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Quick and Easy: Time to Integrate To Nest Test for Severity Assessment in a Murine Inflammatory Bowel Disease Model

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Abstract

Due to recent changes in EU regulations (2010/63/EU) as well as the general requirement to assess the condition of experimental laboratory animals, the development of innovative severity assessment strategies is required. In murine inflammatory bowel disease (IBD) models severity assessment is usually performed by clinical scoring, which is time consuming, stressful for the animals, and necessitates an experienced observer. This mini review looks at methods to identify disturbed animal welfare during experimental colitis by investigating changes in spontaneous animal behavior. We give a brief overview of the existing methods of severity assessment utilized in colitis models, focusing on a recently investigated method, the time to integrate to nest test (TINT). In a study investigating the course of colitis in genetically-susceptible and corresponding wild type mice, the suitability of TINT as a parameter of disturbed welfare was determined. TINT enabled the detection of mouse strain-related differences, but not dextran sulphate sodium (DSS) dose-dependent differences in colitis manifestation. Therefore, TINT may serve as an easily applicable indicator of disturbed animal welfare but cannot replace clinical investigation of animals under experimentation. The development of further severity assessment strategies that better mirror the actual condition of animals used in IBD studies is therefore vital.

Keywords: DSS-colitis; Severity assessment; TINT; Bowel disease

Introduction

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammation of the intestine that presumably stems from a genetically-determined abnormal immune response against the normal intestinal flora [1,2]. Animal models of IBD have been widely used to dissect the various factors contributing to the development of inflammation [3,4]. In this context, the dextran sulphate sodium (DSS)-induced colitis model is well established and widely used [5,6]. Here, intestinal inflammation is induced chemically, which allows for a fully controlled onset, duration, and degree of inflammation, thereby reducing variability within experimental groups. Symptoms of DSS-colitis in mice include weight loss and bloody diarrhea, making a daily welfare-assessment obligatory. The implementation and utilization of non-invasive imaging technologies, especially MRI, has proven to be beneficial as a refinement strategy that further defines the condition of individual animals [7]. However, there is a high demand for easily applicable methods of severity assessment to be utilized in colitis models. Directive 2010/63/EU on the protection of animals used for scientific purposes requires exact severity assessment for all procedures undertaken on laboratory animals. However, quantifiable parameters for the classification of severity into the postulated categories are still lacking. Severity assessment in laboratory animals is a complex issue and requires the recognition of pain and stress using a combination of clinical and physiological measurements. An important parameter is the assessment of animal behavior. For example, pain avoidance behavior, changes in spontaneous behavior, or decreased activity can be detected by an experienced researcher who is able to interpret whether these observations are stress- or pain-specific [8,9]. In mouse colitis models it is common to utilize a clinical disease activity score for severity assessment [10,11]. However, clinical investigation of each individual mouse is time consuming. Handling of the animal is obligatory and causes additional stress to the animal. The time to integrate to nest test (TINT) is a suitable method to detect disturbed animal welfare during the development of intestinal inflammation and during which handling of the animal is not necessary. This easily-performed test is based on the strong instinct mice have to nest and detects disturbed animal welfare that results from painful surgical procedures [12,13]. Nest building is a species-specific behavior in mice as it provides shelter from conspecifics, predators, or direct light and it plays an important role for reproduction and thermoregulation [14,15]. Implementation of TINT under inflammatory conditions in a mouse IBD model presented interesting results. The method was not sensitive enough to detect DSS-dose dependent differences but was able to distinguish strain related differences. Mice which were genetically more susceptible to DSS treatment showed signs of disturbed welfare as determined by clinical observation, weight loss, as well as elevated time intervals for the integration of nesting material as determined by TINT [16].

Burrowing is another spontaneous behavior that can be assigned to nesting behavior and can also be used as an indicator of disturbed animal welfare. Here, the species-typical behavior of mice to spontaneously displace items from tubes within their home cages serves as a parameter to detect welfare disturbance [17]. In an acute DSS-colitis model, decreased burrowing behavior correlated with the onset of intestinal inflammation [18]. Other studies utilizing voluntary wheel running or forced treadmill running merely investigated whether there were possible benefits due to the exercises on the course of intestinal inflammation, but did not utilize these methods to gain information on the welfare of animals [19].

In conclusion, there are only a few studies concerning severity assessment during experimental colitis studies. Although TINT has been shown to be indicative of the well-being of individual animals during a colitis study, to meet the requirements of the Directive 2010/63/EU and to exactly determine the condition of the animals during experimental colitis, further severity assessment strategies are urgently needed.

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