Evaluation of a Microparticle-based Intra-articular Controlled Release System in the Rat Temporomandibular Joint

Paschalia M. Mountziaris[1], Phillip R. Kramer[2], Antonios G. Mikos[1]
[1]Department of Bioengineering, Rice University, Houston, TX, USA.
[2]Department of Biomedical Sciences, Texas A&M Health Science Center, Baylor College of Dentistry, Dallas, TX, USA.

Statement of Purpose: Temporomandibular joint (TMJ) disorders are a heterogeneous group of diseases that cause painful, progressive joint degeneration. Effective pain reduction and restoration of TMJ function remain unmet challenges. Intra-articular injections of corticosteroids and hyaluronic acid are currently used to treat pain, but are complicated by rapid clearance of injected agents, so that frequent injections are needed, increasing the risk of iatrogenic injury. Although microcarrier-based and other sustained release systems exist for various applications, to our knowledge, intra-articular controlled release systems for the TMJ have not yet been developed [1]. In this work, we report the *in vivo* biocompatibility of poly(DL-lactic-*co*-glycolic acid) (PLGA)-based microparticles for intra-articular sustained release in the rat TMJ.

Methods: Microparticles (MPs) consisting of a physical blend of 5% w/w poly(ethylene glycol) (PEG; nominal MW=4600; Aldrich, Milwaukee, WI) in PLGA 50:50 (M_n=42500 ±1600 and polydispersity index = 1.53±0.03 by gel permeation chromatography; Lakeshore Biomaterials, Birmingham, AL) were synthesized using an established ((water-oil)-water) solvent extraction technique [2]. Average MP diameter was 23 ± 2 μm, measured by a morphometric analysis (n=250 MPs). PLGA MPs were selected based on their successful intra-articular application in rodent knees [1]. 25 healthy male Sprague-Dawley rats (250-300g) were used; 22 received bilateral 50 μL intra-articular TMJ injections, consisting of 0 ("Tween"; n=8), 15 ("Low"; n=5), 30 ("Medium"; n=4), or 50 ("High"; n=5) mg of PLGA MPs per mL of 10% v/v Tween 80 (Sigma, St. Louis, MO) in normal saline. Control rats (n=3) had no injections. All rats were kept in sound-attenuated cages equipped with photobeam computer-activated pellet feeders [1,3]. When a rat consumed a 45 mg pellet (Bioserv, Frenchtown, NJ), an infrared beam signaled the computer to record the event and dispense a new pellet; over time, this created a record of meal pattern. Longer meal duration is a specific marker of TMJ pain [3], and is thus a promising non-invasive tool for evaluating novel TMJ therapeutics. Rats were kept in the feeder modules for 2 days prior to injection (for acclimatization), and then for 2-7 days afterwards. Rats from each group were euthanized on post-injection days 2 and 7; fixed, frozen 25 μm-thick sagittal TMJ sections were stained with hematoxylin and eosin (H&E), and light microscopy was used to determine tissue response and MP location.

Results: Excellent *in vivo* biocompatibility was observed for all groups on both post-injection days 2 and 7, with no inflammation or other tissue reaction; microparticles were primarily embedded within the synovial tissue of the superior joint space, adjacent to the TMJ vasculature. After injection, there was no decreasing trend in food intake (Fig. 1, top) compared to baseline, nor was there any increase in meal duration (Fig. 1, bottom), indicating that neither the carrier solution nor the PLGA MP-based drug delivery system impair TMJ function.

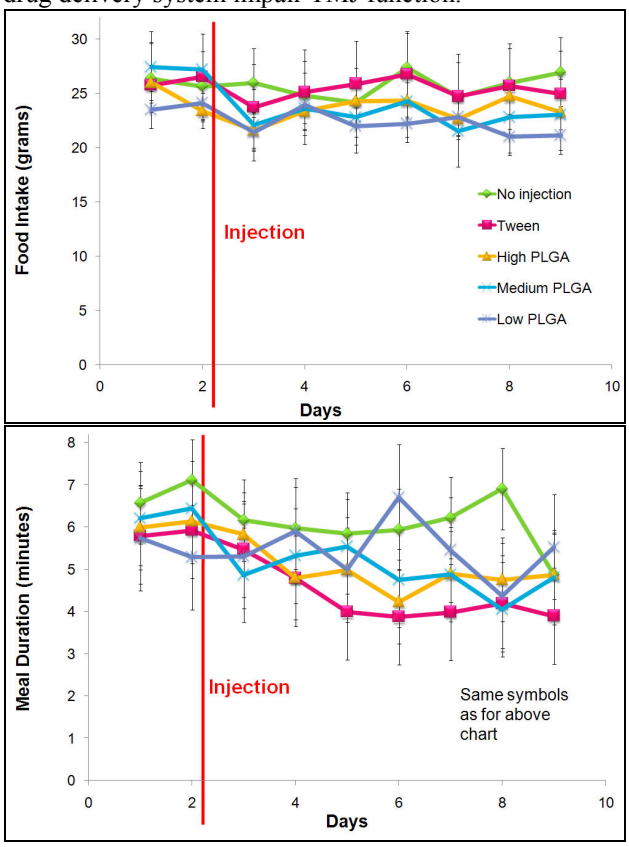

Figure 1. Food intake (top) and meal duration (bottom) before and after intra-articular TMJ injection of PLGA MPs. Groups are shown as defined in the Methods. Data represented as mean values ± standard deviation (n=3-8) as specified for each group in the Methods.

Conclusions: The carrier solution and PLGA MPs described herein are biocompatible, and intra-articular delivery does not impact healthy rat TMJ function. This underscores the exciting potential of these formulations as the basis for the first intra-articular controlled release system for the TMJ. Future studies will characterize both empty and drug-loaded MPs in models of TMJ disorders, with the potential to greatly improve TMJ therapeutics.

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