MATERNO-FETAL MEDICINE

Up-regulated monoamine oxidase in the mouse uterus during the peri-implantation period

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Abstract

Purpose Monoamine oxidases (MAO), functioning as the metabolism of neuroamines, have been reported to be required for endometrial receptivity recently. The aim of this study was to examine the expression patterns of the two subtypes, MAOA and MAOB, during the peri-implantation period and to investigate whether MAOA or MAOB is a useful marker for receptivity.
Methods A total of 30 uteri were collected from females of gestational day 0, 2, 4, 6, 8, and mRNA and protein expression of MAOA/B were examined by real-time PCR, Western blot analysis and Immunohistochemistry analysis, respectively.
Results We found that the mRNA of MAOA expressed in the uteri at all stages of peri-implantation and began to rise on day 4 with a continuous increase up to day 8 of pregnancy, consistent with the changes of MAOA protein expression. The summit of MAOB mRNA and protein level was observed on day 4. Immunohistochemistry analysis revealed that both of MAOA and MAOB were mainly localized in the glandular and luminal epithelium cells, as well as their intense staining signals observed in the trophoblast cells on day 6 and 8.
Conclusions Both MAOA and MAOB were up-regulated in the uteri during the peri-implantation period, which could play a role in mouse embryo implantation and endometrial receptivity; the temporal and spatial marked increase of MAOs may be traced as a useful marker for mouse endometrial receptivity; the expression mode of mouse MAOs should pave a way for further study.

Keywords Embryo implantation · Endometrial receptivity · Monoamine oxidase A · Monoamine oxidase B · Mouse uteri

Introduction

Embryo implantation, as the most relevant limiting factor for successful pregnancy, is a critical step in pregnancy. The formation of endometrial receptivity, which is accurately regulated, is requisite for successful implantation. Physiologically, the human endometrium is receptive on the 19th–24th day of a menstrual cycle, and in the case of mouse, the endometrium is receptive on day 4 following mating. This transitory period is called "implantation window", during which the endometrium undergoes extensive morphological and physiological changes to facilitate implantation of the embryo, it becoming more vascular and edematous, with the glands displaying enhanced secretory activities. It is widely accepted that the menstrual cycle and reproductive process are regulated and controlled by the hypothalamic-pituitary-ovarian (H–P-O) axis, and the entire process involves a series of complicate regulatory factors, hormonal and local, complex neuroendocrine and signaling pathway regulations. Its well-recognized neuroendocrine regulation is a key link of reproductive process covering embryo implantation and endometrial receptivity and neuroendocrine activity is controlled by the neurotransmitters in the central nervous system, but the question remains whether the controlling process happens in the local endometrium.

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Monoamine oxidases, MAOA and MAOB (both under EC 1.4.3.4), are flavine-containing enzymes that catalyze the oxidative deamination of monoamines, involving the inactivation of neurotransmitters (catecholamines and indoleamines) as well as endo- and xenobiotic amines. They play a role in the regulation of nervous activities and are considered as targets for the drugs of neurodegenerative diseases and depressive disorders. There are two subtypes of MAO: MAOA and MAOB, which are bound to the outer mitochondrial membrane and co-expressed in the majority of human tissues [1]. MAOA is more efficient to metabolize 5-HT (5-hydroxytryptamine or serotonin) and NE (norepinephrine), while MAOB favors PEA (β-phenylethylamine) as substrate but both MAOA and MAOB show a same affinity for DA (dopamine). It is reported that low concentrations of clorgyline and selegiline (l-deprenyl) can selectively inhibit MAOA and MAOB, respectively.

In the early 1960s, MAO inhibitors were claimed to be potential anti-fertility drugs for rats [2]. Subsequently, 5-HT and Iproniazid, as one of nonselective inhibitors of MAO, was reported to interrupt pregnancy at the early stage in mice and rabbits [3]. Thereafter, it was found that monoamine oxidase activity increased markedly in the human endometrium during the secretory phase of a menstrual cycle, further confirming that increased MAO was mainly MAOA [4–6]. In the following decades, however, few further studies provide data on the role of MAO in embryo implantation and endometrial receptivity. With the development of high-throughput technologies such as microarray after 2000, multiple publications reported that MAOA expressed highly in the human endometriun during the implantation window via genomics [7–10] which was also proved by our team through suppression subtractive hybridization (SSH) [11]. The intriguing findings promoted us to explore the role of MAO in the process of embryo implantation. However, limited information was available on the expressing pattern of MAO in the endometrium of other mammals. Therefore, we undertook real-time PCR, western bolt and histochemisty analysis to investigate the expressing patterns of the two subtypes of MAO in mouse uteri, which could contribute to the establishment of a useful marker for receptivity in a rodent model for further studies.

Materials and methods

The present study proceeded under the permission of Shanghai Scientific and Technical Committee. License No. SYXK (hu) 2008-0064. All the procedures were conducted after approval of the research ethics committee at the Obstetrics and Gynecology Hospital, Fudan University.

Animals

Virginal female KM mice, weighing 20–30 g, 8–10 weeks old, were obtained from the animal facility at Shanghai Medical School, Fudan University.

Tissue collection

The female mice were mated with the males of the same strain and the day of vaginal plug presented was designated as pregnant day 1. The uteri of mated were collected on day 2, followed by the other three 2-day intervals, each collection composed of six; the other unmated six were designated as day 0 and collected as controls. Each uterus was cut into halves, which were gathered to two groups at random: one for RNA and protein extraction and the other to be stored with 4% paraformaldehyde for immunohistochemistry.

RNA isolation and real-time PCR analysis

Total RNA was isolated from the uteri using Trizol reagent (Invitrogen, USA) based on the manufacturer's instructions, and for the uteri on day 6 and day 8, the embryos were removed and discarded to ensure that the RNA was extracted from uteri exclusively. The cDNA was generated using RevertAidTM First Strand cDNA Synthesis Kit (Fermentas, Canada) as indicated by the manufacturer's protocol. Quantitative PCR was carried out with SYBR Premix Ex Taq (Takara, China), detected by ABI PRISM 7000HT system (Applied Biosystem, USA), and the gene expressions of MAOA and MAOB normalized to that of the β-actin in all samples.

The primers for RT-PCR were described as follows: for MAOA, forward 5′-CAA GCA AGA CAT GCT GAG GAA-3′ and reverse 5′-ATA AGC AAA TTC TCG AGC AGT-3′; for MAOB, forward 5′-AAG ATT CCA GAA GAT GAA ATT-3′ and reverse 5′-GTG GTC AAT CCA AAC AGC TTT-3′; for β-actin, forward 5′-AGA TTA CTG CTC TGG CTC CT-3′ and reverse 5′-CAT CTG CTG GAA GGT GGA CA-3′.

Protein extraction and western blot analysis

The tissues were lysed in RIPA reagent (Beyotime, China) with protease inhibitors (0.5 mmol/L PMSF), and their protein concentration was determined by BCA assay (Beyotime, China).

Separated on 12% SDS polyacrylamide gels, the proteins were blotted onto PVDF membranes, which were then incubated overnight at 4°C in blocking solution containing 5% nonfat dry milk in PBS with 0.1% Tween-20. Subsequently, the membranes were incubated with the primary antibody against MAOA (1:200, MAO-A (H-70), Santa

Cruz Biotechnology, USA), MAOB (1:4,000, Abcam, USA) and β-actin (1:4,000; Abcam, USA), followed by an incubation with horseradish peroxidase-conjugated IgG secondary antibodies (1:5,000, Abcam, USA). The signals were detected using SuperSignal West Pico Chemiluminescent Substrate (Pierce, USA).

Immunohistochemical staining

The paraffin-embedded sections were subjected to a two-step immunohistochemical approach: formalin-fixed and paraffin-embedded sections (4 µm) were deparaffinized, hydrated, and heated in an oven for antigen retrieval, before covering with 0.3% (w/v) hydrogen peroxidase for 30 min to inactivate the endogenous peroxidase. They were then washed in PBS thrice, the sections were treated with the blocking of goat serum for 30 min, and then incubated overnight at 4°C with the primary antibody against MAOA (1:25, MAOA (H-70), Santa Cruz Biotechnology, USA) or against MAOB (1:400, Abcam, USA). Upon three rinses with PBS, the sections were incubated with the secondary antibody linked with horseradish peroxidase for 45 min at room temperature followed by staining the sections with hematoxylin and eosin. PBS instead of primary antibody was used as negative controls.

Statistical analysis

All data were presented as mean ± SE. Statistical analyses were performed using one-way ANOVA, followed by LSD analysis using SPSS 15.0 software, and their values were considered statistically significant at $P < 0.05$. All experiments were repeated three times at least.

Results

The expression of MAOA in mouse uteri during the peri-implantation period

The mRNA levels of MAOA expressions in the uteri of day 0, 2, 4, 6, and 8 were determined via real-time PCR analysis, and they were found to begin to rise on day 4 and the continuously rising tendency was observed on day 8 (Fig. 1).

Western blot analysis was performed to detect the protein levels of MAOA in the uteri during the peri-implantation period. In comparison with the results of real-time PCR, the MAOA expression presented the same moving pattern (Fig. 2).

Immunohistochemistry analysis was conducted to observe the localization of MAOA in the uteri. MAOA staining signals were mainly detected in the epithelial cells
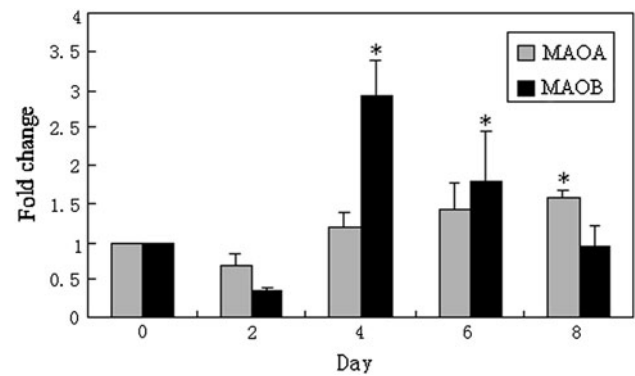

Fig. 1 Expression level of *MAOA* and *MAOB* mRNA in the uteri. Mean fold changes from real-time PCR analysis of mRNA expression of *MAOA* (*grey bar*) and *MAOB* (*dark bar*) in mouse uteri of pregnant day 0, 2, 4, 6, and 8 using the β-actin as the housekeeping gene, each group containing 6 samples, embryos of day 6 and 8 separated from the endometrium. The data were normalized relative to that of day 0 (*$P < 0.05$)
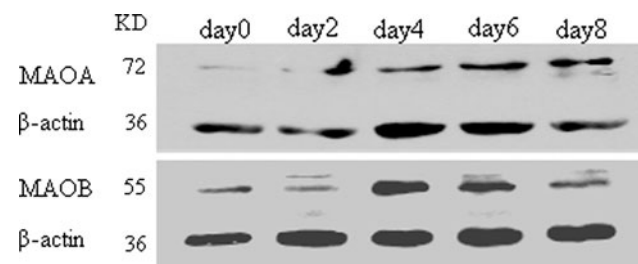

Fig. 2 Expression level of MAOA and MAOB protein. In Western blot analysis of MAOA and MAOB expressed in mouse uterine tissues during the peri-implantation period, the rabbit anti-sera specific for mouse MAOA (1:200) and MAOB (1:4,000) used as the primary antibody. Total protein (30 µg) was extracted from the uteri of pregnant mice from different groups, embryos also separated from the uteri of day 6 and 8. The *upper panel* shows the MAOA and MAOB signal detected from different groups, and the *lower panel* shows the equal of loading samples stained by the rabbit anti-β-actin antibody

of the uterine lumen and glands and enhanced increasingly starting day 4 up to day 8; intense signals were also found in the trophoblast cells on day 6 and day 8; and scattered signals were observed in the muscular layer (Fig. 3a, c, e, g, i).

The expression of MAOB

The mRNA levels of MAOB expression, assessed just as in the case of MAOA, were found to have reached crest value on day 4 (threefolds of that on day 0, $P < 0.05$), and the measured value remained relatively high on day 6, but decreased significantly on day 8 ($P < 0.05$) (Fig. 1).

Western blot analysis was performed to detect the protein levels of the MAOB expression during the peri-implantation period, with its summit on day 4, which was consistent with the results of real-time PCR (Fig. 2).
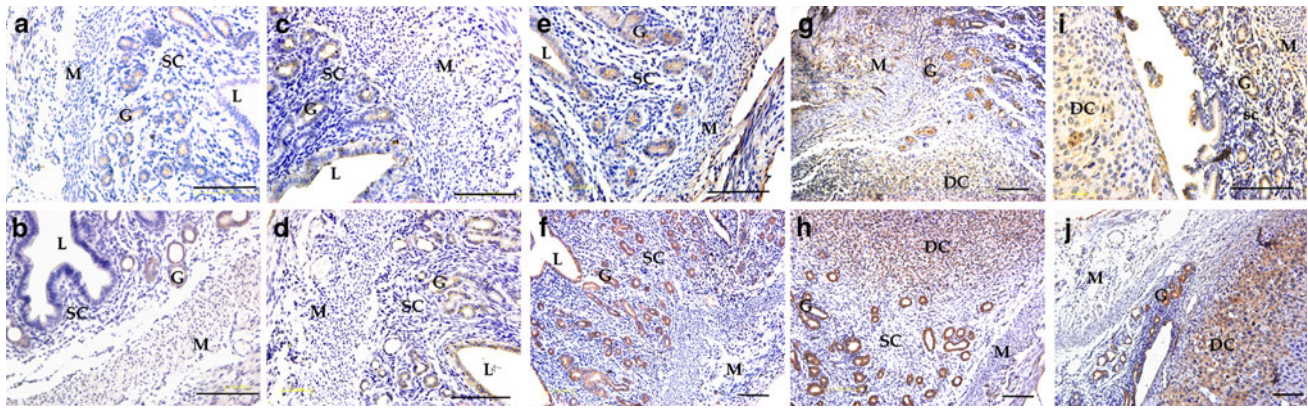
Fig. 3 Immunohistochemical analysis of MAOA and MAOB in mouse uteri. MAOA and MAOB immunohistochemical staining of mouse uterine tissues performed using rabbit anti-sera specific for mouse as the primary antibody, the sections stained with MAOA of day 0 (**a**), day 2 (**c**), day 4 (**e**), day 6 (**g**) and day 8 (**i**); with MAOB of day 0 (**b**), day 2 (**d**), day 4 (**f**), day 6 (**h**) and day 8 (**j**). *L* lumen of uterus; *G* gland; *SC* stromal cells; *DC* decidual cells; *M* muscle. *Scale bars* represent 5 μm

The location of MAOB in the uteri were observed via immunohistochemistry analysis, and the staining signals were almost detected exclusively in the epithelium of the uterine lumen and glands (Fig. 3b, d, f, h, j), with the peak point detected on day 4 (Fig. 3f) and deceased on day 8 (Fig. 3j), as well as with the signal intensity detected in trophoblasts on day 6 and 8 (Fig. 3h, j), which was stronger than that of MAOA (Fig. 3g, i).

Discussion

In recent years, many studies using microarray analyses indicated MAO-A transcript levels increased 6–29-folds in the human endometrium during the receptive phase [7–10], which was in keeping with the previous findings of a marked increase in MAO-A activity in the human endometrium in the mid-luteal phase [4–6], but no evidence suggested that the expression of MAOB, another subtype of MAO, had any alteration during the menstrual cycle. In addition, a deficient expression of MAOA in the endometrium of patients with implantation failure was described [12]. Moreover, studies revealed that progesterone could induce the expression of MAOA and this induction can be boosted by the presentation of 17β-E2 [13, 14]. These data showed that that MAOA, but not MAOB, may play a role in the establishment of human endometrial receptivity.

In the present study, we elucidated the dynamic expressions of the two MAO subtypes in mouse uteri during the peri-implantation period. MAOA began to rise on day 4, the day of implantation window, which was found to be consistent with the previous studies on human beings. Our immunohistochemistry results showed that MAOA was mainly located in lumen and glands epithelial cells and embryo trophoblast cells. The distribution pattern of MAOA and the synchronism of the implantation window

suggested that MAOA might play a role either in the formation of special inter-uterine milieu in favor of embryo implantation or in the crosstalk between the embryo and endometrium facilitating embryo apposition and adhesion. The maintained rising tendency up to day 8 after the implantation window in our study indicated that MAOA might also play a role in the maintenance of pregnancy. And the low expression of MAOA in the placenta from preeclampsia patients indicated that MAOA also participated in the maintenance of pregnancy in human beings [15].

MAOB exhibited a significant increase of its expression at both the mRNA and protein levels during the peri-implantation period, which peaked on day 4 exhibiting nearly three-fold of that on day 0, followed by a sharp decrease on day 8. Immunohistochemistry results showed intense signal of MAOB mainly located in lumen and glands epithelial cells and embryo trophoblast cells. Similar to our results, another microarray-based study on mice showed that MAOB increases sharply in the endometrium on day 4 of pregnancy, coinciding with the implantation window of mice [16]. These results suggested that MAOB participates in the formation of endometrial receptivity and the crosstalk between the embryo and endometrium in mice.

The gene expression profile of both the MAOA and MAOB displayed in our study did not completely accord with previous studies in human beings. There were several researches that revealed structure and properties differences of MAOA and MAOB among species [17–19], thus we hypothesized that the expression patterns of MAOs in the endometrium may also vary within species.

The mechanism and effect of local MAOA and B on embryo implantation and endometrial receptivity may be easily associated with their substrates—monoamines, which are oxidatively deaminated by MAOs in a reaction consuming O_2 and H_2O and produce the corresponding aldehyde, the removed amine moiety and H_2O_2 in

stoichiometric amounts. The general equation is as follows [20]:

$$MAOs + R - CH_2 - NH_3 + O_2 + H_2O$$
$$\rightarrow MAOs + NH_4 + RCHO + H_2O_2$$
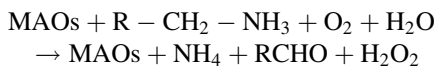
The endometrium has a capability of endogenous monoamine synthesis and monoamine oxidase is one of the main modulator of extracellular monoamine levels excluding the specific monoamine transporters [21]. A study on pre-eclampsia found that the higher plasma free 5-HT levels observed in severe pre-eclampsia could be mainly due to a reduction in placental MAO-A expression and activity and were not limited by the expression and uptake of 5-HT into the placental tissue [15]. Therefore, we postulated that monoamine oxidases might play an important role in the endometrial monoamine modulation during the establishment of endometrial receptivity and pregnancy.

5-hydroxytryptamine (5-HT), norepinephrine (NE) and epinephrine (E) are the main substrates of MAOA. They serve as not only important neurotransmitters but also potent vasoactive mediators to regulate blood flow and capillary permeability [22]. 5-HT is expressed mostly in the gastrointestinal tract of animals regulating intestinal movements, and the remainder is synthesized mostly in the serotonergic neurons in the central nervous system, performing functions such as the regulation of mood, appetite, sleep, muscle contraction, and some cognitive functions [23]. It was reported that 5-HT could cause intense vasoconstriction in the isolated human placental vessels, and its threshold concentration could increase the sensitivity of vessels to other vasoconstrictors [24]. NE and E, the principal neurotransmitters in the sympathetic nervous system, were found to be potent stress hormones. Recently, studies reported that elevated MAOA during the peri-implantation period could enhance the blood flow of endometrium by inactivating its vasoactive substrates to facilitate embryo implantation and decidualization [25, 26], which could be supported by the previous investigation that placenta hemorrhage and embryos loss were found in the pregnant mice and rabbits injected with 5-HT [3].

PEA, an alkaloid, is the main substrate of MAOB. Low concentrations of endogenous PEA are found in those suffering from attention-deficit hyperactivity disorder (ADHD) and often in clinical depression, while levels are elevated in schizophrenia [27, 28]. It also acts as a releasing agent of NE and DA. MAOB and its substrate PEA were considered to be responsible for mood disorder and depression, thus becoming a drug target for anti-depression. It was reported that mood disorder, especially major depressive disorder, could reduce human fertility, even before the first psychiatric admission [29]. Another study observed a negative influence of long-term low dose of a specific MAOB inhibitor on pre-implantation embryo development in rats [30]. But it remains unknown how MAOB and PEA affected fertility and embryo implantation.

DA, the common substrate of MAOA and B, is the primary inhibitor of the prolactin secretion from the anterior pituitary gland [31], but no evidence suggests that DA can inhibit endometrium secretion of prolactin [32]. In peripheral tissues, DA possesses the property as a vasoactive substance as well. DA can cause the dilation of blood vessels, increase blood flow and perfusion to peripheral organs in a low dosage while causing vasoconstriction, elevation of systemic vascular resistance and blood pressure in a high dosage [33]. It was also reported that DA could promote VEGF receptor-2 (VEGFR-2) endocytosis in endothelial cells, prevent VEGF–VEGFR-2 binding and reduce neoangiogenesis [34].

H_2O_2, the common product of MAOA and B, can induce cell apoptosis [35], increase vasopermeability, and promote the expression of VEGF and angiogenesis [36, 37]. We hypothesize these mechanisms may facilitate the establishment of endometrial receptivity and embryo implantation, although this postulate still needs to be verified.

Conclusions

In summary, our findings demonstrated the expression profile of MAOA and MAOB in the mouse uteri for the first time, although their exact mechanism in the process of embryo implantation remains unknown. Both of the two MAO subtypes were found to present an increase in expression during the implantation window, and MAOB decreased significantly by day 8, while MAOA continued to rise. Undoubtedly, our findings can provide a basis for further studies using mouse models on the mechanisms of MAOs in the process of embryo implantation and the spatio-temporal up-regulated MAOB may be considered as a marker for the establishment of mouse endometrial receptivity.

Conflict of interest We declare that we have no conflict of interest.

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