**Anti-inflammatory effect of BK receptor antagonist, R-954, in experimental endometriosis in mice**

CARVALHO, P.R.¹, PAIVA, J.P.¹, SIROIS, P.2, FERNANDES, P.D1.

1Federal University of Rio de Janeiro, Institute of Biomedical Science, Laboratory of Pain and Inflammation. Rio de Janeiro, Brazil. 2Laval University, CHUL Research Center. Quebec, Canada

**Introduction:** Endometriosis is a gynecological condition characterized by the growth of endometrium-like tissues within and outside the pelvic cavity. Currently, available drugs are only efficacious in treating endometriosis-related pain, however it’s not a targeted treatment. The aim of this work is to evaluate the effects of R-954, a bradykinin antagonista, in a murine model of endometriosis.

**Methods:** Female Swiss Webster mice (25-30g, n=7) were anesthetized with intraperitoneal injection of ketamine/xylazine. The abdomen was opened to expose the uterus. One uterine horn was ligated at both the uterotubal junction and the cervical end and the intermediate segment was removed and split longitudinally. Explants with 5-mm were sectioned and anchored onto the peritoneum. After 35 days the abdomen was opened to confirmation of the ectopic cysts, the animals were divided into groups: R-954 (2 and 5 mg/kg, s.c), progesterone (1 mg/kg, p.o) or vehicle. Mice were treated for 15 consecutive days. At the last day the animals were euthanized and peritoneal fluid and ectopic cyst were collected for total cell count and quantification of pro-inflammatory cytokines. The results are presented as mean±SD and statistical analysis were performed by ANOVA followed by Tukey post-test (\*p<0.05). Protocols for animal use received number 33/19 (CEUA/UFRJ).

**Results:** Histological analysis showed that implants presented a simple columnar epithelium associated to an extensive and abundantly vascularized and a significant cellular infiltrate. Treatment with progesterone or both doses of R-954 significantly reduced the cell infiltrate in peritoneum cavity, in 60% (5.4±1.7\* x 103 cells/µL), 67% (4.4±1.8\* x 103 cells/µL) and 71% (3.9±0.7\* x 103 cells/µL), respectively, when compared to the vehicle-treated group (13.6±5.5 x 103 cells/µL). Both doses of R-954 reduced the levels of TNF-α and IL-6 in peritoneal fluid and ectopic cyst. In ectopic cyst while 2 and 5 mg/kg of R-954 reduced in 48% (6.3±1.6\*pg/µg of protein) and 79% (2.5±1.4\*pg/µg of protein), respectively, when compared to vehicle-treated group (12.0±6.3 pg/µg of protein) progesterone did not demonstrate any effect. IL-6 levels were reduced in 75% (2.8±1.8\* pg/µg) to progesterone and 78% (2.0±0.7\*pg/µg of protein) and 85% (1.3±0.9\*pg/µg of protein) to 2 and 5 mg/kg of R-954, respectively, when compared to vehicle-treated group (9±4.2 pg/µg of protein). In the peritoneal fluid, progesterone did not reduce the production of TNF-α, while 2 and 5 mg/kg of R-954 decreased in 68% (222.1±129.7\*pg/mL) and 80% (134.7±39.5\*pg/mL), when compared to vehicle-treated group (686.8±167.7 pg/mL). The cytokine IL-6 was also reduced in 77% (33.4±18.6\* pg/mL) to progesterone and 75% (36.3±13\* pg/mL) and 52% (70.1±44.1\* pg/mL) to 2 and 5 mg/kg of R-954, respectively, when compared to vehicle-treated group (146.8±53.3 pg/mL).

**Conclusions:** Our results indicate that R-954 presents a significant effect reducing the inflammatory status of murine endometriosis suggesting it as a promising compound to further studies as a new substance to be used in treatment of endometriosis.

**Keywords:** Endometriosis, R-954, Inflammation

**Financial support:** CAPES, CNPq and FAPERJ.

**Donation of animals:** Instituto Vital Brazil (Niteroi, Brazil)

**Technical support:** Alan Minho