10.16 ± 0.94†	28.82 ± 2.98†	17.98 ± 1.80†	14.35 ± 1.65†	10.65 ± 1.10†
Kidney	C	14.84 ± 1.72	49.12 ± 4.65	37.54 ± 3.86	28.84 ± 2.64	24.53 ± 2.38
	BA	11.75 ± 1.20*	40.56 ± 3.95*	27.20 ± 2.74†	21.85 ± 2.20†	18.62 ± 1.92†
	KP	12.80 ± 1.34*	41.82 ± 4.05*	29.98 ± 3.22*	23.62 ± 2.38*	20.35 ± 2.12*
	SG	9.32 ± 0.90†	35.32 ± 3.60†	25.54 ± 2.58†	20.96 ± 2.10†	17.76 ± 1.85†
Spleen	C	16.26 ± 1.78	35.35 ± 3.48	35.42 ± 3.45	31.92 ± 3.15	19.26 ± 1.96
	BA	12.92 ± 1.50*	26.28 ± 2.50†	26.30 ± 2.70†	22.85 ± 2.20†	12.35 ± 1.42†
	KP	13.15 ± 1.56*	28.65 ± 2.96*	28.96 ± 2.98*	25.67 ± 2.80*	13.20 ± 1.50†
	SG	10.72 ± 1.20†	24.56 ± 2.35†	24.95 ± 2.58†	20.65 ± 2.05†	11.92 ± 1.20†

Values are means ± SD of six determinations. Each determination was made on a sample pooled from four rats. Abbreviations: C, control group; BA, boswellic acid treated group; KP, ketoprofen treated group; and SG, salai guggal treated group. BA, KP and SG values are compared to C values.

* Significantly different from control group, $P < 0.05$.

† Significantly different from control group, $P < 0.01$.

may be due to an inhibition of enzymes involved in the anabolic pathway of glycosaminoglycans [39, 40].

Our study has shown that the total glysoaminoglycan content in rats treated with BA or SG was not altered (Table 1). The lack of change in the total amount may be explained in different ways. The decreased rate of anabolic process may only involve a smaller fraction (intracellular) of the total pool of sulfated glycosaminoglycans or the diminished synthesis of glycosaminoglycans may be balanced by lower degradation of glycosaminoglycans to reveal these alterations. On the other hand, the KP-treated group showed a significant reduction in [^{35}S]sulfate incorporation evidenced by the diminished level of total glycosaminoglycan content. Hence, it may be stated that the altered change in the content of glycosaminoglycans in the BA- or SG-treated group was due to a decrease in both the synthesis and degradation of glycosaminoglycans. The decreased content of total glycosaminoglycans in the KP-treated group could be explained on the basis that decreased synthesis may have predominated over the decreased catabolism of glycosaminoglycans. Similar results have been observed on glycosaminoglycan synthesis using ibuprofen [6], phenylbutazone [33], Oxyphenbutazone [41], and isoxican [42].

Our studies further demonstrate that the catabolism of glycosaminoglycans in the BA-, SG- and KP-treated groups was found to be decreased significantly as evidenced by a decrease in the activities of the glycohydrolases (Tables 2–4). It is well established that these enzymes are involved in the degradative process of glycosaminoglycans. The decreased urinary excretions of hexosamine and uronic acid also suggest the reduced catabolism of glycosaminoglycans in drug-treated animals (Fig. 1). However, the decreased excretion of urinary hexosamine may represent the metabolism of glycoproteins and other hexosamine-containing compounds as a whole. It is interesting to note that the degradation of both glycosaminoglycans and hexosamine-containing substances was found to be reduced in drug-treated animals. The present study has, therefore, clearly indicated that BA, SG and KP act on the biosynthesis and degradation of glycosaminoglycans.

Glycosaminoglycans play an important role during inflammation and wound healing [43–45]. The inflammatory process includes the formation of new ground substance [46] with an increased rate of synthesis of proteoglycans and cell proliferation [47]. The inhibiting action of BA, SG, or KP on the biosynthesis of glycosaminoglycans may, therefore, indicate the significance of the action of anti-inflammatory agents on connective tissue components.

Based on the results of the present and earlier studies [3, 4, 23], it appears that BA, SG and KP have significant effects on the metabolism of glycosaminoglycans. The results also suggest that these non-steroidal anti-inflammatory agents have these beneficial effects by suppressing the proliferating tissue and preventing the degradation of connective tissue in inflammatory conditions.

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