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

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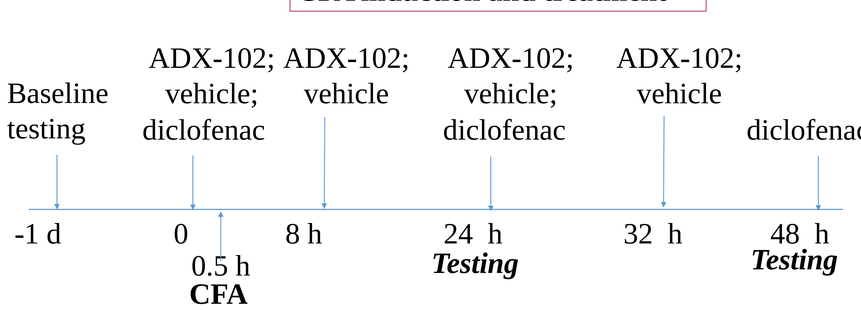
INTRODUCTION

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.

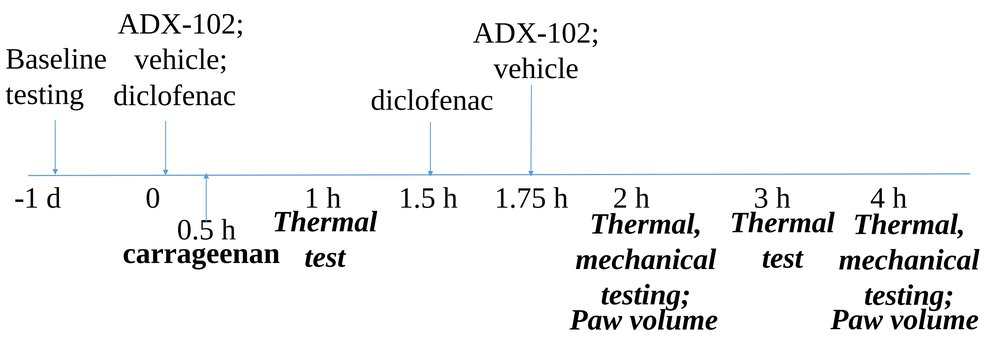
ADX-102 is a novel small molecule that covalently binds aldehydes, including malondialdehyde and 4-hydroxynonenal, which have been shown to mediate inflammatory pain. For that reason, the effect of ADX-102 on acute inflammatory pain was tested in the carrageenan-induced and Complete Freund's Adjuvant (CFA)-induced models in mice.

METHODS

CFA induction and treatment



Carrageenan induction and treatment



SUMMARY/CONCLUSIONS

ADX-102 mediated dose-dependent reductions in nociceptive behavior in both models of acute pain. 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.

RESULTS

In the CFA-induced pain model, treatment with 100 mg/kg QD or 100 mg/kg BID ADX-102 resulted in statistically significant reductions in thermal hypersensitivity as measured by the Hargreave's plantar test (Figure 1). Only the 100 mg/kg BID dose of ADX-102 showed an effect on mechanical sensitivity, as assessed by the Von Frey force test (Figure 2). Paw thickness, a measure of swelling, showed a modest effect at the 30 and 100 mg/kg BID doses (Figure 3).

In the carrageenan-induced pain 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 (Figure 4), but did not affect mechanical hypersensitivity (Figure 5). Paw thickness, a measure of swelling, showed a modest effect at the 100 mg/kg QD dose (Figure 6). There were no changes in body weight as a result of treatment in any group.

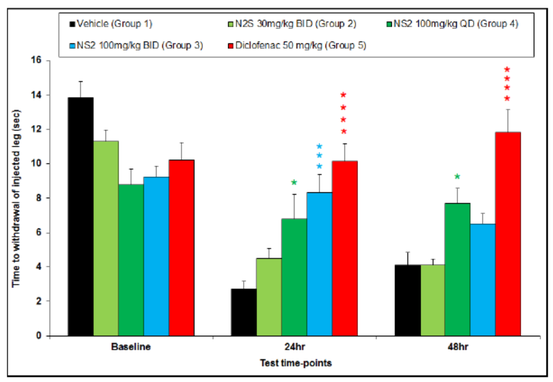


Figure 1: ADX-102 resulted in a dose-dependent reduction in thermal sensitivity in the Hargreave's Plantar Test.

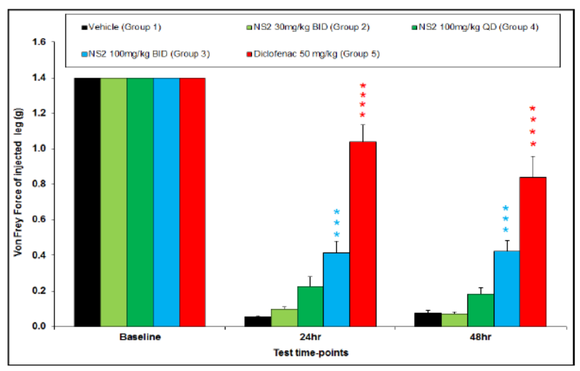


Figure 2: ADX-102 resulted in a significant reduction in to mechanical sensitivity in the Von Frey test at the highest dose tested.

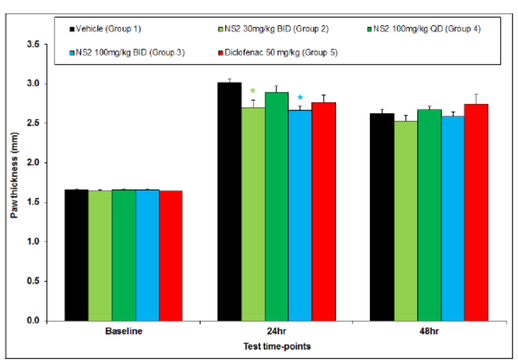


Figure 3: At 24 hours, minor reductions in paw thickness were seen at 2 doses of ADX-102.

* p <0.05 vs. Vehicle using two-way ANOVA followed by Tukey test
**p <0.01 vs. Vehicle using two-way ANOVA followed by Tukey test

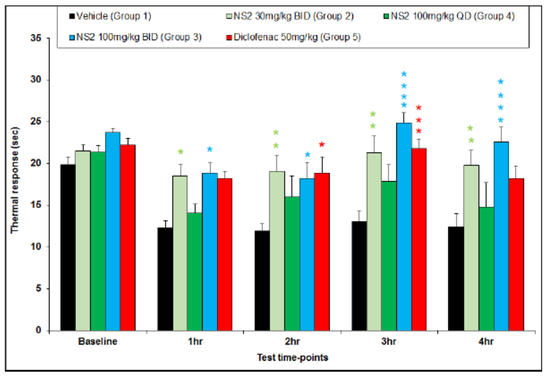


Figure 4: When administered BID, ADX-102 resulted in a dose-dependent reduction in thermal sensitivity.

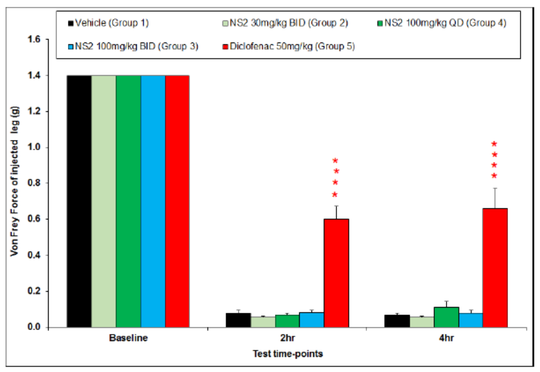


Figure 5: ADX-102 did not reduce sensitivity to a mechanical force in the Von Frey Force test.

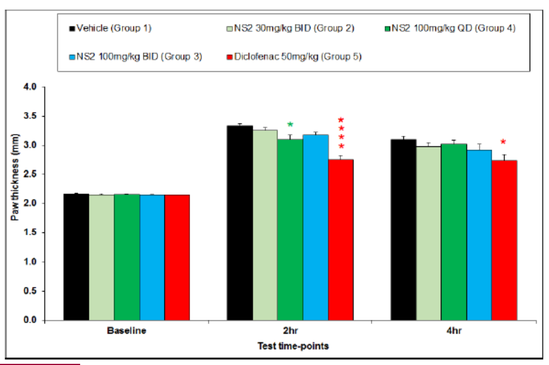


Figure 6: At 24 hours, a minor reduction in paw thickness was seen with the 100 mg/kg QD dose of ADX-102.

***p<0.001 vs. Vehicle using two-way ANOVA followed by Tukey test
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