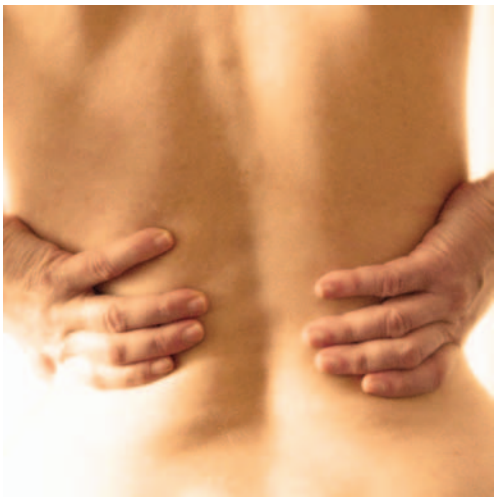
Back Pain and the Mineralocorticoid Receptor

Is There a Connection?

WHEN the key words "back pain" and "steroid" are encountered together, we implicitly picture an epidural steroid injection utilizing a glucocorticoid with or without a local anesthetic. The use of glucocorticoids as a therapeutic intervention to reduce painful radicular symptoms (presumably through a reduction of inflammation) remains an overwhelming cornerstone of interventional pain practices the world over. However, the efficacy of such interventions has not met expectations despite improved insight on patient selection and emerging consensus on image-guided delivery.

What accounts for such divergent and often lackluster outcomes in the use of glucocorticoids in the treatment of back pain? If we dispense with the notion that such shortcomings are due to a failure of patient selection, therapeutic timing, quality or utilization of imaging, we are faced with the daunting realization that there is something fundamentally askew with our understanding of the action of spinal/epidural glucocorticoids. Perhaps there are additional spinal-ganglionic steroid-receptor pathways that confound the resolution of injury-induced neuroinflammation and pain. In fact, it often appears as if such inflammation-driven pain is resistant to glucocorticoid therapy. How could this be?



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The study by Dong *et al.*[1] in the laboratory of *JM Zhang*, featured in this issue challenges the way we think mechanistically about inflammatory back pain and perhaps one day its management. Dong *et al.* elegantly demonstrate that the selective mineralocorticoid receptor (MR) antagonist—eplerenone—can prevent the development of behavior measures of mechanical hyperalgesia and allodynia after experimentally induced local inflammation of the L5 dorsal root ganglion (DRG). They convincingly demonstrate that prevention of pain behaviors with eplerenone correlate with suppression of the inflammation-induced hyperexcitability of DRG neurons *ex vivo* and *in vitro.* One may ask how blockade of the MR—a nuclear steroid receptor best known for its activation by aldosterone in the distal nephron—may be considered a plausible candidate for the treatment of neuraxial inflammatory pain.

The MR and Nociception

Because little is currently known about the relationship of the MR in the pain pathway, questions far outnumber answers. Nevertheless, examining the action of aldosterone on the MR in nonneuronal target tissues is a logical starting point. On the basis of this literature, one of the overarching themes distinguishing steroid receptor activation or inhibition is the regulation of gene expression through modification of RNA transcription.[2] Although *nongenomic* actions of MR have been described, which are independent of gene transcription,[2,3] which occur in a time frame of less than 15 min, the report by Dong *et al.*[1] best supports a genomic–transcription-based mechanism of action. Therefore, steroid hormones, such as aldosterone have as their predominant action, the ability to bind to steroid receptors in the cytosol and through their binding initiate receptor activation translocation into the nucleus. In what has become known as the classic genomic model, the activated MR subsequently binds to specific upstream genomic

◆ This Editorial View accompanies the following article: Dong F, Xie W, Strong JA, Zhang J-M: Mineralocorticoid receptor blocker eplerenone reduces pain behaviors *in vivo* and decreases excitability in small diameter sensory neurons from local inflamed dorsal root ganglia *in vitro*. ANESTHESIOLOGY 2012; 117:1102–12.

Image: J. P. Rathmell.

Accepted for publication August 20, 2012. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

 Anesthesiology 2012; 117:951–2

transcriptional regulatory sites of target genes to either activate or repress RNA gene transcription. The consequence of such a genomic model implies receptor-mediated changes in gene expression initiated approximately 30-60 min after receptor activation that can persist for days, weeks, or even months. In the example of aldosterone binding to MRs expressed in the epithelial of the distal nephron, the consequence of transcriptional activation of the target genes is to enhance reabsorption of sodium and the secretion of potassium. These physiologic endpoints are achieved by transcription-dependent changes in activity and/or abundance of luminal sodium channels (ENaC), potassium channels, and serosal Na^+/K^+ adenosine triphosphatase. If such a genomic model of MR activation exists in the sensory neurons of DRG in response to inflammation, acute inflammatory events may have long-term consequences.

Building on this genomic model, Dong *et al.* used Zymosan-A, a preparation of protein–carbohydrate complexes derived from yeast cell walls to induce local inflammation in the L5 DRG.[1,4] Subsequently, the authors observed a decrease in mechanical thresholds and rearing behavior as well as a concomitant increase in MR nuclear translocations in the neurons of the affected DRG. Importantly, all these endpoints could be reduced or prevented by the concurrent application of the MR receptor antagonist eplerenone over the L5 DRG. Impressively, neurons derived from DRG exposed to *in vivo* inflammation exhibited hyperexcitable physiology that could be partially reversed *in vitro* by eplerenone.[1] Taken together, these findings support the hypothesis that inflammation-induced activation of MR receptors expressed in DRG neurons help drive the development and persistence of inflammatory neuraxial pain. This is plausible on several accounts because its principle agonist, aldosterone, is proinflammatory and provokes fibrosis in the cardiovascular system.[5] In contrast, MR receptor antagonists such as spironolactone have been shown to block the deleterious effects of aldosterone and MR activation.[6] Moreover, because MRs typically regulate genes critical for electrochemical potential gradients and ion-channel function in epithelium, they may indeed modulate nociceptive ion-channel expression in sensory neurons. This may be an especially enticing direction of investigation, given that aldosterone has been reported to activate many of the same pathways known to positively modulate and/or activate members of the transient potential receptor ion-channel family such as the capsaicin receptor–TRPV1.[7]

One of the more provocative considerations arising from this study[1] is whether the spinal action of glucocorticoids either through exogenous administration or by endogenous release inadvertently drives inflammation and nociception through the activation of the sensory neuronal MR. Although cortisol and aldosterone have similar binding affinities to the MR, cortisol is much more abundant than aldosterone in the circulation, raising the issue of why MRs are not chronically activated. One explanation is dependent on the coexpression of 11-β hydroxysteroid dehydrogenase type 2, an enzyme that converts cortisol to an inactive form (cortisone) that is unable to bind the MR.[8] Although such studies have provided some justification for a differential steroid effect, by limiting cortisol's action on the MR, they do not fully explain the apparent selective activation by aldosterone in other tissues where 11-β hydroxysteroid dehydrogenase type 2 may be lacking. Given the potential conflict between glucocorticoid and mineralocorticoid receptor activation, would the combination of a glucocorticoid plus an MR antagonist (eplerenone) in neuraxial models of inflammation provide a therapeutic benefit? In fact, such an approach utilizing a combination of dexamethasone plus spironolactone in a chronic compression model of DRG was reported to direct a dose-dependent suppression of mechanical allodynia and thermal hyperalgesia.[9]

As this field moves forward, the use of genetically modified mice containing a deletion/modification of the MR in experimental models of pain will help clarify the extent of MR's role across a spectrum of neuraxial models of pain. Beyond raising the exciting possibility of an improved therapeutic strategy in the treatment of back pain, this study also has highlighted the importance of better understanding MRs in the initiation and maintenance of inflammatory pain.

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References

1. Dong F, Xie W, Strong JA, Zhang J-M: Mineralocorticoid receptor blocker eplerenone reduces pain behaviors *in vivo* and decreases excitability in small diameter sensory neurons from local inflamed dorsal root ganglia *in vitro*. ANESTHESIOLOGY 2012; 117:1102–12
2. Booth RE, Johnson JP, Stockand JD: Aldosterone. Adv Physiol Educ 2002; 26:8–20
3. Karst H, Berger S, Turiault M, Tronche F, Schütz G, Joëls M: Mineralocorticoid receptors are indispensable for nongenomic modulation of hippocampal glutamate transmission by corticosterone. Proc Natl Acad Sci USA 2005; 102:19204–7
4. Xie WR, Deng H, Li H, Bowen TL, Strong JA, Zhang JM: Robust increase of cutaneous sensitivity, cytokine production and sympathetic sprouting in rats with localized inflammatory irritation of the spinal ganglia. Neuroscience 2006; 142:809–22
5. Rickard AJ, Young MJ: Corticosteroid receptors, macrophages and cardiovascular disease. J Mol Endocrinol 2009; 42:449–59
6. Rogerson FM, Yao Y, Smith BJ, Fuller PJ: Differences in the determinants of eplerenone, spironolactone and aldosterone binding to the mineralocorticoid receptor. Clin Exp Pharmacol Physiol 2004; 31:704–9
7. Schumacher MA: Transient receptor potential channels in pain and inflammation: Therapeutic opportunities. Pain Pract 2010; 10:185–200
8. Funder JW, Pearce PT, Smith R, Smith AI: Mineralocorticoid action: Target tissue specificity is enzyme, not receptor, mediated. Science 1988; 242:583–5
9. Gu X, Peng L, Yang D, Ma Q, Zheng Y, Liu C, Zhu B, Song L, Sun X, Ma Z: The respective and interaction effects of spinal GRs and MRs on radicular pain induced by chronic compression of the dorsal root ganglion in the rat. Brain Res 2011; 1396:88–95