GENERAL
INTRODUCTION
Implantation is a process during which the embryo makes a close physical and physiological contact with the endometrial epithelium for the establishment of pregnancy. The most essential feature of this process is the synchronized development of early embryo to the blastocyst stage on one hand and differentiation of the endometrium to the receptive stage on the other (Carson et al., 2000). This is followed by a ‘two-way’ interaction between the activated blastocyst and the endometrial luminal epithelium to initiate the process of implantation (Dey, 1996; Psychoyos, 1986). Uterine receptivity is the capacity of the uterine mucosa to facilitate successful implantation of blastocyst. However, the period of uterine receptivity is restricted to a limited time schedule, during which only the implantation can be achieved. This period is known as ‘Implantation window’ (Harper, 1992).

A successful implantation depends on two important factors, the embryo quality and the uterine receptivity, which are responsible for the attachment and invasion of the blastocyst into the endometrium. The phenomena of endometrial sensitization and trophoblast attachment may thus be considered as the two main prerequisite factors for the establishment of pregnancy as the impaired uterine receptivity becomes one of the major reasons for the failure of assisted reproductive techniques (ART) (Herrler, Von Rango and Beier, 2003; Edwards, 1995). The uterine receptivity is primarily coordinated by the two ovarian hormones, progesterone (P₄) and estrogen (E₂), which modulate uterine events in spatiotemporal manner. The time of maximal uterine receptivity varies from
species to species. In Human, it lasts from day 20-24 of menstrual cycle; in mouse it appears on day 4 post-coitum (p.c.) and in rat on day 5 p.c.

The uterine receptivity is characterized by appearance of certain biological markers in the endometrial epithelium, particularly close to the site of embryo attachment. These markers specially appear during the implantation window and disappear after this period (Zhu et al., 1998b). Some of these are: Pinopods (the morphological marker), Leukaemia inhibitory factor (LIF), Interleukin-1 (IL-1), Heparin binding-epidermal growth factor (HB-EGF), Colony-stimulating factor-1 (CSF-1), Insulin-like growth factor binding protein-1 (IGFBP-1), Keratinocyte growth factor (KGF), Cell adhesion molecules, Calcitonin, Hox and Cox genes etc (the biochemical and molecular markers). These are vital biomarkers of uterine receptivity (Cavagna and Mantese, 2003).

During the implantation window, the endometrium and the embryo express cell adhesion molecules, which contribute to the blastocyst attachment on the endometrial epithelium (Yelian et al., 1995). Some of these are: Trophinin-Tasin-Bystin complex, Cadherins, Selectins, CD 44, Heparan sulphate proteoglycan (HSPG), H type-1, Lewis Y, oligosaccharides and integrins (Giudice, 1999). Among these more emphasis has been laid on the integrins as the most vital cell-cell adhesion molecule in recent years.
The integrins are transmembrane glycoproteins (Albelda and Buck, 1990) and comprise a large family of cation-dependent heterodimeric receptors that are composed of non-covalently linked α and β subunits (Hynes, 1992). The major functions of integrins are to mediate cell-cell and cell-substratum attachment (or adhesion). They also play vital role in embryonic development, maintenance of cell/tissue architecture, fertilization, placentation, inflammatory response, wound healing, angiogenesis etc. The interaction between the embryo and the endometrial epithelium around implantation may be considered as analogous to the leukocyte-endothelial cell interactions and metastatic processes in which the integrins are predominant adhesion molecule in the attachment process (Lessey et al., 1992). The integrins are regulated, spatially and temporally, within the uterus throughout the reproductive cycle and early pregnancy (Tabibzadeh, 1992; Lessey et al., 1992, 1994a). The subunits α₂, α₃, α₆, β₁, β₄ and β₅ are expressed constitutively in the endometrial epithelium. Among these the subunits α₁, α₄, α₅, β₃ and β₆ exhibits regulated epithelial expression in different patterns and at least three integrins (α₁β₁, α₄β₁ and α₅β₃) appear on endometrial epithelium around the implantation window. The apical pole of the luminal epithelium expresses both α₃β₃ and α₅β₅ (Aplin et al., 1996; Lessey et al., 1996a) and these integrins (α₅β₃ and α₅β₅) are also expressed on the apical surface of the blastocyst (Sutherland et al., 1993; Campbell et al., 1995b).

The integrins recognize and bind to the RGD (arginine-glycine-aspartic acid) amino acid sequence of its ligands. This sequence is mainly involved in the
trophoblast attachment and outgrowth (Yelian et al., 1995). Therefore, blocking of integrins or its ligand binding sequence may result in prevention or reduction of implantation (Illera et al., 2000, 2003) and poor or decreased $\alpha_\nu\beta_3$ expression has been observed in human subjects facing luteal phase deficiency (LPD) (Lessey et al., 1992), endometriosis (Lessey et al., 1994b), unexplained infertility (Lessey et al., 1995) and hydrosalpinges (Meyer et al., 1997).

Most of the data on endometrial integrins have come from clinical studies. Some experimental studies are also available in other mammalian species such as mouse (Illera et al., 2000), rabbit (Illera et al., 2003), baboon (Fazleabas et al., 1997), bovine (Kimmins and MacLaren, 1999) porcine (Jeffery et al., 1996), goat (Garcia et al., 2004) and sheep (Johnson et al., 2001); however, the distribution of $\alpha_\nu\beta_3$ integrin in rat model is still not known. Rat being a spontaneous ovulator, it serves as an excellent model for the study of implantation and establishment of $\alpha_\nu\beta_3$ integrin as a marker of uterine receptivity is very much essential for the proper understanding of the mechanisms/factors regulating the process of implantation.

The objective of the present investigation is to study i) whether the $\alpha_\nu\beta_3$ integrin is expressed in rat endometrial epithelial cells during preimplantation (day 4 and day 5 p.c.), ii) its regulatory expression under the influence of ovarian steroids and embryo and iii) its functional role during implantation by function blocking studies in utero. It is assumed that the findings emerged from this might
be helpful in: i) establishing $\alpha_\beta_1$ integrin as marker of uterine receptivity in rat, ii) defining its role in eliciting uterine receptivity during implantation window, iii) designing new molecules for anti-adhesive potentiality evaluation in lower animals, a new approach in the development of female fertility regulating agents and iv) extrapolation of findings from animal studies to human may also provide some clues for the management of infertility.