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ADX-102, a novel aldehyde trap, reduces nociceptive behavior in mouse models of carrageenan and CFA induced pain

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A variety of aldehyde species have been shown to activate ion channels, such as TRPA1 and TRPV1, involved in mediating pain. Furthermore, aldehyde dehydrogenase 2 which diminishes aldehyde loads by oxidizing aldehydes to acids has been shown to modulate acute inflammatory pain in animal models. Thus, aldehyde signaling represents a novel therapeutic target for the treatment of pain. ADX-102 is a novel small molecule that covalently binds aldehydes including malondialdehyde and 4-hydroxynonenal, which have been shown to mediate inflammatory pain. For that reason, the effect of ADX-102 on acute inflammatory pain was tested in the carrageenan-induced and Complete Freund's Adjuvant (CFA)-induced models in mice. ADX-102 was administered intraperitoneally prior to and after pain induction, at different doses and schedules (30 mg/kg twice daily [BID], 100 mg/kg once daily [QD], or 100 mg/kg BID). Thermal hypersensitivity, mechanical hypersensitivity and paw swelling were assessed at various times to explore the effect of modulating aldehyde signaling on different molecular mechanisms underlying pain. Diclofenac was used as a positive control and vehicle was used as a negative control. ADX-102 mediated dose-dependent reductions in nociceptive behavior in both models of acute pain. In the CFA model, treatment with 100 mg/kg QD or 100 mg/kg BID ADX-102 resulted in statistically significant reductions in thermal hypersensitivity, but reduced mechanical hypersensitivity only after treatment with 100 mg/kg ADX-102 BID. In the carrageenan model, ADX-102 treatment resulted in statistically significant reductions in thermal hypersensitivity at ADX-102 doses of 30 mg/kg BID and 100 mg/kg BID, but did not affect mechanical hypersensitivity. Minor effects on paw swelling were observed in both models. The data imply that ADX-102 may differentially affect thermal and mechanical pain pathways. Overall, the results support the role of aldehyde signaling in pain and suggest that aldehyde traps represent a novel approach for the treatment of pain.

Biography

Susan Macdonald received her PhD from the University of Massachusetts Medical School and did Post-doctoral work at Onyx Pharmaceuticals. She has extensive experience in Research and Development in the biopharmaceutical industry and is currently Vice President of Research and Development at Aldeyra Therapeutics, a biotechnology company developing a proprietary family of aldehyde traps, which sequester and allow for the degradation of toxic aldehydes, and thus have broad therapeutic potential. She has published numerous articles and book chapters.

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