AN INHIBITOR OF LEUKEMIA INHIBITORY FACTOR SIGNALLING BLOCKS EMBRYO IMPLANTATION IN THE MOUSE

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Embryo implantation is a critical step in the establishment of pregnancy. Endometrial leukemia inhibitory factor (LIF) is essential for embryo implantation in the mouse (1). Uterine LIF is expressed in the luminal epithelium on Day 3 of pregnancy (D3) (D0 = day of plug detection) and signals via activation of signal transducer and activator of transcription (Stat) 3 (2). We examined the effect of a novel LIF signalling inhibitor on the phosphorylation (p) of Stat3 during early pregnancy and on embryo implantation in the mouse. We injected LIF inhibitor into one uterine horn and PBS into the other uterine horn of the mouse at D3 and examined the effect on pStat3 immunostaining in the luminal epithelium between 30 and 360 min later. We found no immunoreactive pStat3 in luminal epithelium following treatment with LIF inhibitor at 60 and 90 min but variable staining at other time points. The PBS-treated uterine horn showed intense immunostaining at all times. LIF inhibitor (1mg/kg body weight per day) or PBS was administered to mice (a) subcutaneously, (b) intraperitoneally, at 8-hourly intervals for 3 days from D2, or (c) continuously into the peritoneal cavity via Alzet pumps from D2. No effect was seen on implantation at D6. When LIF antagonist (3.5mg/kg/day) or PBS were administered by Alzet pumps from D2 together with ip injections, 4-hourly from D3 for 36 h, there were no implantation sites in the uteri of treated mice ($n = 5$) while the control mice ($n = 4$) had 3.6 ± 0.5 sites ($P < 0.001$). Histologically, the uteri of the treated mice resembled non-pregnant uterus, while the control uterus resembled post-implantation uterus. The results demonstrate that treatment of mice during early pregnancy with a novel LIF inhibitor blocks LIF action in vivo and embryo implantation. This knowledge is important for development of novel contraceptives.

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