

## Dose-dependent Effect of Oxytocin on 5-Fluorouracil-induced Intestinal Mucositis in Rats

Ugochukwu CHUKWUNYERE <sup>1\*</sup>, Ahmet Özer SEHIRLI <sup>2</sup>, Serkan SAYINER <sup>3</sup>, Deniz CEYLANLI <sup>3</sup>, Merve MERCAN <sup>1</sup>, Şule ÇETINEL <sup>4</sup>, İhsan ÇALIŞ <sup>5</sup> & Nurettin ABACIOĞLU <sup>1</sup>

<sup>1</sup> Department of Pharmacology, Faculty of Pharmacy, Near East University, 99138 Nicosia, Turkish Republic of Northern Cyprus

<sup>2</sup> Department of Pharmacology, Faculty of Dentistry, Near East University, 99138 Nicosia, Turkish Republic of Northern Cyprus

<sup>3</sup> Department of Biochemistry, Faculty of Veterinary Medicine, Near East University, 99138 Nicosia, Turkish Republic of Northern Cyprus

<sup>4</sup> Department of Histology and Embryology, School of Medicine, Marmara University, 34722 Istanbul, Turkey.

<sup>5</sup> Department of Pharmacognosy, Faculty of Pharmacy, Near East University, 99138 Nicosia, Turkish Republic of Northern Cyprus

**SUMMARY.** The aim of this study was to investigate the cytoprotective effect of different doses of oxytocin (OT) and the underlying mechanisms of OT in the 5-FU model of intestinal mucositis. Twelve-week-old female albino Wistar rats were divided into five groups of six (n = 6) rats each (Control, OT 0.5 mg/kg, 5-FU+saline, 5-FU+OT 0.5 mg/kg, and 5-FU+OT 1 mg/kg). Mucositis was induced by a single intraperitoneal injection of 5-FU (400 mg/kg) on day 1, followed by four days of treatment with saline or intraperitoneal OT 0.5 or 1 mg/kg. OT reduced the severity of intestinal tissue damage by significantly ( $p < 0.05-0.0001$ ) decreasing the 5-FU-induced increase in serum levels of malondialdehyde (MDA), tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1-beta (IL-1 $\beta$ ), and matrix metalloproteinases (MMP-1, -2, -8) compared to the saline-treated 5-FU group. OT treatment especially the high dose (1 mg/kg oxytocin) significantly ( $p < 0.01-0.001$ ) decreased the 5-FU-induced increase in alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) and also increased tissue inhibitor of metalloproteinases (TIMP)-1 expression in the serum. The results suggest that oxytocin prevents damage to intestinal tissues caused by 5-fluorouracil.

**RESUMEN.** El objetivo de este estudio fue investigar el efecto citoprotector de diferentes dosis de oxitocina (OT) y los mecanismos subyacentes de OT en el modelo 5-FU de mucositis intestinal. Se dividieron ratas Wistar albinas hembra de doce semanas de edad en cinco grupos de seis (n = 6) ratas cada uno (control, OT 0,5 mg/kg, 5-FU+solución salina, 5-FU+OT 0,5 mg/kg y 5-FU+OT 1 mg/kg). La mucositis se indujo mediante una sola inyección intraperitoneal de 5-FU (400 mg/kg) el día 1, seguida de cuatro días de tratamiento con solución salina por sonda oral u OT intraperitoneal 0,5 o 1 mg/kg. La OT redujo significativamente ( $p < 0.05-0.0001$ ) la gravedad del daño tisular intestinal al disminuir el aumento inducido por 5-FU en los niveles séricos de malondialdehído (MDA), factor de necrosis tumoral alfa (TNF- $\alpha$ ), interleucina-1-beta (IL-1 $\beta$ ) y metaloproteinasas de matriz (MMP-1, -2, -8) en comparación con el grupo de 5-FU tratado con solución salina. El tratamiento con TO, especialmente la dosis alta (1 mg/kg de oxitocina), disminuyó significativamente ( $p < 0,01-0,001$ ) el aumento inducido por 5-FU de la fosfatasa alcalina (ALP) y la lactato deshidrogenasa (LDH) y también aumentó el inhibidor tisular de la expresión de las metaloproteinasas (TIMP)-1 en el suero. Los resultados sugieren que la oxitocina previene el daño a los tejidos intestinales causado por el 5-fluorouracilo.

**KEY WORDS:** cytokine, cytotoxic chemotherapy, 5-fluorouracil, mucositis, oxytocin.

\* Author to whom correspondence should be addressed. E-mail: ugochukwu.chukwunyere@neu.edu.tr