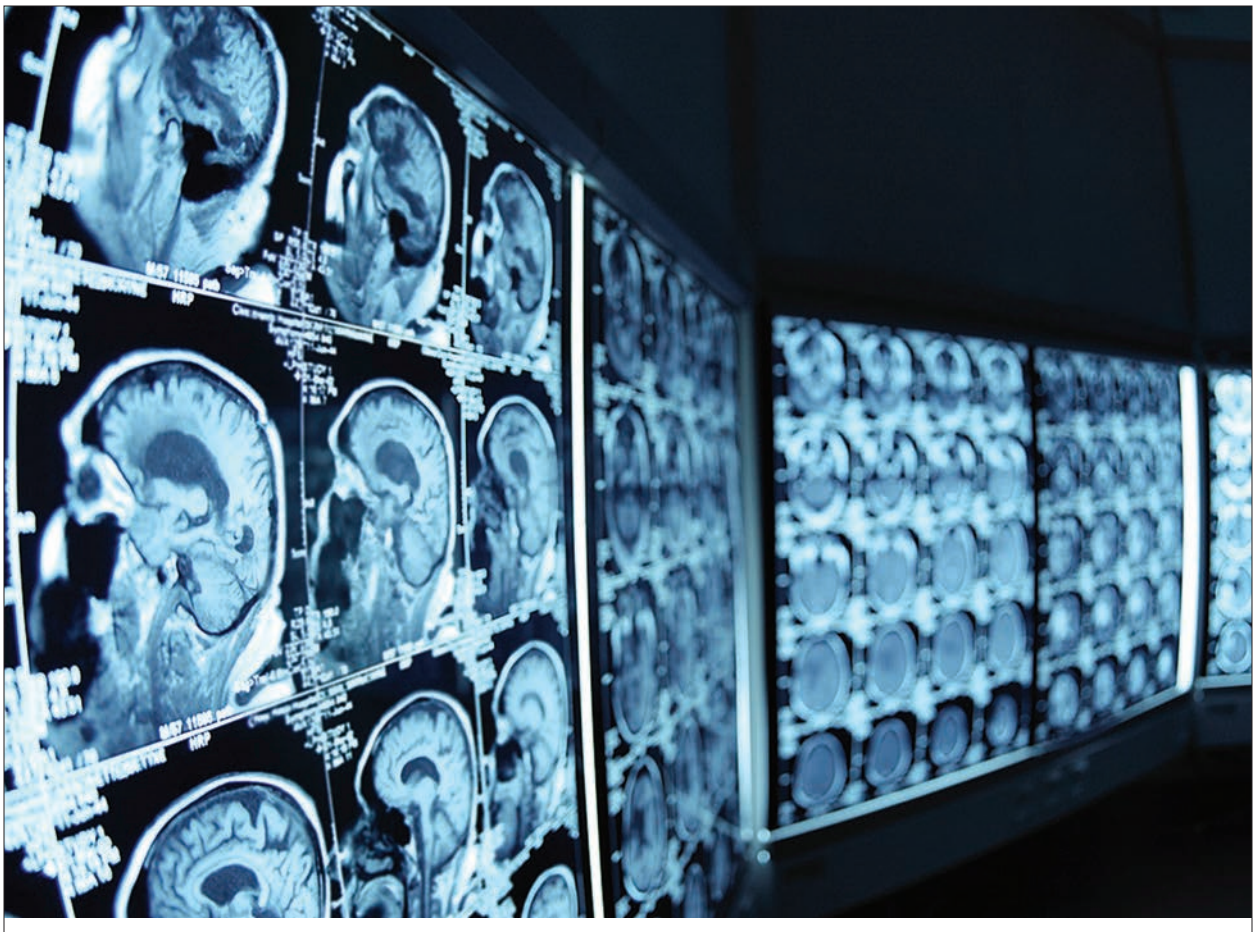

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Protective Effect of Aspirin on γ Radiation Induced Chromosomal Aberrations in Swiss Albino Male Mice

Marowa Al Mathkour and Entissar Al Suhaibani
College of Science, King Saud University, Riyadh, Saudi Arabia

Corresponding Author: Marowa Al Mathkour, College of Science, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

In order to reveal the anticlastogenic potency of aspirin, we evaluated the protective ability of aspirin on chromosome aberrations induced by γ-ray. Aspirin at doses of 0.5, 5 and 50 mg kg^{-1} was administrated intraperitoneally at 72 h before the γ-ray irradiation. The anticlastogenic activity of aspirin on chromosome aberrations induced by γ-ray was determined in the chromosomal aberration test CA *in vivo*. We consider aspirin can be used as preventive agents against exposure of X-ray. The objective of this investigation was to develop and evaluate potential radio-protective of Aspirin through assessment of structural Chromosomal Aberrations (CA) induced by γ-ray in Swiss Albino male mice. Aspirin at doses of 0.5, 5 and 50 mg kg^{-1} was intra-peritoneal injected to Swiss Albino male mice 72 h before 2 or 4 Gy doses of γ radiation exposure. Following mice exposing to 2 Gy γ radiation, great structural chromosomal aberrations occurred. With injection of 0.5 mg kg^{-1} with 2 or 4 Gy radiation, the chromosomal aberrations, were significantly reduced in all structural aberrations ($p<0.0001$). With the increase of Aspirin doses (5 and 50 mg kg^{-1}) the radio-protective effect still significantly valid ($p<0.05$), but relatively lower than radio-protective provided with low dose (0.5 mg kg^{-1}). Therefore, the radio-protective role of Aspirin was found to be statistically significant. The present study suggests that Aspirin pretreatment provides protection against radiation induced structural chromosomal aberrations.

Key words: Aspirin, chromosomal aberrations, radio-protective

INTRODUCTION

Recent studies, nonsteroidal anti-inflammatory drugs (NSAID's), especially aspirin, can reduce the incidence of colorectal adenomas and carcinomas (Baron and Sandler, 2000). Thun *et al.* (1991) used Aspirin at low doses and said it may reduce the risk of fatal colon cancer when used 16 or more times per month for at least one year. Moreover, Thun *et al.* (1993) found that Aspirin may resulted in decrease of the threat of cancer of the esophagus, stomach, colon and rectum. Also, Zaridze *et al.* (1999) states that Aspirin had protective effect of against non-cardia gastric cancer but it did not had the same affect against the risk of the gastric cardia cancer. Giardiello *et al.* (1993) demonstrated that NSAIDs are inhibited the cancer in various animal models and several cell strains. some studies pointed out the role of Aspirin in preventing the azoxymethane (AOM)-induced colon cancer and aberrant crypt foci and reduced prostaglandin E2 levels (Li *et al.*, 1999). As well as it role with difluoromethylornithine in the inhibition of colon cancer induced by AOM. Duperron and Castonfuay (1997) showed the inhibited way by Aspirin and suhndac for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (by tobacco-specific nitrosamine)

which induced lung tumorigenesis in A/J mice. also, Sulindac had incomplete effect that reduced the number and size of colorectal adenomas in patients with familial adenomatous polyposis. Oxidative damage of DNA was induced by generation of ROS by exogenous chemicals, radiation or endogenous oxidative stress. ROSs are involved in mutation, chromosome aberration, tumor promotion and cancer development. Aspirin interacts with free radicals both directly and indirectly, some studies reported that the ability of Aspirin to scavenge or quench various oxygen-free radicals or prevent their formation (Saini *et al*., 1998). While, *in vivo* studies concluded that X-ray generated intracellular Reactive Oxygen Species (ROS) and damaged DNA directly and/or indirectly in *E. coli* (Yonezawa and Nishioka, 1999). Although, the MMC or X-ray-induced chromosome aberrations were suppressed when vanillin was administrated orally to mice after MMC-administration or X-ray irradiation (Sasaki *et al*., 1990). Therefore, the current study was designed to investigate the effect of Aspirin on the genotoxicity exposed by γ radiation.

MATERIALS AND METHODS

Experimental animals: Swiss albino male mice (Mus musculus) eight-weeks old SWR/J mice with body weight of 24±2 g, were used from animal house of the King Saud University, Riyadh, Saudi Arabia.

Treatments: The animals were divided into three groups of five mice. Group one was injected intraperitoneally (ip) with progressive Aspirin concentrations (0.5, 5 and 50 mg kg^{-1}). Whereas, group two was exposed to 2 and 4 Gy γ radiation. While group three was injected with the same Aspirin concentrations 72 h before whole body was exposed to 2 and 4 Gy γ radiation.

Investigated chemical: Aspirin (aspegic ®) was used for animals Injection, which was purchased from Synthelabo France Le Plessis Robinson.

Irradiation: Irradiation Mice were irradiated by Cobalt-60 Source (Gamma cell-220-Nordion International Inc. Kanata. Canada) at AlDreiah radiation unit King Saud University. The mice were irradiated with 2 and 4 Gy doses. Whole body irradiation was given to unanesthetized mice, which were placed in ventilated Perspex cages.

Metaphase preparation: At 24 h after treatment all the animals were intraperitoneally (ip) with 0.05 colchicine and 2 h later they were sacrificed by cervical dislocation. Both femurs were dissected out. Briefly, bone marrow from the femur was aspirated, washed in saline, treated hypotonically (0.565% KCl), fixed in (Carnoy's fixative) methanol-acetic acid (3:1 The cells were spreadon clean slides and stained by 3% Giemsa (Sigma, USA).

Analysis of chromosomal aberrations (CA): Chromosomal aberrations were scored using oil immersion (with 100×object lens) under a light microscope. A total of 100 metaphase were scored per animal. Different types of aberrations like chromosome breaks, fragments, rings and dicentrics were scored. When breaks involved both the chromatids it was termed as "chromosome type" aberration, while "chromatid type" aberration involved only one chromatid. If the deleted portion had no apparent relation to a specific chromosome, it was called a fragment (Bender *et al*., 1988).

Statistical analysis: Significant differences between the treated groups data were tested by using Mann-Whitney test. A value of $p<0.01$ was considered to be significant.

RESULTS

This study assessed the protective effect of Aspirin on γ radiation induced chromosomal aberrations in Swiss Albino male mice. The comparison of distribution of structural chromosomal aberrations between the negative control group of animals that were given distilled water and the group one of animals were injected by different Aspirin concentrations it was not a statistically significant Table 1.

As shown in Table 2 Aspirin treatment seemed to have no considerable effect, but the proportions of structural chromosomal aberrations were relatively increased with increase of Aspirin concentrations.

In group two, the radiation significantly was increased the structural chromosomal aberrations. The rates of the structural chromosomal aberrations (fragment, ring, dicentric and break) increased when exposed to 2 Gy radiation dose constituting 61.3%. While the chromosomal aberrations represent 80.4% when the radiation dose elevated to 4 Gy.

In the group three, pre-treatment animals with Aspirin significantly reduced the percentage of chromosomal aberrations comparing with group were treated by radiation only. In the animals were exposed to 2 Gy and pretreated with 0.5 mg kg^{-1} of Aspirin the percentage of chromosomal aberrations was 34% compared to the group exposed to 2 Gy dose without Aspirin, which was 61.3% and this different was found statistically significant $p<0.01$. While, the rates of chromosomal aberrations were significantly decreased to 43.21% in the animals were exposed to the same dose of γ radiation and pretreated with 5 mg kg^{-1} of Aspirin. Also, there was a decrease in the rates of chromosomal aberrations to 46% in the animals pretreated with 50 mg kg^{-1} of Aspirin and exposed to 2 Gy of γ radiation. The comparison of structural chromosomal aberrations induced by 2 Gy of γ radiation exposure only and 2 Gy of γ radiation with pre-treatment of different concentrations of Aspirin was shown in Table 3.

Although, a reasonable reduction of chromosomal aberrations induced by 4 Gy of γ radiation was noticed in animals pretreated with different concentrations of Aspirin. In the animals that were treated with 0.5 mg kg^{-1} of Aspirin and exposed to 4 Gy the rates of chromosomal aberrations were decreased to 56.21% compared to 80.4% chromosomal aberrations were induced by 4 Gy of

Table 1: Comparison of distribution of chromosomal aberrations between the negative control and s chromosomal aberrations induced by different Aspirin concentration

	Structural aberrations				
Doses	Dicentric	Break	Ring	Fragment	Total
Negative control	0	0	0	0	0
0.5 mg kg^{-1}	-	1	-	-	1
5 mg kg^{-1}	-	1	1	-	2
50 mg kg^{-1}	1	2	-	1	4

Table 2: Comparison of structural chromosomal aberrations after 2 and 4 Gy radiation

	Frequency structural aberrations				
Doses	Dicentric	Break	Ring	Fragment	Total
Negative control	0	0.00	0.00	0.00	0
2 Gy	160	0.15	0.40	0.60	275
p-value	0.01	0.01	0.01	0.01	
4 Gy	245	0.25	0.50	0.80	400
p-value	0.01	0.01	0.01	0.01	

Table 3: Comparison of structural chromosomal aberrations after 2 Gy radiation exposure only and 2 Gy radiation with different doses of Aspirin

	Frequency structural aberrations				
Doses	Dicentric	Break	Ring	Fragment	Total
2 GY	160	0.15	0.40	0.60	0.275
2 GY+0.5 mg kg^{-1}	110	0.10	0.20	0.30	0.170
p-value	0.01	0.01	0.01	0.01	0.001
2 GY+5 mg kg^{-1}	125	0.20	0.35	0.35	0.215
p-value	0.01	0.01	0.01	0.01	0.001
2 GY+50 mg kg^{-1}	140	0.10	0.35	0.45	0.230
p-value	0.01	0.01	0.01	0.01	0.001

Table 4: Comparison of structural chromosomal aberrations after 4 Gy radiation exposure only and 2 Gy radiation with different doses of Aspirin

	Frequency structural aberrations				
Doses	Dicentric	Break	Ring	Fragment	Total
4 GY	245	0.25	0.50	0.80	0.400
4 GY+0.5 mg kg^{-1}	190	0.10	0.25	0.55	0.280
p-value	0.01	0.01	0.01	0.01	0.001
4 GY+5 mg kg^{-1}	200	0.15	0.40	0.60	0.315
p-value	0.01	0.01	0.01	0.01	0.001
4 GY+50 mg kg^{-1}	220	0.15	0.45	0.70	0.350
p-value	0.01	0.01	0.01	0.01	0.001

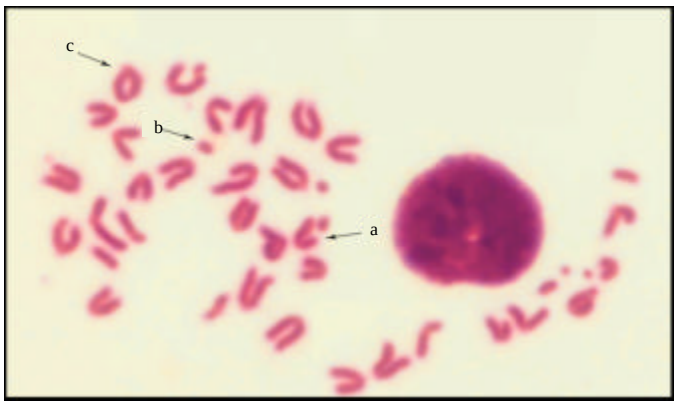

Fig. 1: Describes chromosomal aberrations in the group treated by 50 mg kg^{-1} of Aspirin and exposed to 4 Gy of γ radiation, (a) Break chromosome, (b) Fragments chromosome and (c) Ring chromosome

γ radiation only and this different was found to statistically significant $p<0.01$. While, the rates of chromosomal aberrations were significantly decreased to 63% in the animals were exposed to the same dose of γ radiation and pretreated with 5 mg kg^{-1} of Aspirin. Also, there was a significantly decrease in the rate of chromosomal aberrations in animals were treated with 50 mg kg^{-1} of Aspirin and exposed to the same dose of γ radiation 70% (Fig. 1). The Comparison of structural chromosomal aberrations induced by 4 Gy radiation exposure only and 4 Gy radiation with different doses of Aspirin was shown in Table 4.

Since, the increase of Aspirin doses to 5 and 50 mg kg^{-1} the radio-protective effect was l significantly valid ($p<0.05$), but relatively lower than the radio-protective provided with low dose of 0.5 mg kg^{-1} of Aspirin.

DISCUSSION

In this study, the anti-clastogenic activity of aspirin was examined on structural chromosomal aberrations induced by γ radiation using a mouse chromosomal aberration test. The chromosomal aberrations were significantly decreased when the aspirin was injected intraperitoneally before exposure to radiation. Aspirin is rapidly hydrolyzed to salicylic acid in the intestinal wall, liver and erythrocytes. Salicylic acid is further metabolized in the liver and kidneys into its glycine conjugate salicyluric acid and its glucuronic acid conjugates, salicylphenolic glucronide and salicylacyl glucuronide. Hydrolysis of aspirin to salicylate in the plasma occurs with a half-life of 15-20 min (IARC, 1997). Approximately 88 and 86% of aspirin administrated intra-venenously or orally was excreted in urine as most of salicylic acid and its conjugated forms, glucuronide and sulphate, within 48 h, respectively (Iwamoto *et al*., 1982). Butting in consideration these reports and our results, it is safe to say that aspirin itself and salicylic acid, the first main metabolite of aspirin, reduced the clastogenicity induced by γ radiation. Furthermore, γ-ray irradiation generates the ROS's and DNA damage. Aspirin, as is well known, has the ability to scavenge or quench various oxygen free radicals (Aruoma and Halliwell,1988). Therefore, the radical scavenging ability of aspirin was determined. The ability of the hydoroxyl radical-scavenging properties of aspirin at pharmacologically relevant concentrations markedly inhibited oxidative DNA damage induced by either H_2O_2/Cu (II) or hydroquinone/Cu(II) system (Hsu and Li, 2002). Saini *et al.* (1998) reported that aspirin showed a concentration-dependent inhibition of the radiation induced production of ROS in cultured J774A.1 macrophage cells. Yonezawa and Nishioka (1999) concluded that X-ray generated intracellular ROSs and damaged DNA directly and/or indirectly in *E. coli*. It is considered that aspirin and salicylic acid may play a role of chemo-protective against γ-ray induced ROSs. Oxygen radicals are involved in mutation, chromosome aberration, tumor promotion and cancer development.

CONCLUSION

In this report, our results considered that NSAIDs such as aspirin has the anticlastogenic ability and/or to protect DNA-damage by γ-ray. aspirin can be used as preventive agents against exposure to γ-ray. Although, the exact mechanism involved in the protective effect of aspirin is not clearly understood, more intensive research is required to clarify the mechanism of anticlastogenic and antioxidative of aspirin.

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