THE COX-2 INHIBITOR MELOXICAM IMPROVES DELAYED TRANSIENT DEPRESSIVE BEHAVIOR IN ADULT MICE AFTER SPLENECTOMY

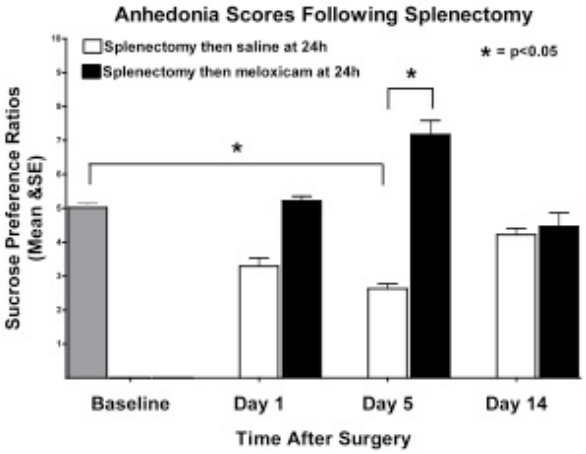
Tanya Stolper, BA; Nemahun Vincent, BA, Jeffrey Chan, BA, Alex Bekker, MD, PhD, Michael Haile, MD
New York University Langone Medical Center, New York, New York

Introduction: Mood disorders are related to both cognitive deficits and inflammation. Previously we found that after splenectomy, adult mice developed a delayed transient neuro-inflammation and concurrent short term memory dysfunction that were both relieved by the NSAID meloxicam (MEL) at 24hrs (1). We tested the hypothesis that anhedonia, the inability to experience pleasure, would present in a similar manner following splenectomy. Anhedonia is a hallmark of depression and the sucrose preference test is a well standardized test for depressive behavior in rodents.

Method: After IACUC approval 20 Swiss Webster male mice (35-45 g, 6-8 wks old) were randomized into 2 groups: 1) splenectomy then i.p. saline (SAL) at 24 hrs & 2) splenectomy then i.p. MEL at 24 hrs. All mice were trained before surgery according to our sucrose preference protocol. Mice were kept singly with tap water freely available from two graduated cylinders. Baseline sucrose preference ratios were then established as the ratio of sucrose to water consumption. Every 4th night for two weeks animals were fluid restricted before being given a choice of either 2% sucrose or water in the morning for two hours. On day 0 splenectomy was carried out under 1.5% isoflurane in 30% O2 / 70% N2 with a 1 cm incision, vessel ligation with 6-0 silk suture, and closure with 4-0 silk. Testing sucrose preference ratios were then established on days 1, 5, and 14.

Results: We used the Kruskal Wallis test to reject the null hypothesis that the distributions for baseline, d5 MEL, d5 SAL were equal ($p=0.02$). Then using pair wise tests (2-tailed t-test), we rejected the null hypothesis that d5 MEL = d5 SAL ($p<0.01$), and that baseline = d5 SAL ($p=0.01$). Splenectomy caused anhedonia in a delayed transient manner. Sucrose preference was at baseline on day 1, was present by day 5 and restored to baseline by day 14. MEL prevented anhedonia on day 5.

Conclusion: An inflammatory process along with its resolution and treatment may explain these findings. Splenectomized adult mice developed a time course of depressive behavior ameliorated by meloxicam that was similar to our previous findings for short term memory dysfunction and neuro-inflammation (1). Cytokines trigger and sensitize brain stress circuits that may impair mood related dopaminergic and erotonergic neurotransmission (2). COX-2 therapy was effective in our study at 24 hrs when cytokine release peaks after brain damage in rodents (3). These findings underscore the need for research into the association of mood disorders and delirium in the post-operative period.



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