韓國受精卵移植研究會誌(1991) 第6卷 第1號
Korean J. Emb. Trans. (1991) Vol.6, No.1 pp.46~55

Effects of Platelet-Activating Factor (PAF) on the Initiation of Implantation in Rat

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흰쥐의 임신초기에 있어서 PAF(Platelet-Activating Factor)가 착상에 미치는 영향

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초 록

본 연구의 목적은 흰쥐의 임신 초기에 있어서 착상의 유발에 PAF의 관련여부를 PAF의 수용체 길항제인 BN-52021의 작용과 비교하여 결정하기 위함이다.

임신 초기 각일에 점증하는 용량의 BN-52021 (체중 200g당 10㎍ 내지 1.25mg)이 근육내로 주사되었을때 10㎍ 내지 250㎍ 용량에서는 대조구에 비하여 착상 부위의 수 혹은 이것을 가진 흰쥐의 수에 대하여 현저한 영향을 미치지 아니하였으나 1.25mg 투여 경우에는 현저히 감소된 효과를 나타내었다($P<0.05$).

PAF(1㎍) 경우에는 대조구와 비교하여 현저한 차이는 없었다.

임신 초기 각일에 BN-52021(1.25mg)과 점증하는 용량의 PAF(0.04㎍ 내지 1.0㎍)가 동시에 투여된 경우에는 PAF의 농도가 증가함에 따라서 착상 부위의 수도 증가하는 경향이었으나 현저하지는 아니하였다.

본 실험의 결과는 PAF는 흰쥐의 임신 초기 반응에 관련된다는 사실을 보여준다.

INTRODUCTION

Platelet-activating factor (PAF, PAF-acether, AGEPC, APRL) is a naturally ocurring etherphospholipid (1-0-alkyl-2(R)-acetyl-glyceryl-3-phosphorylcholine) that is generated by specific activation of rabbit basophils, human and rabbit polymorphonuclears (PMNLs), human macrophages and eosinophils in response to a variety of stimuli (Vargaftig *et al.*, 1981). The present interest in platelet-activating factor is justified by potential physiological role in various conditions, such as inflammatory conditions, transplant rejection, immue response, and pregnancy and increase in vascular permeability, being accompanied by platelet accumulation (Pirotzke *et al.*, 1985; Archer *et al.*, 1984; Braquet *et al.*, 1984). Platelet-activating factor may be the first physiological signal produced by the embryo for maternal recognition of pregnancy.

Platelet-activating factor, like leukotriens, exhibit the initial vasopermeation and vaodilation properties involved in the decidual reaction (Pirotzky *et al.*, 1984; Lewis and Austen, 1981; Draz on *et al.*, 1980). Increased uterine vascular permeability is one of the earlist indicators of blastocyst implantation (Psychoyos, 1973). Subsequent to changes in vascular permeability and possibly as a consequence of those changes, uterine endometrial stromal cells in many species are transformed to glycogen-laden decidual cells. The differentiation of uterine stroma cell into decidual cells occurs in the pregnant rat during the implantation of blastocyst (Finn, 1971). PAF is also present in the rabbit uterus during early pregnancy in concentration required to initiate cutaneous

permeability (Angle *et al.*, 1985) and in human amniotic fluid (Billah *et al.*, 1985; Billah and Johnston 1983). The mammarian embryo produces PAF within 6h of fertilization at levels which cause significant intravascular platelet activation and the extend of platelet activation is correlation with the number of embryos present in the reproductive tract (O'Neill, 1985a). In the mouse (O'Neill, 1985b, 1987) and human (O'Neill, 1987), this embryo-derived PAF induces a mild thrombocytopenia during the first days of pregnancy and embryo-derived and PAF may promote platelet activation and subsequently release factors which stimulate the blastocyst activation and consequent implantation (O'Neill *et al.*, .1985c).

The decidua-like reaction induced by PAF may involves the generation of cyclooxygenase metabolites of arachidonic acid since it was inhibited by indomethacin (Acker *et al.*, 1987, 1989). Mediators other than prostaglandins may therefore modulate implantation. Serevral mediators in the process of implantation have been implicated as effectors of both vascular permeability and decidualization including histamine, oestrogen, progesterone, prostaglandins and leukotriens(Tawfik and Dey, 1988; Jones *et al.*, 1986; Kennedy, 1977; Saksena *et al.*, 1976; Shelesnyak, 1957).

Pakrasi *et al.* (1985) and Tawfik *et al.* (1987) observed increases in intrauterine concentrations of prostaglandins and leukotriens in rat at the time of embryo implantation. Platelet-activating factor concentrations were low in the non-pregnant uterus. However, uterine PAF increased dramatically during pregnancy to a maximum on day 4, just before implantation in the rabbit (Angle *et al.*, 1988). In addition, the involvement of PAF in implantation has been suggested since this mediator exhibits the biological activity of 'early pregnancy factor' (Orozco *et al.*, 1986; O'Neill, 1985c) and injection of PAF into the left uterine horn in rat induced a dose-dependent decidua-like reaction in the pseudopregnant rat, this reaction being blocked by the specific PAF antagonist, BN-52021 (Acker *et al.*, 1989).

Although, taken toghether, PAF may be ralated to implantation in rat, Milligan and Finn (1990) could not successful in attept to trigger a decidual cell response in the uteri of hormonally sensitized, ovariectomized mice by instilling PAF-acether(1-1,000 ng) intraluminally.

But recently Rabinovici and Angle(1991) suggested that progesterone secretion is significantly increased by PAF from cultured human luteiniz ing granulosa cells obtained from women undergoing *in vitro* fertilization, imply the relationship of PAF to the implantation process from another possible aspect.

O'Neill (1991) insist that PAF plays an important roles as a direct autocrine growth factor for the preimplantation embryo.

As above-mentioned, there are many evidences that PAF may play potential role in the onset of events associated with implantation in the rat.

The objective of this investigation is to determine whether PAF is related to implantation in rat, compared with PAF-antagonist, BN-52021.

MATERIALS AND METHODS

1. Drugs

The following substances were obtained as noted:

PAF (L-α-phosphatidylcholine, β-Acetyl-r-O-Alkyl) was purchased from Sigma Chemical (ST. Louis, MO, USA). BN-52021, a specific PAF antagonist (Braquet *et al.*, 1985; 1987) was gifted from I.H.B. Res. Laboratories (Le Plessis-Robinson, France). PAF was dissolved in phosphate-buffered saline solution (PBS) containing 0.25% bovine serum albumin (Sigma) (PBS-BSA). BN-52021 was initially dissolved in dimethylsulphoxide (DMSO) and futher diluted in PBS to the appropriciate concentration. The concentration of

DMSO in the injected solution containing BN-52021 never exceed 0.1% (v/v). This highest concentraion of DMSO used did not interfere with the experiments.

2. Animals

Sprague-Dawley female rats weighing 180-200 g (Yuhan Yang Haeng Co, Ltd.) were used throughout the experiments.

Day 0 of pregnancy was defined by the present of copulatory plugs and spermarozoa in the vaginal tract.

3. Experimental Protocol

In one experiment, increasing dose of BN-52021 was intramuscularly injected in a volume of 100 μl containing this substance at the dose of 10 μg to 1.25 mg per 200 g body weight on day 0, 1, 2, 3, 4, or 5 of pregnancy.

In another experiment, PAF or BN-52021 was intramuscularly injected in a volume of 100 μl containing these substances at the dose of 1 μg or 1.25 mg, respectively per 200 g of body weight on various day of pregnancy.

In another experiment, the combination of BN-52021 (1.25 mg/200 g, B.W.) and PAF (0.04 to 1.0 μg/200 g, B.W.) was intramuscularly injected in a volume of 100 μl containing these substances on various day of pregnancy. In case of control, solvent alone was injected. The animals were sacrificed after 8 or 12 day and the number of implanted sites were determined at 15 minutes after intravenous injection of trypan blue in solution in physiologic saline.

4. Statistical analysis

Student's t test was used to establish the significance of the difference between two means. Values of $P<0.05$ were taken as significant.

RESULTS

1. The number of rats with implanted sites

In the experiment which increasing doses of BN-52021 (10 μg to 1.25 mg) were intramuscularly injected on various days of pregnancy, doses of 10 μg to 250 μg BN-52021 could not evidence an inhibitory effect significantly on the number of rats with implanted sites (Table 1).

In another experiment which BN-52021 (1.25 mg) or PAF (1.0 μg) was injected, no significant effect of PAF compared with that of

Table 1. Effect of various concentrations of BN-52021 on implantation in rat

Day of pregnancy	Implantations rate (%)				No. of implanted sites(mean±SD)			
	10μg	50μg	250μg	1.25mg	10μg	50μg	250μg	1.25mg
0	100.0	75.0	87.5	85.7	15.8±1.5	14.2±1.9	14.8±1.6	13.0±1.5[b]
1	83.3	71.4	100.0	90.9	14.2±0.8[b]	15.0±1.9	13.6±1.1[b]	13.8±1.2[b]
2	100.0	100.0	71.4	85.5	14.8±1.1	13.2±1.1[b]	13.8±1.9[b]	13.3±1.0[b]
3	87.5	100.0	71.4	71.4	16.4±1.5	14.8±1.9	12.8±1.1[b]	12.2±1.5[b]
4	87.5	87.5	100.0	85.7	15.6±1.1	15.6±1.8	14.6±1.5	12.5±2.4[b]
5	85.7	77.8	77.8	100.0	15.8±1.1	13.0±1.2[b]	14.8±1.6	14.2±1.7[b]

In case of control group, the rate of implantation was 100.0%, and the number of implanted sites was 16.2±0.8[a]
a and b values with different superscript differ significantly($P<0.05$).
BN-52021 was intramuscularly injected in a volume of 100μl containing this substance at increasing doses of 10μg, 50μg, 250μg or 1.25mg per 200g body weight on day 0, 1, 2, 3, 4, or 5 of pregnancy. The number of implanted sites was determined on day 8 or 12 of pregnancy.

control was observed since most PAF-treated rats presented implated sites, showing the numbers similar to those of the untreated rats. However, in rats treated with BN-52021 on each day the rate of pregnancy was 85.7% (day 0), 90.9% (day 1), 85.7% (day 2), 71.4% (day 3), and 85.7% (day 4), respectively (Table 2). When BN-52021 was administrated on day 5 of pregnancy, the marked effect of this substance was not observed.

2. The number of implanted sites

In the experiment which increasing doses of BN-52021 (10 μg to 1.25 mg) were intramuscularly injected on various days of pregnancy, doses of 10 μg to 250 μg BN-52021 could not evidence an inhibitory effect on the number of implanted sites significantly (Table 1).

In another experiment which BN-52021 (1.25 mg) or PAF (1.0 μg) was injected, when PAF was administered on each day of pregnancy, the number of implanted sites was not statistically different from that of control. But in case of BN-52021 the number of implated sites was significantly different from that of control (on day 0, 1, 2, 3, 4, or 5 of pregnancy, 13.0±1.5, 13.8±1.2, 13.3±1.0, 12.2±1.5, 12.5±2.4 or 14.2±1.7, respectively) versus 16.2±0.8 ($P<0.05$). In this time, the maximum of inhibition was 12.2±1.5 or 12.5±2.4 on day 3 or day 4 of pregnancy, respectively (Table 2).

In another experiment which BN-52021 (1.25 mg) and the concomitant doses of PAF (0.04 μg to 1.0 μg) were injected on various days of pregnancy, the number of implanted sites intended to increase with the increasing concentrations of PAF, but not significantly (Figure 1).

DISCUSSION

PAF has been implicated in many aspects of inflammation including the activation of platelets and leukocyte and the exhibition of vasomotor

Table 2. Effects of PAF and antagonist BN-52021 on implantation rate in pregnant rat

Day of pregnancy	Treatment	No. of rats	No. of rats with implanted sites	Implantation rate	No. of implanted sites
Day 0	Control	10	10	100.0	16.2±0.8[a]
	BN-52021	14	12	85.7	13.0±1.5[b]
	PAF	7	7	100.0	15.8±0.8
Day 1	BN-52021	11	10	90.9	13.8±1.2[b]
	PAF	8	7	87.5	15.8±0.8
Day 2	BN-52021	7	6	85.7	13.3±1.0[b]
	PAF	9	9	100.0	15.4±0.5
Day 3	BN-52021	7	5	71.4	12.2±1.5[b]
	PAF	13	12	92.3	16.6±0.5
Day 4	BN-52021	7	6	85.7	12.5±2.4[b]
	PAF	10	9	90.0	15.6±1.1
Day 5	BN-52021	8	8	100.0	14.2±1.7[b]
	PAF	8	8	100.0	16.6±2.1

a and b values with different superscript differ significantly($P<0.05$).

PAF or BN-52021 was intramuscularly injected in a volume of 100μl containing these substances at doses of 1μg or 1.25mg per 200g body weight, respectively, on day 0, 1, 2, 3, 4, or 5 of pregnancy. The number of implanted sites was determined on day 8 or 12 of pregnancy.

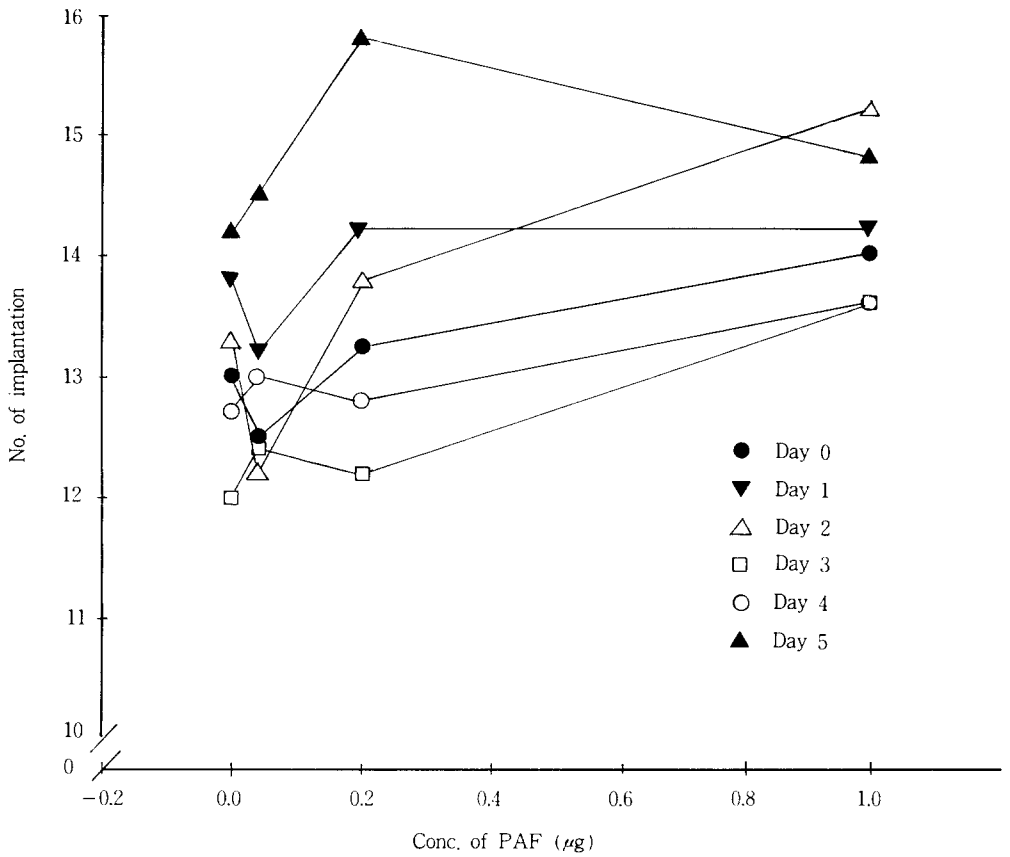

Fig. 1. Effect of BN-52021(1.25mg) and concomitant doses of PAF on implantation in rat.

PAF was intramuscularly injected in a volume of 100μl containing this substance at increasing doses of 0.04μg, 0.2μg, 1.0μg per 200g body weight with BN-52021(1.25mg per 200g body weight) on day 0, 1, 2, 3, 4, or 5 of pregnancy. The number of implanted sites was determined on day 8 or 12 of pregnancy.

and vasopermeant properties, inducing the secretion of vasoactive substances, such as prostaglandins and leukotriens.

Since the response of the uterus of an implanting blastocyst appears to resemble an inflammatory-like reaction (Finn, 1977) and one oritical step in implantation is an increase in vasopermeability (Psychoyos, 1961), the involvement of PAF in implantation can be expected. The result from present study provides the evidence to support the possibility that PAF has either a critical or a principal role in the process of implantation. In the present study, we used to PAF antagonist, BN-52021, investigate a possible role of PAF for implantation. The PAF antagonist, BN-52021 inhibited implantation in rat (Table 2). Treatment with BN-52021 on day 0, 1, 2, 3 or 4 of pregnancy gave 14.3%, 9.1%, 14.3%, 28.6%, and 14.3% of implaantation inhibition, respectively, but the same treatment on day 5 could'nt give any inhibition.

In addition, the number of implated sites in BN-52021-treated rats was markedly reduced as compared with that of control (on days 0, 1, 2, 3, 4 or 5 of pregnancy, 13.0±1.5, 13.8±1.2, 13.3 ±1.0, 12.2±1.5, 12.5±2.4 or 14.2±1.7) versus 16 .2±0.8 ($P<0.05$).

When PAF was administered on each day

of pregnancy, the results were similar to that of untreated rats. This study confirms provious observations (Spinks and O'Neill, 1987, 1988) that PAF-specific receptor antagonist inhibit implantation in mice.

The report (Acker *et al.*, 1989) that PAF into their left uterine horn induced a dose-dependent decidua-like reaction in the pseudopregnant rat, also supports the present result. As shown in this result(Fig. 1), the fact that the number of implanted sites increased with increasung doses of PAF potentially support our hypothesis that PAF may participate in the process of implantation in rat.

But Milligan and Finn(1990) could not success attempts to trigger a decidual cell response by PAF in the uterus of hormonally sensitized, ovariectomized mice and at the same time PAF had little effect on uterine vascular permeabilty.

The possibilty for this discrepancy is that the difference may be related to the precise endocrine conditions : in present study, as studied by Acker *et al.*, (1989) intact animal were used (Acker *et al.*,: intact, pseudopregnant animals), while Milligan and Finn(1990) used ovariectomized, hormone-primed females. Another possibility may be difference in sensitivity to PAF between rat and mouse.

The inhibitory effect of BN-52021 on implantation rate in rat was maximal when BN-52021 was administered at day 3 or day 4 of pregnancy. This result may be imply that PAF is most required for most implantation at day 3 or day 4 of pregnany in rat. Acker *et al.*, (1989) reported that the decidua-like reaction induced by PAF in pseudopregnancy rat was maximal at day 4 of pseudopregnancy (this time point corresponds to the maximum sensitivity of the uterus in response to any stimulations) and suggested that PAF may be imported in preparation of the endometrium for implantaion rather than implantation *per se*. And also in this respect, Milligan and Finn(1990) are not consistent with our opinion. Such interpretation of the different results may be compounded by pharmacolgical uncertainties such as biological activity, dose level of administered substances.

The observation of changes in PAF concentrations in the rabbit uterus at the time of implantation by Angle *et al.* (1988) is helpful in view of the time of involvement of PAF in implantation.

The precise mode of a correlation that induces the initiation of implantation is not well known. Arachidonic acid metabolites are known to be involved in the implantation related events.

There are some evidences to suggest that prostaglandins (PGs) may be involved in the induction such changes. PGs are higher in the sites of increased vascular permeability (Sharma, 1979; Kennedy and Zamecnik, 1978). PGE_2 induces changes in local vascular permeability and stromal oedema which precede implantation (Kennedy, 1983). Indomethacin, an inhibitor of PG synthesis, alters the local increase in endometrial vascular permeability involved in the decidual reaction (Phillips and Poyser, 1981; Lundkvist and Nilsson, 1980; Evans and Kennedy, 1978; Hoffman *et al.*, 1978) and blocks or delays implantation (Kennedy, 1986; Kennedy, 1977, 1980; El-Banna, 1980; Saksena *et al.*, 1976). The endometrium contains specific receptors for PGE_2 (Kennedy *et al.*, 1983, 1986; Hofman *et al.*, 1985) which are only situated on the stromal cell (Kennedy *et al.*, 1983).

Leukotriens (LTs) exhibit vasomotor properties (Lewis and Austen, 1981; Drazen *et al.*, 1980) and play a role in the decidual reaction and whose antagonist, the lipoxygenase blocker, also inhibited ovoimplantation when admistered on day 4 of pregnancy(Sagrillo *et al.*, 1987). As well, PGs and LTs exhibit increased concentrations at the time of embryo implamntation in rat (Tawfik *et al.*, 1987; Malathy *et al.*, 1986). These observations

indicate that such metabolites of arachidonic acid mediate the earliest stage of embryo implantation.

PAF being associated with such metabolites of arachidonic acid, the involvement of PAF in implantation has also been suggested since this mediator is present in increased concentrations in the rabbit uterus during the early phase of gestation (Angle *et al.*, 1985), futher, PAF is known to mediate production and action of arachidonic acid metabolites. PAF has been shown to stimulate the release of eicosanoids from several haemopoietic cells including platelets (Shaw *et al.*, 1981) and neutrophils (Roubin *et al.*, 1983), and to stimulate PGE_2 synthesis from rat mesangial cells (Schlondorff *et al.*, 1984) and human amnion (Billah *et al.*, 1985).

Synthetic PAF increased the synthesis of PGE_2 by glandular epithelial cell of mid-secretory endometrium and promoted a slight decline in the release of $PGF_2\alpha$ such that the ratio of $PGF_2\alpha$ to $PGF_2\alpha$ released into the medium was reduced. At the same time the stromal cells of the endometrium released smaller amounts of both $PGF_2\alpha$ and $PGE_2\alpha$ into medium, being not affected by PAF, at least in the *in vitro* system study (Smith and Kelly, 1988).

PAF induces the secretion of LT from various cell types and tissues (Braquet *et al.*, 1987; Piper and Stewart, 1986; Chilton *et al.*, 1982) which are known to alter vascular permeability. Acker *et al.* (1989) suggested that the decidua-like reaction induced by PAF involve the generation of the cyclooxygenase metabolites of arachidonic acid since it is inhibited by indomethacin (Acker *et al.*, 1987, 1989).

It is therefore possible to speculate that the effects of PAF are mediated via the generation of PGs or LTs, whose consequence is the initiation of implantation.

In mice embryo-derived PAF causes thrombocytopenia, and initial responses to fertilization, exhibits the biological activity of early pregnancy factor (Orozco *et al.*, 1986; O'Neill, 1985c) known to be an effective immunosuppressor to inhibit maternal rejection of the foetus (Morton, 1984).

Rabinovici and Angle(1991) reported that PAF induced progesterone secretion in lutenlizing granulosa cells *in vitro*.

Taken together, a possible role of PAF in early pregnancy may be the endometrium preparation for implantation via the mediation of the production or the action of arachidonic acid metabolites (Paracrine interactions between PAF and prostaglandins in regulation of endometrial cell function with or without oestradiol or progesterone; Alecozay *et al.*, 1991) ; direct effects on the embryo through receptor-mediated stimulation and activation of target cells ; the maintenance of progesterone production, serving as part of the antiluteolytic mechanism of early pregnancy, or the induction of progesterone secretion, influencing corpus luteum formation. And also the role of PAF in early pregnancy explained by unique feature by the manner in which the embryo processes PAF or its antagonists (Braquet *et al.*, 1985).

Futher studies are required to investigate the specific mode of action of PAF, including the effect of PAF on endogenous arachidonic metabolites (PGs, LTs) and their receptors, a correlation between PAF and early pregnancy factor and cyclic nucleotides, and changes in the amount of PAF-specific receptor in uterine tissue during early pregnancy, etc.

ABSTRACT

The study was carried to determine whether PAF is related to the initiation of implantation in rat, compared with PAF antagonist, BN-520 21. Increasing doses of BN-52021 (10μg to 1.25 mg) were intramuscularly injected on various days of early pregnancy, the doses of 10μg to 250μg BN-52021 could not evidence a significantly inhibitory effect on the number of rats with embryo

or the number of implanted sites, but the dose of 1.25mg BN-52021 showed the significantly reduced number of implanted sites ($P<0.05$), compared with that of control, while when PAF (1.0μg) was injected, the number of rats with implanted sites or the number of implanted sites was not statistically different from that of control. BN-52021 (1.25mg) and concomitant doses of PAF (0.04μg to 1.0μg) were injected on various days of pregnancy, the number of implanted sites intended to increase with the increasing concentration of PAF, but not significantly.

The results suggested that PAF may participate in the process of implantation in rat.

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