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Horseradish and radish peroxidases eaten with fish could help explain observed associations between fish consumption and protection from age-related dementia

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ABSTRACT

A juxtaposition of regional cuisines and recent prospective studies of fish consumption in China and Japan points to fresh horseradish and/or radish (HRR) as possible contributors to delaying age-related dementia. The hypothesis is that the inverse association found sometimes between fish intake and cognitive decline is partially due to exposure of the oral cavity to active peroxidases from HRR served in conjunction with fish. This hypothesis can be tested by specifically looking at whether HRR is consumed with fish and whether such HRR is prepared in a way that preserves activity of HRR peroxidases. It is possible that by putting active HRR peroxidases in their mouths, elderly people supplement their age-diminished salivary antioxidant capacity and break down additional hydrogen peroxide (H_2O_2) in the oral cavity before it can migrate into the brain, thus decreasing the incidence of brain cell death induction by chronically-elevated H_2O_2. Intentional exposure of the oral cavity to active HRR peroxidases could be a prophylactic for delaying dementia. Because vegetable peroxidases are inactivated by gastric juices, it will be difficult to obtain benefit from HRR peroxidases' antioxidant effect via ingestion in encapsulated dietary supplements.

Background

Many studies have reported an inverse association between fish intake and cognitive decline in the elderly [1]. However, recent prospective studies yield results that paint a confusing picture of how exactly one is to obtain that seemingly fish-provided protection from dementia. One influential theory has been that the beneficial effect of fish intake comes from the omega-3 polyunsaturated fatty acids (ω-3 PUFAs) in fish, but studies have repeatedly failed to find that ω-3 PUFAs alone provide significant protection from cognitive decline [2,3]. A study in Japan found a protective effect associated with blood levels of one ω-3 PUFA which is high in marine fish [4], while a study in China found a protective effect associated with consumption of lean, fresh-water fish which are low in ω-3 PUFAs compared to marine fish [5]. Other studies find no clear protective benefit from increased fish consumption [6,7].

Hypothesis

I propose this hypothesis: the inverse association sometimes observed between fish intake and cognitive decline could be partially due to the oral cavity being exposed to active peroxidases from horseradish and/or radish (HRR) served in conjunction with fish.

Evaluation

Evidence to support hypothesis

Evidence to support this hypothesis comes principally from three studies which found a significant cognitive benefit from fish consumption. These studies were done in China, Japan, and Norway.

A prospective study in China found a significant slowing in cognitive decline accrued to elderly people (≥65 years of age) who ate fish at least once a week [5]. The study population's fish intake consisted of primarily freshwater carp, which is low in ω-3 PUFAs. In China, soup is a regular part of traditional meals, and carp is often prepared in a soup that contains a whole fish and a generous

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amount of freshly cut white (daikon) radish (*Raphanus sativus*). Daikon radish is an excellent source of peroxidase [8]. While vegetable peroxidase isoenzymes are heat labile, they can regenerate after cooling [9] and are more heat stable in the presence of free calcium ions [10]; calcium is provided by the fish bones [11] included in Chinese carp soup. Consequently, Chinese carp soup with daikon radish appears to be a good source of active radish peroxidase.

Nearby in Japan, a prospective study found that cognitive benefit from fish consumption was associated with the ω-3 PUFA docosahexaenoic acid (DHA) from marine fish intake [4]. Marine fish in Japan is regularly eaten as part of sushi and sashimi dishes, for raw marine fish contains fewer hazardous parasites than raw freshwater fish. Sushi and sashimi are typically accompanied by "wasabi" paste—which is mostly reconstituted powdered horseradish (*Armoracia rusticana*)—and fresh daikon radish slices. Horseradish peroxidase is an exceptionally strong enzyme that is stable at typical mouth pH levels [12,13].

Additional evidence for the hypothesis comes from an observational study out of Hordaland, Norway which found a clear, dose-dependent association between fish consumption and better cognitive performance [14]. In this coastal region of western Norway, fish is eaten by nearly everyone, and traditional Scandinavian sauces for commonly eaten fish frequently contain substantial amounts of fresh horseradish.

Countries in which prospective studies fail to find a clear cognitive protection benefit from fish consumption appear to be places where HRR is either not regularly eaten with fish, such as the Netherlands [7], or where HRR accompanying fish is often cooked or pickled in acidic environments of low enough pH to inactivate peroxidases [15], such as South Korea [16].

Possible mechanistic explanation for hypothesis

Why would eating active HRR peroxidases be protective against cognitive decline? I speculate that the answer lies with peroxidases' function as antioxidant enzymes and specifically their effectiveness at breaking down hydrogen peroxide (H_2O_2) into water. As people age, the concentration of salivary peroxidase does not significantly change, but overall salivary antioxidant capacity—as assessed by quantifying the H_2O_2 remaining after the antioxidants in saliva samples react with exogenously-provided H_2O_2—in old adults is reduced to approximately half that of young adults [17].

H_2O_2 is considered by many people to be benign or even helpful. They wash wounds with it, even though that is now discouraged due to H_2O_2's ability to produce significant tissue damage [18]. Some people drink it, seeking tantalizing health benefits promised on questionable websites; unfortunately, drinking H_2O_2 can result in a cerebral infarction [19]. H_2O_2 is a common ingredient in tooth whitening treatments, despite its having been recently shown to induce apoptosis in human gingival fibroblasts [20]. H_2O_2 in small amounts does play some beneficial roles in cells [21,22].

Nonetheless, H_2O_2 is also one of the reactive molecules involved in the oxidative stress that many hypothesize to be implicated in Alzheimer's disease (AD) and other aging-related neurodegenerative diseases [23–27]. Bursts of hydrogen peroxide generation occur during an early stage of amyloid plaque formation in both AD and familial British dementia [28], and H_2O_2 promotes production of amyloid β-peptide, plaques of which are a hallmark characteristic of AD [29]. H_2O_2-reducing agents have been proposed as a route to AD therapy [30,31].

H_2O_2, which occurs in the mouth endogenously and as a product of oral bacteria, is a small molecule that diffuses easily in the extracellular matrix due to its lack of electrical charge [32] and is readily aerosolized and carried in exhaled breath [33,34]. H_2O_2 also disrupts epithelial barrier function [35,36], induces endothelial cell permeability and endothelial barrier dysfunction [37,38], and promotes bone resorption [39]. Further, H_2O_2 appears to "unlock" the blood-brain barrier, as was shown in a 2014 rat study [40] in which H_2O_2 placed in the nasal cavity enabled easy delivery of exogenous dopamine from the nose into the brain, as well as in other non-human mammal studies [37,41,42]. During swallowing, saliva is regularly propelled from the oral cavity into the oropharynx, so elevated salivary H_2O_2 could result in extra pharyngeal H_2O_2 moving toward the brain either by exhalation through the nasal cavity or by diffusion within the pharyngeal lining. That extra H_2O_2 could then pass into the braincase through cranial fissures and foramina, particularly the cribriform foramina, which are currently being explored as a pathway for nose-to-brain delivery of therapeutics [43].

There is evidence to support the idea that a dementia-inducing factor begins its work near the nasal cavity, for located over the cribriform foramina is the intracranial portion of the olfactory system, dysfunction of which has been repeatedly observed to correlate with very early AD and other neurodegenerative diseases [44]. Additionally, a 2013 imaging study found that AD appears to start in the lateral entorhinal cortex [45], which is in close proximity to the nasopharynx.

While H_2O_2's cytotoxic potential is well-established, it tends not to induce cell death unless a sufficiently high amount of H_2O_2 is inside a cell for a sufficiently long period of time [46]; in other words, the relationship between intracellular H_2O_2 and its induction of apoptosis is both time- and dose-dependent and requires that a threshold of H_2O_2 quantity be reached and sustained before it causes cell death. By putting active HRR peroxidases in their mouths, elderly people can supplement their salivary antioxidant capacity and break down extra H_2O_2 in the oral cavity before it can lead to an increase in H_2O_2 levels in nearby brain regions, thus reducing the occurrence of sustained, elevated cerebral H_2O_2 levels that induce neuronal apoptosis. In this way, HRR consumption could protect against cognitive decline.

Possible contradictory evidence

Two countries stand out for their consumption of fresh HRR: Japan and France. Japan has been notable as a place where the traditional cuisine appears to afford some protection from age-related cognitive decline [47]. However, France does not exhibit a lower prevalence of dementia than is seen in other western European countries. Does France's dementia prevalence undercut the hypothesis above? Not necessarily, for in France fresh radishes are typically either sautéed in or eaten with butter, the best dietary source of butyric acid, and butyric acid in high concentrations has been shown to elevate H_2O_2 in gingival tissue blood [48] and neuronal cells [49]. Consequently, any H_2O_2-diminishing benefit from French radish consumption could be being negated by butyric acid-induced H_2O_2 from the butyric acid in butter accompanying the radishes.

Evaluation of hypothesis

This hypothesis should be fairly straightforward to evaluate. It would require adding two survey questions in future studies of fish consumption and dementia: "1) Do you eat any horseradish or radish with your fish?" "2) If yes, how is the horseradish or radish prepared and eaten?"

Consequences

If this hypothesis has merit, intentional exposure of the oral cavity to active HRR peroxidases could be a prophylactic for delay-