Published in final edited form as:

Brain Behav Immun. 2018 November ; 74: 45–46. doi:10.1016/j.bbi.2018.08.012.

High-fat diet and post-operative pain: why the hospital cafeteria may matter

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Keywords

pain; obesity; inflammation; postoperative pain; high-fat diet

Obesity, an increasing problem globally, is well known to be associated with conditions such as diabetes, cardiovascular disease, and cancer. Less often appreciated is its association with chronic pain conditions, which have higher incidence and severity in obese subjects (Okifuji and Hare, 2015). This has been examined in rodent models of neuropathic and inflammatory pain, using genetic and diet-induced obesity models. However, few preclinical studies have examined effects of obesity on postoperative pain, which is distinct from inflammatory and neuropathic pain (Brennan, 2011). Postoperative pain is clinically interesting in light of the large number of surgeries performed each year, and the relatively high incidence of postoperative pain becoming chronic.

The new study by Guillemot-Legris et al. (Guillemot-Legris et al., 2018) is an interesting addition to this field. They examined the effects of a high-fat diet on a postoperative pain model in mice. High-fat diets, an established method for studying diet-induced obesity in rodents, reproduce many of the metabolic changes seen in human obesity, including increased weight and percent body fat, and impaired glucose handling (but not frank diabetes). They used the paw-incision model of postoperative pain, in which the hind paw skin and muscle are incised and sutured. This leads to paw hypersensitivity to mechanical and thermal stimuli, and increased spontaneous pain, both also observed in human surgery patients (Brennan, 2011). Normally these pain behaviors resolve over 1–2 weeks in this model. However, in mice maintained on a high-fat diet, Guillemot-Legris et al. observed a dramatic prolongation of mechanical hypersensitivity. Mice fed normal low-fat chow recovered to normal baseline mechanical sensitivity by 15 days, while the high-fat diet mice showed no signs of recovery for at least 23 weeks.

These findings were qualitatively similar to those observed in a rat study using the same pain model (Song et al., 2018) in which a high-fat diet prolonged pain, albeit by ~12 days rather

The author declares no competing interests.

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than months. This difference may reflect the shorter duration and lower fat content of the diet exposure used in the rat study. It should also be noted that the mechanical sensitivity in both studies reached a near floor value even in the animals fed low-fat chow, which made it difficult to observe a further increase induced by the high-fat diets. Hence in applying these studies to human patients, the difference between prolongation of pain and increased severity of pain may be somewhat arbitrary. In two inflammatory pain models in which it was possible to “tone down” the pain model by reducing doses of the inflaming agents, marked increases in pain severity could be induced by high-fat diet exposure (Song et al., 2017). However, it is more difficult to “tone down” the paw incision model.

In another rat study using the paw incision model, caloric restriction further reduced the magnitude of mechanical hypersensitivity compared to normal low-fat chow feeding (Liu et al., 2017), complementing the findings of the high-fat diet studies.

In humans, obesity can prolong wound healing (Pierpont et al., 2014), but Guillemot-Legris et al. found that this did not account for the marked prolongation of pain behaviors. Instead, they provide evidence for mechanisms related to inflammation. Obesity entails chronic low-grade inflammation (Lumeng, 2013). Consistent with this, Guillemot-Legris et al. observed that high-fat diet, alone or in combination with paw excision, led to increases in mRNA in sciatic nerve and/or spinal cord for pro-inflammatory cytokines such as interleukin-1 β , tumor necrosis factor α , and monocyte chemoattractant protein 1, as well as some pro-analgesic neurotrophins and markers of endoplasmic reticulum stress. Some of these agents have been previously implicated as possible mediators of obesity’s effects. An interesting result from the study is that the gene expression profiles were also obtained in brain stem and in the excised paw, where, for the most part, these pro-inflammatory mediators were less affected by diet or paw incision. Conversely, incubation of isolated sciatic nerve with low doses of lipopolysaccharide could mimic some of these changes in gene expression of pro-inflammatory mediators. Lipopolysaccharide is not used merely as an experimental mimic of inflammation, rather, it has been proposed as one of the mediators by which obesity induces low-grade inflammation (Saad et al., 2016).

Overall, the findings in this study suggest it may be worthwhile to examine mechanisms acting locally in the peripheral nervous system or spinal cord, rather than focusing only on systemic metabolic variables, in order to understand how obesity increases pain.

Finally, Guillemot-Legris et al. examined the effects of switching mice from the high-fat diet back to the low-fat chow, either at the time of paw incision, or 10 weeks later. In both cases the mechanical hypersensitivity was reversed; in the latter experiment, they also demonstrated reversal of many of the pro-inflammatory changes in gene expression. Importantly, the time course of the pain behaviors did not directly track the observed weight loss, but rather lagged behind. In the abovementioned rat study, rapid effects of short-term diet change on paw-incision pain could also be observed (Song et al., 2018).

More generally, preclinical studies show some dissociation between effects of diet per se on pain vs. effects of obesity on pain (e.g., (Song et al., 2017; Totsch et al., 2016)). This has important implications for clinical practice and clinical research. Losing weight is

notoriously difficult, and surgeries are not always planned far ahead of time, so it is encouraging to think that even changing the diet at the time of surgery will mitigate some of the negative effects of obesity on post-operative pain. Many studies in humans show positive effects of particular diet changes (including altering the type of fat consumed) on chronic pain conditions such as arthritis. Effecting short-term changes to patients' perioperative diet, in the controlled environment of the hospital, may be even more feasible and deserves attention from clinical nutrition researchers.

Finally, many clinical studies of obesity use body weight or body mass index as the primary variable indicating obesity, but these preclinical studies suggest that the far messier task of ascertaining short and long-term dietary intake may also be necessary.

Acknowledgements:

supported in part by NIH grants NS045594, NS055860 and AR068989 to Jun-Ming Zhang.

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