Human Smoking – Animal Passive Smoking: What Do We Learn from It about Inflammatory Bowel Disease?

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There have recently been marked advances in elucidating the genetic factors involved in inflammatory bowel disease (IBD) [1, 2]. At the same time, epidemiological studies have clearly demonstrated a major effect on the part of environmental factors [3, 4]. It is now strongly believed that combinations of distinct genetic backgrounds and environmental elements comprise the main factors in the pathogenesis of IBD [5]. Among the various environmental factors, the most established one is the effect of smoking [6, 7]. Numerous studies, although not all, have clearly demonstrated a protective effect of smoking on ulcerative colitis (UC) and its deleterious effect on Crohn's disease (CD). Thus, current smokers are less likely to develop UC whereas previous smokers are at a higher risk of developing UC than non-smokers, especially during the first years following the cessation of smoking [8–11]. A protective effect of smoking was further demonstrated by the therapeutic effect of nicotine patches to ameliorate disease activity in UC patients [12].

There have been far fewer investigations into the effects of passive smoking on IBD. Sandler et al. [13] reported that passive smoking decreases the risk of UC, while Persson et al. [10] found an increased risk of CD only in individuals exposed to environmental tobacco smoke in childhood. Interestingly, Lashner et al. [14] found a positive association between the passive exposure to smoking around the time of birth in both CD (OR 5.3) and UC (OR 2.1) patients. We have not found any ef-

fect of smoking on IBD adult patients [15]. Nicotine was even tried as a therapeutic approach or as a preventive measurement in UC patients in remission to prevent relapse [16]. Most of the current data demonstrate an association between smoking and IBD based on epidemiologic evidence. Those studies, however, concentrated more on evaluating direct smoking, and so little information exists on the effect of passive smoking, which is more complicated to assess in an epidemiologic study design. Therefore, the data are highly conflicting, unlike those on the effect of direct smoking. In contrast, while it is quite difficult to study the effect of smoking on laboratory animals, it is far more feasible to technically study the effect of 'passive smoking' on them and this is what was checked in the study by Sun et al. [17]. They induced experimental colitis by a well-established model of administering trinitrobenzene sulfonic acid (TNBS) enemas to rats. Passive smoking was induced by exposing the rats to 2 or 4% cigarette smoke-filled air for 1 h during 8 consecutive days. The authors found that exposure to smoking improved the colonic inflammation, as assessed by the enhanced appearance of the colonic mucosa, by the histological inflammation score and by increased myeloperoxidase activity and tissue TNF α levels, which are well-recognized markers of colitis activity. Thus, the effect of smoking on colitis can be demonstrated at all levels, specifically, macroscopically, microscopically and molecularly, including the main inflammatory mediator,

TNF α . Furthermore, they showed [17] that the effect of smoking may be mediated by colonic $\alpha 7$ nicotinic acetylcholine receptor, which was up-regulated by the presence of cigarette smoking.

The mechanism by which smoking affects IBD is unclear. Several studies have suggested nicotine as being the mediator [18]. Indeed, it was shown [12, 16] that nicotine may have a therapeutic effect in UC patients either by means of transdermal nicotine patches or by nicotine enemas. Their study also provides another line of evidence that nicotine has a deleterious effect in TNBS-induced colitis via colonic $\alpha 7$ nicotinic acetylcholine receptors. There are, however, some limitations to the study that need to be considered. The authors used four rat groups: normal non-exposed controls, rats with TNBS-induced colitis, and rats with colitis which were exposed to 2 and 4% cigarette smoke air. This experimental design lacks another crucial control group, that of non-ill rats exposed to passive smoking. Without that group, it is not possible to conclude anything about the effects of cigarette smoke on animals with colitis in comparison to normal animals. Another piece of data that this study fails to provide is the

blood nicotine level of the animals that were exposed to cigarette smoke. The colitis in this study was induced by TNBS, which is an acceptable model of Crohn's colitis (Th1 type) [19]. In the current study by Sun et al. [17], a short duration of TNBS administration for 8 days was used, which is more compatible with acute colitis. In order to induce chronic colitis, up to 8 weeks of treatment would be superior. As expected, in $\alpha 5$ nicotinic acetylcholine receptor knockout mice, Orr Urtegar et al. [18] found in a UC model that they developed more severe experimental colitis than the wild-type mice. Finally, although the study very nicely shows that passive smoking increases inflammation in TNBS-induced colonic colitis, it cannot mimic the 'human model' in which passive smoking occurs during prolonged periods and not for as few as 8 days. In addition, smoking concentration in a realistic setting is not constant nor is it limited to 1 h/day. Moreover, many other environmental factors that can be synergistic or antagonistic play a role in human exposure and they do not exist in animal models. Those limitations notwithstanding, this study adds important information to the mysterious effect of smoking in IBD.

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