The novel CGRP receptor antagonist BIBN4096BS alleviates a postoperative intestinal inflammation and prevents postoperative ileus.

Abdominal surgery results in neuronal mediator release and subsequent acute intestinal hypomotility. This phase is followed by a longer lasting inflammatory phase resulting in postoperative ileus (POI). Calcitonin gene-related peptide (CGRP) has been shown to induce motility disturbances and in addition may be a candidate mediator to elicit neurogenic inflammation. We hypothesized that CGRP contributes to intestinal inflammation and POI. The effect of CGRP in POI was tested in mice treated with the highly specific CGRP receptor antagonist BIBN4096BS and in CGRP receptor-deficient (RAMP-1(-/-)) mice. POI severity was analyzed by cytokine expression, muscular inflammation and gastrointestinal (GI) transit. Peritoneal and muscularis macrophages and mast cells were analyzed for CGRP receptor expression and functional response to CGRP stimulation. Intestinal manipulation (IM) resulted in CGRP release from myenteric nerves, and a concurrent increased interleukin (IL)-6 and IL-1β transcription and leukocyte infiltration in the muscularis externa and increased GI transit time. CGRP potentiates IM-induced cytokine transcription within the muscularis externa and peritoneal macrophages. BIBN4096BS reduced cytokine levels and leukocyte infiltration and normalized GI transit. RAMP1(-/-)
mice showed a significantly reduced leukocyte influx. CGRP receptor was expressed in muscularis and peritoneal macrophages but not mast cells. CGRP mediated macrophage activation but failed to induce mast cell degranulation and cytokine expression. CGRP is immediately released during abdominal surgery and induces a neurogenic inflammation via activation of abdominal macrophages. BIBN4096BS prevented IM-induced inflammation and restored GI motility. These findings suggest that CGRP receptor antagonism could be instrumental in the prevention of POI.