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Intestinal worms eating neuropsychiatric disorders? Apparently so

Henry H. Kou, William Parker *

Department of Surgery, Duke University Medical Center, Durham, NC, USA

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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.

* Corresponding author.
E-mail addresses: Henry.Kou@Duke.edu (H.H. Kou), William.Parker@Duke.edu (W. Parker).

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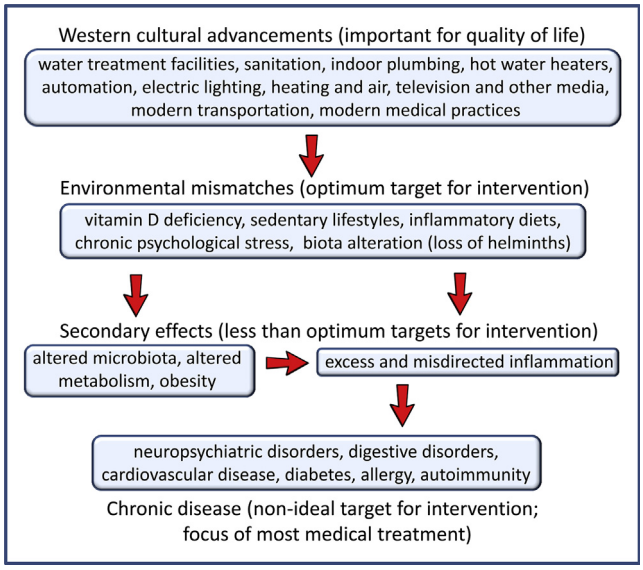

Fig. 1. Loss of helminths as one of several underlying causes of disease in Western society. In this model, chronic disease results from increased non-adaptive (unproductive) inflammation, which is turn results from several environmental mismatches that are a direct consequence of important aspects of 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

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mentioned above, work with TSO has proven to be challenging. Several studies have been completed with the human hookworm (*Necator americanus*), but the organism is potentially limited by its communicability and its tendency to cause adverse side effects when administered at therapeutic levels. Thus, the discovery of HDCs as a potential therapeutic agent is exciting in several regards (Smyth et al., 2017). First, production is relatively straight forward. Second, the therapeutic life stage of the rat tapeworm, the HDC, is raised in grain beetles, which are non-toxic to humans. Third, the risk of adverse side effects is apparently low compared to the hookworm. Fourth, the organisms do not leave the lumen of the gut, in contrast to the other organisms (whipworms and hookworms) that have been used for helminth therapy. Fifth, the organisms generally do not survive long in humans and are not communicable via human-to-human transmission. Finally, as described above, the organisms appear to be generally effective in the treatment of a variety of inflammation-related conditions, including several neuropsychiatric disorders. Thus, it is hoped that the availability of this particular helminth may promote research in the field and incisive evaluation of the potential for helminths to treat neuropsychiatric disease.

The history of helminth therapy is fraught with somewhat arbitrary selection of helminths, often determined much more by accessibility of a helminth to a particular investigator or producer rather than by selection criteria based on potential for treatment of disease. Indeed, numerous helminths are available that might be used for treatment of disease (Lukes et al., 2014), and a systematic evaluation of helminths as well as genetic modification of helminths for the treatment of disease is expected to expand this frontier dramatically, potentially affecting a wider range of disease than previously imagined.

4. There is still a long way to go: Pitfalls and unknowns

In the face of great promise, several factors are of concern when considering the use of helminths for the treatment of inflammatory disease. One of the primary concerns is that helminths might be viewed as a magic bullet for disease, akin to a pharmaceutical that effectively eliminates the underlying problem without adverse effects. Our view is that controlled addition of helminths to the human population should be part of a balanced approach to public health that involves effective management strategies for other inflammation-inducing factors, including inflammatory diets, sedentary lifestyles, chronic psychological stress, and vitamin D insufficiency.

Another factor that has dampened enthusiasm for helminth therapy involves policy issues associated with a lack of incentive for development of the therapy (Tilp et al., 2013). The market for an effective immune-modulating helminth certainly exists, but helminths are currently treated as a drug in the US system, and the cost of drug development is extremely high. Initial investors may find it difficult to recover their investment, and the pioneering but unsuccessful commercial work with TSO may unfortunately be viewed as a warning sign to potential investors. Further, the current drug pipeline, designed for patented and well-defined chemicals, may simply not apply to helminths. Helminth production may be difficult to "standardize" in the way that a pharmaceutical can be, and may be more related to farming than to chemistry. The conditions of growth as well as the means of preparation of helminths for the patient may be important, and these factors, based on our socio-medical work, may need several rounds of optimization for a given helminth. The current drug pipeline is simply not geared for this sort of endeavor. Thus, we have argued that new regulations are important for the field to move forward (Bono-Lunn et al., 2016).

5. Promise for the future of helminth therapy and neuropsychiatric disease: The next steps

The field of helminth therapy is not at a standstill, despite obstacles. Work with the hookworm is proceeding, although dosing regimens based on a one-dose-fits-all approach may need to be set aside in favor of a systematic but flexible dose escalation plan that balances benefits with adverse effects on an individual basis. Indeed, such a scheme may be necessary for any study involving helminth therapy. In a very real sense, helminth therapy can be considered "exercise for the immune system", and it is now apparent from socio-medical studies that the need for helminth-based immune exercise is highly variable depending on the individual. Further, given the absence of intellectual property in the field at the present time, benevolent donors are urgently needed to provide funding to incisively test the effect of helminth therapy on a few critical and potentially high-profile diseases. The intuitive place to start with such tests involves diseases that have (a) poor outcomes with current standard of care, and (b) a profile consistent with disease that can be treated with helminths. One hypothesis that is based on socio-medical data is that diseases which are persistent are less treatable with helminth therapy than are diseases which are episodic, or relapsing and remitting. Finally (c), the lowest hanging fruit will have some prior published evidence, potentially from either socio-medical studies or from studies using animal models, that supports the hypothesis that helminth therapy will be effective.

Neuropsychiatric diseases do indeed fit the criteria as low hanging fruit, with the need being great and the profile fitting diseases that typically respond to helminths based on available data. The relative risk of exposure to a benign helminth, so far as is known, is trivial by comparison to the need, making the approach attractive from a regulatory perspective. Diseases other than neuropsychiatric disorders are also potential targets for initial studies with helminth therapy. Relapsing-remitting multiple sclerosis, other autoimmune conditions, and possibly Parkinson's disease are promising examples, and qualify as low-hanging fruit. However, the incidence of these autoimmune-related conditions in the Western world pales in comparison with that of neuropsychiatric disease, and it is hoped that the utility of helminth therapy for neuropsychiatric diseases will be tested both incisively and soon.

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