d(CH$_2$)$_5$Tyr(Me)Arg 预先阻断外侧隔核的 V1型受体，可完全消除 Arg 在该核团的心血管效应. 用酚妥拉明预先阻断外周 α 受体，可完全消除 Arg 在外侧隔核的升压效应，但不影响其加快心率效应. **结论**：Arg 可作用于外侧隔核的 V1型受体，发挥对心血管活动的中枢控制作用.

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Toxicity to transferred rat embryos after aspirin treatment during preimplantation stage *in vivo*[1]

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KEY WORDS aspirin; teratogens; blastocyst; embryo transfer; fetal development; drug-induced abnormalities

AIM: To explore the relationship between drug-induced blastopathies and post-implantation embryotoxicity or developmental defects. **METHODS**: Pregnant rats on d 3 were given intragastrically aspirin (0.25, 0.5, and 1 g·kg^{-1}). On d 4, the blastocysts were transferred into the uterine horns of pseudopregnant rats (made by mating with ♂ rats which had been given intragastrically 3-chloro-1,2-propanediol 5 mg·kg^{-1} for 5 d). Uterine contents were examined at term. **RESULTS**: The frequency of blastocysts with morphological alterations (FBMA) was increased on d 4 of gestation. The implantation rate was lower than that of the controls. A dose-related increase in resorption (55.2 %, 69.5 %, and 85.2 %) and malformation rate (3.8 %, 44.4 %, and 25 %), and decrease in viability rate of fetuses (44.8 %, 30.5 %, and 14.8 %) were observed in test groups with correlations to FBMA. **CONCLUTION**: Embryotoxicity and fetal malformations were induced by treatment of aspirin before implantation in a dose-dependent manner.

Preimplantation embryos were believed fairly resistant to teratogenic actions of chemicals to be obeying the "all-or-nothing" law[1,2], which, however, did not conform to all cases[2,3]. Previous works[4,5] showed that the preimplantation embryos were highly sensitive to the treatment of rats with aspirin causing both abnormal blastocysts and malformations in the surviving fetuses. The present study was carried out to analyze whether the toxic effects observed at term after preimplantation treatment with aspirin were induced by maternal effects or by direct effects of aspirin on the embryos.

MATERIALS AND METHODS

Aspirin (Shandong Xinghua Pharmaceutical Corp, China). Sprague-Dawley rats, 8 wk, virgins, weighing 186 ± *s* 13 g, ♂, adults, weighing 213 ± *s* 22 g, from Shanghai Institute of Planned Parenthood Research & Bantin and Kingman Universal Ltd were housed under 12-h light/12-h dark, 21 ± 1 ℃, 55 ± 5 % relative humidity for 2 wk before rats ♀ : ♂ (4 : 1) were mated during the night. The next morning when sperms were found in the vaginal smear was defined as d 0 of gestation. The mated females were divided randomly into experimental groups (n = 11) given on d 3 at 9:00 AM by ig aspirin 0.25, 0.5, and 1 g·kg^{-1} dissolved in 0.5 % CMC (almost equal to 1/2 LD_{50} of rats). Control group was treated with 0.5 % CMC 5 mL·kg^{-1}.

Pseudopregnancy in recipient ♀ rats Four ♀ rats were placed overnight with one ♂ rat which had been given ig 3-chloro-1,2-propanediol 5 mg·kg^{-1} × 5 d to be deprived of fertility ability[6]. The day when spermatozoa were found in the vaginal smear was taken as d 0 of pseudopregnancy.

Blastocysts evaluation and embryo transfer Pregnant and pseudopregnant females served as donors and recipients of embryos, respectively. On d 4 at 1 — 3 PM, the blastocysts were flushed from the uteri of donors using the HEPES-buffered medium M_2. The collected embryos were examined under a phase-contrast microscope (× 40)

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for morphological abnormalities[2,5,7-9]. The blastulation or the conditions of parietal trophoblast, inner cell mass, and the frequency of blastocysts with morphologicol alterations (FBMA) were evaluated.

Puncturing the uterine horn with a needle (№ 4) on the antimesometrial side close to the utero-bubai junction. A pipette with a tip of 10 μm diameter put 3—5 embryos in a small volume of medium into each horn by synchronous transfer.

Evaluation of the transferred embryo development in recipients Recipients were killed on d 16 after the transfer while the fetuses were 20 d old. Uterine contents were examined[10]. The rate of implantations (RI), rate of embryo resorptions (RER), and rate of live fetuses (RLF) on d 20 of gestation (RLF) were recorded. The fetuses were examined for external malformations. Half of them were fixed in Bouin's solution for viscera examination, and the other half were processed for skeletal examination.

Meantime, 157 blastocysts from 20 non-vehicle control donors were transferred into 20 recipients to evaluate the reliability of embryo transfer experiments.

Data were compared by X^2 test.

RESULTS

When pregnant females ig aspirin 0.5 and 1 $g \cdot kg^{-1}$ on d 3 of pregnancy, FBMA were 23.2 % and 38.3 %, respectively, higher than that of control group which was 7 % ($P<0.01$, Tab 1). FBMA showed a dose-dependent increase ($r=0.999$).

RI in all aspirin groups were markedly low compared with the control ($P<0.05$). But no significant differences were seen among aspirin groups ($P>0.05$). RER and RLF of transferred embryos were 40.8 % and 59.2 %, respectively, in control group. When pregnant rats were given ig aspirin 0.5 and 1 $g \cdot kg^{-1}$, RER were 69.5 % and 85.2 %, RLF were 30.5 % and 14.8 %, respectively, which were obviously different from those of control ($P<0.01$, Tab 1). They showed a dose-dependent increase and decrease ($r=0.986$, $r=-0.986$), respectively.

No abnormal fetus was found in the control group at term. There was 1 fetus showed abnormalities in aspirin 0.25 $g \cdot kg^{-1}$ group. In aspirin 0.5 $g \cdot kg^{-1}$ group, 8 fetuses manifested malformations, in which there were 1 anasarca (dead fetus), 1 absence of sternebra, 3 hydronephrosis, 1 anorchism, and 2 hydrocephalus. Two abnormal fetuses appeared in 1 $g \cdot kg^{-1}$ group, one was hydronephrosis, and the other was hydrocephalus.

RI, RER, and RLF in control group were 83.5 %, 40.8 %, and 59.2 %, respectively, very similar to those in non-vehicle control group (79.8 %, 42.1 %, and 57.9 %, respectively).

DISCUSSION

In this study, after treatment with aspirin to donors on d 3 of pregnancy, FBMA was similar to the previous works reported[5], whereas RI in various groups were not in a dose-dependent manner although they were low compared to control. This indicates that the abnormal blastocysts, at least in part, got the successful implantation and further development capacity in the uteri of recipients. When RER was compared to the number of implantations, there was a dose-related increase with FBMA. It demonstrated that the further development capacity of transferred embryos still related with preimplantation

Tab 1. Development, in pseudopregnant recipients, of d 4 rat embryos transferred after *in vivo* exposure to aspirin on d 3 of gestation. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control.

Aspirin/ $g \cdot kg^{-1}$	Embryos transferred	Blastocysts with morphological alterations/%	Implantation /%	Embryo resorptions/% (of transplantation)	Embryo resorptions/% (of implantation)	Live fetuses at term/%	Fetuses with malformation/%
0	85	7.0 (6/85)	83.5 (71/85)	34.1 (29/85)	40.8 (29/71)	59.2 (42/71)	0 (0/42)
0.25	83	14.4^a (12/83)	69.9^b (58/83)	38.6^a (32/83)	55.2^a (32/58)	44.8^a (26/58)	3.8^a (1/26)
0.5	86	23.2^c (20/86)	68.6^b (59/86)	47.7^a (41/86)	69.5^c (41/59)	30.5^c (18/59)	44.4^c (8/18)
1	81	38.3^c (31/81)	66.7^b (54/81)	56.8^c (46/81)	85.2^c (46/54)	14.8^c (8/54)	25^c (2/8)

52-54

injury. These embryos had the ability to implant themselves in the uteri of recipients but lost the subsequent development capacity. These abnormalities were similar to those in former work[5].

The effects of aspirin on fetus may be different from that of teratogenic effects mediated by postimplantation maternal environment. In conclusion, embryotoxicity and fetal malformations were induced by the treatment of aspirin before implantation in a dose-dependent manner.

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大鼠胚泡植入前期给亲代阿司匹林致移植胚胎的毒性[1]

R971.1 R321.6

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关键词 阿司匹林; 致畸胎物; 胚泡; 胚胎移植; 胎儿发育; 药源性畸形

目的: 探索药源性胚泡异常与着床后胚胎毒性和发育缺陷间的关系. **方法**: 大鼠在孕 d 3 ig 阿司匹林(0.25, 0.5, 和1 g·kg^{-1}). 孕 d 4将胚泡移植于假孕大鼠(与连续5 d ig 氯丙二醇5 mg·kg^{-1}↑大鼠交配获得)子宫内. 临产前检查子宫内胚胎. **结果**: 孕 d 4给药组胚泡异常率增高, 着床率低于对照组, 试验组的胚胎吸收率(55.2 %, 69.5 %, 和 85.2 %)与畸胎率(3.8 %, 44.4 %, 和25 %)呈剂量依赖性增高, 活胎率降低(44.8 %, 30.5 %, 和14.8 %), 并与胚泡异常率呈相关性. **结论**: 大鼠在胚泡植入前给阿司匹林可导致呈剂量依赖关系的胚胎毒性和畸胎.

Information for authors

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