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Arnold Kahn
Buck Institute for Age Research, Novato, CA, US

Anders Olsen
Aarhus University, Gustav Wieds Vej, Denmark

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Arnold Kahn □ Buck Institute for Age Research, Novato, CA, US

Anders Olsen □ Dept.of Molecular Biology, Aarhus University, Gustav Wieds Vej, Denmark

□ Despite the fact that the phenomenon of hormesis has been known for many years it is still very much an area of controversy just how useful hormetic treatments are in preventing age-related human diseases and increasing life expectancy. Since there are no data in humans demonstrating hormesis as an effective anti-ageing strategy we turn to a simple model organism for insight. In this review we explore what can be predicted about the usefulness of hormetic treatments in humans based upon studies conducted in the soil nematode *Caenorhabditis elegans*.

Keywords: hormesis, C. elegans , Aging , Age-related disease, intervention

Despite the fact that the phenomenon of hormesis has been known for almost a century it is still very much an area of controversy just how useful hormetic treatments are in preventing age-related human diseases and increasing life expectancy. To date, there is no compelling evidence that hormesis is an effective approach for human subjects, if the goal is to achieve not only increased stress resistance but also the increase in longevity so well documented in model organisms. However, if a narrower definition is taken, there are some promising, indeed provocative, findings in the recent literature suggesting that hormesis could be an important strategy for improving human health. For example, Marini *et al.* (2008), suggested that using low level activation ('hormetic levels') of the ionotropic glutamate receptor in brain neurons (which triggers endogenous neuronal survival pathways) might be an effective strategy for preventing neurodegenerative disorders as well as a therapeutic tool for augmenting cell survival following such damaging, potentially fatal disorders as stroke (Marini *et al.* 2008). On a generally similar note, data on mice indicate that caloric restriction (specifically short term starvation) used as an activator of hormesis, increases the stress resistance of normal but not glioma or neuroblastoma cells *in vivo* to high doses of etoposide, a chemotherapy drug (Raffaghello *et al.* 2008). These findings were so compelling that Johnson et. al. are planning a clinical trial using a generally similar approach (specifically alternate day dieting) to improve normal cell and tissue survival in cancer patients scheduled to be treated

Address correspondence to Anders Olsen, Dept.of Molecular Biology, Aarhus University, Gustav Wieds Vej 10C, DK-8000, Denmark. Phone +45 30698155; ano@mb.au.dk

with oxidative damage-producing chemotherapy drugs (Johnson *et al.* 2009). An even more novel idea for employing hormesis to improve human health is based, in large part, on the observation that cancer incidence is lower in countries where there is a high infectious disease burden (Deocaris *et al.* 2005). This observation led to the hypothesis (the mimotope-hormesis hypothesis) that the lower incidence of cancer is due to an increased auto-immune response triggered by epitopes (antigens) associated with the infection that mimic the epitopes found on tumor cells. This idea of stimulating the immune system as one way that a hormesis-type prophylaxis can be achieved in humans is also discussed in a recent paper by Dietert and Piepebrink (Dietert and Piepenbrink 2008). Here, the essential notion is to find strategies, using potential hormetic agents in utero, to insure, if not augment, the shift (maturation) at birth from a T helper 2 (Th2) cell to a more T helper 1 (Th1) cell based immune system. It is this shift that is essential to having normal and long-term immune function later in life (Dietert and Piepenbrink 2008).

Since there are no data in humans demonstrating hormesis as an effective anti-ageing strategy that can delay or prevent either the onset of age-related diseases or aging *per se*, we turn to simple model organisms for insight. Many studies have shown that hormesis has anti-aging effects in model organisms including yeast, worms, flies and, if the effects of dietary restriction are included, rodents. In particular, the soil nematode *C. elegans* has been widely used for studying hormesis and its effect on stress resistance, aging and longevity. In the following discussion, we explore what can be predicted about the usefulness of hormetic treatments in humans based upon studies conducted in *C. elegans*.

There is strong correlation between aging and stress resistance in *C. elegans* in that most long lived mutants are also resistant to various forms of stress (Lithgow and Walker 2002). In some mutants, this increase in stress resistance stems from increased levels of repair and damage prevention systems. In other mutants, however, the underlying mechanism remains to be identified. Since transgenic over-expression of enzymes involved in maintenance and repair, such as *hsp-16* (Walker and Lithgow 2003) and *hsp-70* (Yokoyama *et al.* 2002), can lead to increased stress resistance and lifespan in *C. elegans*, it is plausible that hormesis simply acts by stimulating various repair and maintenance pathways. If so, in principle that approach should also be applicable to humans where aging is also thought to arise from accumulation of molecular damage.

WHAT STRESSOR AND DOSE SHOULD ONE USE IN HUMANS?

In *C. elegans*, a hormetic response following exposure to a mild stress can be measured by means of increased tolerance to a subsequent stress

challenge. This phenomenon has been reported for several different kinds of stress including heat (Lithgow *et al.* 1994; Yashin *et al.* 2001; Cypser and Johnson 2002; Olsen *et al.* 2006), oxidative stress (Cypser and Johnson 2002), ionizing radiation (Johnson and Hartman 1988), starvation (Kaeberlein *et al.* 2006; Honjoh *et al.* 2009) as well as treatment with various different chemicals and synthetic compounds (Melov *et al.* 2000; Wu *et al.* 2002; Petrascheck *et al.* 2007). It is clear, therefore, that there are a number of potential hormesis 'inducers' ('stressors) to choose from. However, common for all these treatments is the importance of selecting the optimal dose since all treatments are toxic if either the dose or the length of exposure exceeds a critical value. So choosing the right dose is critical but that is by no means a trivial task.

Despite the very controlled environment under which nematodes are kept in the laboratory, as well as the fact that the population is isogenic, it is still challenging to find a dose that is consistently hormetic. The literature has many examples of identical hormesis experiments giving different results. Sometimes a treatment is beneficial, sometimes the same treatment has no effect, and in the worst cases the exact same treatment can in fact have a negative effect. Moreover, a proper biomarker for a successful hormetic treatment has not been identified; something that would be absolutely essential for monitoring the effects of hormesis in humans. Not only do most humans have unique genetic identities but, as a species, we are also exposed to very different levels of natural hormetic 'stressors' including variations in diet, climate, pollution, health status etc. On top of this (and in large part in response to the latter), there are epigenetic modifications that vary from individual-to-invidual resulting downstream in differences in gene expression and phenotype. Consequently, it seems, that like the personalized medicine currently being discussed, hormetic treatment would have to be designed to fit each individual.

WHEN SHOULD A HORMETIC TREATMENT BE GIVEN?

Provided that the issue of dose is resolved, other aspects need consideration too. Particularly, the time of treatment could be critical. In *C. elegans* a single hormetic treatment given early in life (1 day of adulthood) is sufficient to increase lifespan (Lithgow *et al.* 1995; Olsen *et al.* 2006). Although heat treatments given repeatedly throughout life do increase the lifespan a little further than a single treatment the gain is rather modest (Olsen *et al.* 2006). Moreover, while treatment in late life does elicit the induction of chaperones, it does not significantly increase lifespan (Olsen *et al.* 2006). In terms of humans, a single hormetic treatment given early in life would appear to be the most appealing approach. However, most, if not all, hormetic treatments in *C. elegans* severely compromise the fertility of the treated animal; making, by extension, early

treatments a much less attractive approach in humans. Little is known about the persistence of the hormesis into the next generation, but our data suggest that the hormetic effect may pass through multiple generations and have severe effects on both the fertility and fecundity of progeny (unpublished results). Therefore, for now, the only feasible treatment time in humans appears to be in the post-reproductive period. Clearly, much more research needs to be done in simple organisms to establish if late treatments have any beneficial effects before one can even start to predict if humans will benefit from such a treatment strategy.

IS HORMESIS A DEAD END?

The evidence, to date makes it clear that it is not yet possible to devise an evidence-based hormesis treatment for humans based upon the findings from small animal models. Does this mean that work on hormesis is at a dead end and that the studies in simple model organisms are not worth while continuing? We think not. Only by understanding the underlying mechanisms of a successful hormetic treatment in these simple systems can we start translating the findings to humans. Because of the findings on, for example *C. elegans*, we have a much better understanding of the molecular mechanisms activated by hormetic treatments such as mild heat treatment (Lithgow *et al.* 1994; Yashin *et al.* 2001; Cypser and Johnson 2002; Olsen *et al.* 2006) or short term starvation (Honjoh *et al.* 2009). Such studies are very important because in order to shift hormesis from current status as an interesting research paradigm to a treatment strategy, we need a much better understanding of the mechanistic, molecular basis of homesis. We also need a way of measuring the intrinsic molecular stress levels of each individual. The latter is likely to prove particularly challenging because of the strong possibility that there will be tissue and/or organ specific differences in response to treatment even within the same individual. Thus, in terms of drug treatment, one could imagine developing tissue specific therapies but that requires a way of measuring the intrinsic stress level of individual tissues and organs. It is not currently feasible to do this. The dangers inherent in using too high a dose of any given hormetic treatment are self-evident and remain a major obstacle when considering treating normal healthy individuals. Is seems much more likely that hormetic therapy will become popular as treatment when used as an adjunct to other treatment strategies for serious illnesses. For example, as in the previously mentioned study, dietary restriction (starvation) markedly increased the effectiveness of chemotherapy in mice (Longo *et al.* 2008).

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