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FK866 an inhibitor of the pro-inflammatory cytokine visfatin attenuates pain and inflammation in a rodent model of acute inflammation and obesity

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Introduction: Nicotinamide phosphoribosyltransferase (Nampt)-derived nicotinamide adenine dinucleotide (NAD+) promotes inflammation by sustaining immune cell viability and promoting cytokine production.[1] Pharmacological inhibition of Nampt blocks activity of the pro-inflammatory cytokine visfatin, which has also been linked to inflammatory conditions such as pain and obesity.[2,3,4] The aim of this study was to determine whether treatment with the visfatin inhibitor, FK866, has any anti-inflammatory and/or analgesic effects in normal and obese rats.

Method: The effect of intraperitoneal (i.p.) injection of FK866 (3, 10 mg/kg) or vehicle on carrageenan (3%)-induced thermal and mechanical hyperalgesia and paw oedema was measured in: 1) adult male Wistar rats (n = 6-8/group) fed a normal diet (2.9% of fat), and 2) adult male Wistar rats (n = 6/group) fed a high fat diet (HFD; 22% fat) for 12 weeks (an established model of obesity).

Results: Carrageenan induced significant thermal and mechanical hyperalgesia and paw oedema in the injected paw in vehicle treated animals. Pre-administration of FK866 (10 mg/kg) significantly attenuated thermal and mechanical hyperalgesia at 6 hours ($P < 0.05$ vs. vehicle) and reduced paw oedema ($P < 0.05$ vs. vehicle). Obese rats displayed potentiated mechanical and thermal hyperalgesia, and paw oedema (all $P < 0.05$) compared to rats fed a normal diet. Pre-administration of FK866 (10 mg/kg) to obese rats significantly attenuated mechanical hyperalgesia, and paw oedema (both $P < 0.05$ vs. HFD + vehicle group), restoring potentiated responses to normal levels ($p > 0.05$ vs. rats fed a normal diet + vehicle).

Conclusion: These data show that FK866 has powerful anti-inflammatory and analgesic properties at higher dose, suggesting that visfatin plays a crucial role in inflammatory pain. The potentiated response to pain and inflammation obsedved in obese rats fits well with the hypothesis that obesity is a chronic low-grade inflammatory disorder. The reversal of this effect by blocking visfatin indicates a key role for this cytokine in pain pathogenesis with obesity.

References:

1. Montecucco F et al. (2013). *Antioxidants & redox signaling* **18.6**: 630-641.

2. Busso N et al. (2008). *PloS one* **3.5**: e2267

3. Revollo JR et al. (2007). *Current opinion in gastroenterology* **23.2**: 164-170 4. Sethi, J et al. (2005). *Trends in molecular medicine,* **11(8)**: 44-347.