Brain Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/bres

Research report

Intestinal worms eating neuropsychiatric disorders? Apparently so

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ARTICLE INFO

Article history:
Received 18 October 2017
Received in revised form 15 January 2018
Accepted 19 January 2018
Available online xxxx

Keywords:
Allergy
Autoimmunity
Biota
Biome
Helminth
Inflammation

ABSTRACT

A number of factors in Western society, including inflammatory diets, sedentary lifestyles, vitamin D deficiency and chronic psychological stress, are known to induce inflammation and to be associated with neuropsychiatric disorders. One factor that is emerging as a potential inflammation inducing factor is biota depletion, or loss of biodiversity from the ecosystem of the human body as a result of industrialization. Originally known as the "hygiene hypothesis", biota alteration theory describes the effects of biota alteration on the human immune system. Work on this topic has pinpointed depletion of helminths as a key loss to the body's ecosystem in Western society, and suggests that some exposure to helminths, ubiquitous prior to the modern era, may be necessary for normal immune system development. Sociomedical studies of humans "self-treating" with helminths as well as limited studies in animal models strongly suggest that helminth therapy may be a productive approach toward treating a range of neuropsychiatric disorders, including chronic fatigue, migraine headaches, depression and anxiety disorders. However, helminth therapy faces some daunting hurdles, including the lack of a financial incentive for development, despite a tremendous potential market for the organisms. It is argued that benevolent donation for early trials as well as changes in regulatory policy to accommodate helminth therapy may be important for the field to develop. It is hoped that future success with some high-profile trials can propel the field, now dominated more by self-treatment than by clinical trials, forward into the main stream of medicine.

1. Introduction

The factors associated with Western society that lead to inflammation have been of interest for more than a century. Stress was identified very early on as a risk factor (Blackley, 1873), and the role of sedentary lifestyles (Gleeson et al., 2004; Moller et al., 1996), vitamin D deficiency (Holick, 2007), and inflammatory diets (Gleeson et al., 2004; Sears and Ricordi, 2011; Sears, 2015) in the induction of inflammation have come into clearer focus. In contrast, one factor that has remained somewhat more elusive is the role of the human biota, the life associated with the ecosystem of the human body, in the induction of inflammation. Thinking in the latter part of the 1900′s centered on the "hygiene hypothesis", the general idea that our sanitation and use of hygiene products such as soap had left our body without sufficient stimulation, and that this lack of stimulation had weakened the immune system (Strachan, 1989). More recent work has focused on the role of the gut microbiota in inflammation, but most changes in the gut microbiota as a result of Western culture are apparently diet-induced (Kau et al., 2011; Muegge et al., 2011; Yatsunenko et al., 2012), not sanitation induced. Thus, typical Western culture-associated changes in the microbiota are apparently not a primary or ultimate cause of inflammation in Western society, but rather a down-stream effect of Western culture (Fig. 1). On the other hand, Western culture has resulted in an almost complete loss of helminths and protozoans from the human biota (Rook et al., 2014b). Extensive work in animal models and in humans probing the role of this profound loss of biodiversity from the human biota has led us and others to the conclusion that loss of complex eukaryotic symbionts such as helminths and protists is indeed a primary cause of inflammation in Western society (Bilbo et al., 2011; Lukes et al., 2015; Parker et al., 2012; Parker and Ollerton, 2013; Weinstock, 2012; Zaccone et al., 2006).

Over the past two decades, the field of psychiatry has developed an understanding of the role of inflammation in a variety of neuropsychiatric conditions, including migraine headaches, anxiety disorders, depression, and chronic fatigue (Dantzer et al., 2008; Krishnadas and Cavanagh, 2012; Lakhan and Kirchgessner, 2010;

Abbreviations: TSO, Trichuris suis ova; HDC, Hymenolepis diminuta cysticercoids.

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https://doi.org/10.1016/j.brainres.2018.01.023
0006-8993/

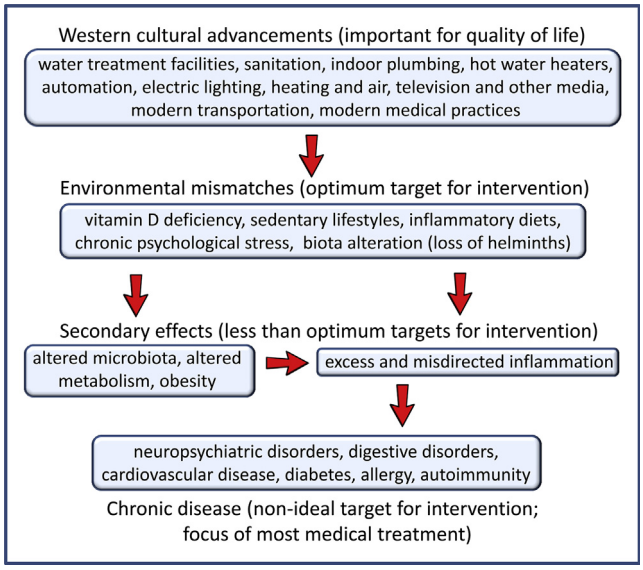

Fig. 1. Loss of helminths as one of several underlying causes of disease in Western society. In this model, chronic disease results from increased non-adaptive (unproductive) inflammation, which is turn results from several environmental mismatches that are a direct consequence of important aspects of modern culture. Although average changes in the microbiota are secondary effects of altered diet, some changes to the microbiota are due to modern medicine (e.g., antibiotic use) and are thus primary.

Raison et al., 2010; Rook et al., 2014a; Rook, 2009; Rook and Lowry, 2009). Knowing that many neuropsychiatric disorders are associated with inflammation, and knowing that helminths are a potential therapeutic agent that might help resolve inflammatory related conditions, it stands to reason that helminth therapy is a reasonable approach to consider for neuropsychiatric conditions. Indeed, several scientists have hypothesized that exposure to organisms such as helminths that have been largely lost to Western society may profoundly affect neuropsychiatric disorders (Becker, 2007; Raison et al., 2010).

Probably because of a lack of incentive for development rather than any fear of helminths (Bono-Lunn et al., 2016), the field of helminth therapy has been very slow to catch on. In the 1970s, Turton found that intentional exposure to hookworms eliminated hay fever (Turton, 1976), but nobody pursued the issue for another 30 years despite the fact that hay fever was and still is otherwise incurable. In 1999, Weinstock and colleagues revealed that patients with inflammatory bowel disease who had been treated with the porcine whipworm (*Trichuris suis* ova, TSO) were literally "begging to be retreated" (Newman, 1999). This was based on a greater than 70% cure rate for patients who had, for the most part, proven resistant to pharmaceutical treatment (Summers et al., 2005; Weinstock, 2012). Soon thereafter, exposure to a variety of helminths was shown to have great potential for treating multiple sclerosis (Correale and Farez, 2007), but efforts in the field were tied up with the commercial development of TSO, an endeavor which eventually ground to a halt after a decade, perhaps due to technical difficulties in preserving the organisms in an active form (Cheng et al., 2015). During the same period, however, thousands of individuals began "self-treating" using products provided by a number of commercial vendors of therapeutic helminths, including Garin Agletti, Detlev Goj, and Jasper Lawrence (Cheng et al., 2015). These individuals remained the sole suppliers of helminths to self-treaters for a number of years, and their work eventually provided a rich source of information for socio-medical studies aimed at evaluating the effects of helminths on individuals using the organisms for therapeutic purposes (Flowers and Hopkins, 2013).

2. Self-treatment and the possible rise of depression-eating worms

In early 2013, we embarked on a study to evaluate the practices and outcomes of individuals self-treating with helminths. The four-pronged socio-medical study utilized (a) interviews with helminth providers, (b) surveys from individuals self-treating with helminths, (c) publicly available information regarding self-treatment with helminths, and (d) interviews with physicians treating patients who self-treated with helminths. This eventually resulted in reports of over 1000 self-treatment experiences under conditions in which survivor bias could be largely eliminated and, to an extent, the placebo effect could be ruled out as the major contributor to the observed effects (Cheng et al., 2015; Liu et al., 2016; Smyth et al., 2017). These studies led to the conclusion that the life stage of the rat tapeworm which lives in insects (*Hymenolepis diminuta* cysticercoids, HDCs) was apparently being used effectively as a therapeutic agent to relieve a wide range of neuropsychiatric disorders (Cheng et al., 2015; Liu et al., 2016; Smyth et al., 2017).

Although it has been predicted that helminths may have a beneficial therapeutic effect in the treatment of neuropsychiatric disorders (Becker, 2007; Raison et al., 2010), work in this field is very much exploration of a new frontier. That being said, results from the socio-medical study described above are very promising. Using survey methods, we found that 10 individuals self-treating with HDCs for depression and anxiety disorders rated the therapeutic effectiveness of the organisms as high (8.7 average on a 10-point scale) and adverse side effects as very low (0.7 average on a 10-point scale) (Cheng et al., 2015). These ratings are very favorable compared to the ratings these same individuals gave to conventional medical treatments (4.9/10 on effectiveness, and 5.3/10 for side effects) (Cheng et al., 2015). All the survey participants utilized HDCs, suggesting that this organism may be an effective alternative therapy compared to current standard treatments for depression (Cheng et al., 2015; Liu et al., 2016). Importantly, the duration of chronic neuropsychiatric disease in the survey participants approached three decades on average, suggesting the drift toward the mean probably did not account for the results. Reports by survey participants were similar to reports by physicians' observations of patients (Liu et al., 2016), lending further credence to the results.

Following up on results from socio-medical studies, work by Bilbo and colleagues using a laboratory model showed that colonization with *H. diminuta* protects rats from inflammation-induced cognitive dysfunction (Williamson et al., 2016). However, this study utilized an "exposure from birth" model in which the parents of the study animals were exposed to either helminths or placebo prior to pregnancy. Thus, studies using an animal model demonstrated that helminths could prevent inflammation-associated neurological dysfunction, but did not address their utility for treatment of preexisting disease. Still, the results are consistent with the idea that helminths may indeed be effective therapeutic agents for neuropsychiatric disorders, as has been predicted (Becker, 2007; Raison et al., 2010). These predictions are based on the now widely appreciated "gut-brain axis", which connects emotional and cognitive centers of the brain with the bowel in a bidirectional fashion (Carabotti et al., 2015).

3. Breaking through the bottleneck: Finding more suitable worms for clinical trials

A major bottleneck in the field of helminth therapy has been the paucity of helminths that might be useful for clinical trials. As

Please cite this article in press as: Kou, H.H., Parker, W. Intestinal worms eating neuropsychiatric disorders? Apparently so. Brain Res (2018), https://doi.org/10.1016/j.brainres.2018.01.023