EFFECT OF L-GLUTAMINE ON ACETYLSALICYLIC ACID-INDUCED GASTRIC LESIONS IN PREGNANT AND NON-PREGNANT RATS

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A previous study from this laboratory indicated that acetylsalicylic acid (ASA) could induce much more severe damage in the stomach of pregnant rats as compared to non-pregnant ones (1). The present authors have confirmed in a series of experiments that L-glutamine is capable of inhibiting ASA-induced gastric lesions in rats (2-5). This study was carried out to determine whether or not L-glutamine also inhibits the enhanced irritable activity of ASA on the gastric mucosa of pregnant rats.

Female Donryu rats, weighing 200-240 g, were used. Mating of rats was done as described previously (1). The rats which were found to contain sperm in their vaginal smear were considered pregnant (Day 0 of pregnancy). Both non-pregnant and pregnant rats (Day 18-20 pregnancy) were deprived of food for 24 hr after which the pylorus was ligated under ether anesthesia. ASA 100 mg/kg suspended in 1% carboxymethylcellulose (CMC) solution was given p.o. to the rats 10 min after pylorus ligation. Seven hr after ASA dosing, the animals were sacrificed and the stomach of each was removed, inflated by injecting 1% formalin solution and immersed in 1% formalin solution for 10 min. The stomach was then incised along the greater curvature and examined for lesions in the glandular portion. The length of each lesion (mm) was measured individually under the dissecting microscope (10X), summed and used as a lesion index. At the time of autopsy, the gastric contents were collected through the esophagus and analyzed for volume and acidity; the acidity was determined by titration of the gastric juice with 0.1 N NaOH to pH 7.0 on the pH meter which is expressed as mEq/L. The concentrations of Na⁺ and K⁺ ions were measured by flamephotometry. The pepsin activity was determined by Anson's method (6) and expressed as mg tyrosine per ml. L-glutamine, suspended in 1% CMC solution, was given p.o. to the rats immediately after pylorus ligation. The control rats were administered 1% CMC solution alone. Student's t-test was employed to determine the statistical significance.

ASA-induced gastric lesions in non-pregnant female rats were markedly inhibited by L-glutamine (p.o.) in a dose of 750 mg/kg (Table I). It was confirmed that ASA induced much more serious damage in the stomach of pregnant rats as compared to non-pregnant rats. In pregnant rats treated with ASA, the volume of gastric juice and Na⁺ ion concentration were significantly higher but the acidity and pepsin activity were lower than those of normal rats. When L-glutamine at 250 or 750 mg/kg was given p.o. to pregnant rats prior to ASA dosing, ASA-induced gastric lesions were dose-dependently inhibited. How-

TABLE 1. Effect of L-glutamine on acetylsalicylic acid (ASA)-induced gastric lesions in pregnant or non-pregnant rats

Group	Treatment	Dose (mg/kg)	No. of rats	ASA lesions		Volume (ml)	Gastric contents			Pepsin (mg/ml)
				Lesion index (mm)	% Inhibition		Acidity	Na ⁺ (mEq/L)	K ⁺	
Non-pregnant rats										
1	Control		14	25.2±5.0		10.5±0.6	66.9±4.4	70.2±2.8	6.7±0.5	21.0±0.8
2	L-glutamine	750	10	2.8±1.4	88.9	10.6±0.6	104.1±3.4	49.9±3.7	5.6±0.6	20.3±0.7
Pregnant rats										
3	Control		10	60.6±9.3		13.4±1.2	53.3±3.4	97.4±6.1	6.8±1.0	15.6±1.4
4	L-glutamine	83.3	10	54.4±6.8	10.2	14.1±0.5	67.7±6.4	88.0±5.5	5.3±0.4	17.4±1.6
5		250	10	31.1±7.4	48.7	13.4±0.9	85.4±5.2	68.1±7.5	5.6±0.6	16.1±1.7
6		750	10	9.5±2.2	84.3	13.3±0.5	100.9±2.8	51.4±3.3	5.2±0.7	13.4±1.1
				1:3 <0.01		1:3 <0.05	1:3 <0.05	1:3 <0.01		1:3 <0.01
P value				1:2 <0.001			1:2 <0.001	1:2 <0.001		
				3:5 <0.001			3:5 <0.001	3:5 <0.01		
				3:6 <0.001			3:6 <0.001	3:6 <0.001		

All values represent mean±S.E.

ever, the dose of L-glutamine, 83.3 mg/kg, was too small to exert a significant inhibition on ASA lesions in pregnant rats. The analysis of gastric contents in both non-pregnant and pregnant rats revealed a dose-dependent increase of acidity and decrease of Na⁺ ion concentration in response to ASA + L-glutamine as compared to those seen with ASA alone. The concentration of K⁺ ion and pepsin activity in response to ASA + L-glutamine remained unchanged.

These studies provide evidence that L-glutamine inhibits ASA lesions developed in pregnant rats as well as in non-pregnant ones. The mechanism of the aggravation of ASA lesions in pregnant rats is unknown. Hypersecretion of acid during pregnancy in rats (7) and increased acid back diffusion in response to ASA as evidenced in this experiment may partly contribute to the mechanism. Menguy and co-workers (8) demonstrated that women, who are empirically known to experience severe bleeding with ASA, have a lowered activity of serum ASA-hydrolase, an enzyme which metabolizes ASA to salicylic acid. In a preliminary study, we found that ASA-hydrolase activity in the blood of pregnant rats was significantly lower than that of non-pregnant ones (unpublished data). Therefore, the aggravation of ASA lesions in pregnant rats may be assumed to be partly due to the high level of ASA concentration in the blood at a certain period as a result of its reduced metabolism. From the standpoint of the action of ASA on the stomach, if the present findings in rats can be validly extrapolated to humans, it would appear that ASA may be prescribed for women who are pregnant when L-glutamine is ingested concomitantly.

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BEHAVIORAL AND NEUROCHEMICAL CHANGES FOLLOWING ADMINISTRATION OF 6-HYDROXYDOPAMINE INTO THE VENTRAL TEGMENTAL AREA OF THE MIDBRAIN

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The mesolimbic dopaminergic (DA) neurons are known to project to the olfactory tubercle and nucleus accumbens from A-10 cell bodies at the ventral tegmental area around