Calcitonin and glucocorticoids – a novel approach to anti-inflammatory co-therapy

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Rheumatoid arthritis (RA) is a common autoimmune disease (1% prevalence; 3:1 women to men ratio) characterised by chronic progressive joint destruction and pain, and accompanied by extra-articular manifestations, such as lung fibrosis. Glucocorticoids (GCs) are the most powerful anti-inflammatory agents that we possess, and play an important role the treatment of chronic inflammatory diseases, including RA, yet their associated catalogue of profoundly adverse effects renders prolonged prescription problematic. GCs enhance osteoclastogenesis, resulting in increased bone resorption and ultimately GC-induced osteoporosis. Calcitonin (CT), on the other hand, attenuates bone resorption. Here we investigate the co-therapeutic synergy elicited through the combined administration of sub-therapeutic GCs and CT in rat collagen-induced arthritis, a model of RA.

Rats (female Lewis, 150-170 g body weight) were immunised with bovine collagen-II and Freund’s complete adjuvant by intradermal injection on day 0. Clinical manifestations of the collagen-induced arthritis (CIA) reaction were evident from day 11, and peaked at day 18. Daily drug treatments of glucocorticoid and calcitonin were given between days 11 and 18 by intraperitoneal injection. Body weight, paw volume and clinical score were recorded for each hind paw at the start of the experiment and throughout the CIA reaction phase, after which hind paws and plasma samples were taken for biochemical analyses of cytokines and bone resorption markers.

The rat CIA reaction is highly steroid sensitive. Glucocorticoid treatment (30 µg/kg i.p.) reduces paw swelling and clinical scores by around 80% (n=25, P<0.01), but the dose response to the glucocorticoid shows a sudden cessation of efficacy at 3-10 µg/kg. Calcitonin (1.0 µg/kg i.p.) did not affect or slightly augmented the CIA response when given alone; however, in combination with a sub-therapeutic GC dose (7.5µg/kg), yielded attenuations in paw oedema and clinical score comparable to those achieved by the four-fold higher, therapeutic dose. The co-therapy also impacted upon biochemical markers, with attenuations of bone resorption marker CTX-I in plasma (≥50% reduction; n=7 P<0.05), and neutrophil chemoattractant CXCL5 in paw extracts (~40% reduction; n=7 P<0.05).

Steroid dose reduction made possible by the anti-inflammatory synergy, together with the osteoprotective property of calcitonin, affords us a promising new outlook for the management of steroid-sensitive chronic inflammatory diseases.

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