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The Evolutionary Significance of Fever in Immune Response

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Abstract

Fever, although part of the second line of defense in immune response, is still a topic of discussion on whether an increase in body temperature during an infection is more beneficial than harmful. Fever is considered a beneficial response to infection because of the incapability of pathogens to survive the increased temperature, and fever's ability to increase mobilization of immune cells. Other than this regular benefit of increase in body temperature, fever therapy is being considered as a safer, less expensive, and more effective cancer treatment. However, fever is also currently looked down upon by physicians and the public due to its harmful effects such as seizures if not maintained within a certain range and increased risk of Autism spectrum disorders in children of pregnant mothers who had an uncontrolled fever. The preservation of fever response over generations and its similarity in several organisms indicates its evolutionary advantage despite some harmful effects associated with this response and could be an intermediate adaptation for survival. Further research can be done to better control fevers and keep them within the safe range instead of completely alleviating them, such as letting a fever run its course to fight infections better and faster under certain circumstances, increase awareness on how to monitor a fever, and increase awareness on individuals who are at higher risk of the negative consequences of fever.

Keywords: *Fever, Immunity, Thermoregulation, Behavioral, Survival*

The Evolutionary Significance of Fever in Immune Response

Fever: An Example in Evolutionary Medicine

Evolutionary medicine is an application of evolution to maintain our health and wellness by understanding how to prevent and treat disease. Examples include cancer, antibiotic resistance, autoimmune disorders, anxiety, pain, and fever. Fever has always been seen as the body's natural inflammatory response to fight infections. In fact, characterizing fever as part of the immune response first started with Hippocrates in the 5th century BC (Ray & Schulman, 2015). Benefits of fever include fighting against infections, fighting against allergies, and in recent studies; fever induction to treat and complete remission of cancer (Martin, 2016; Reuter et al., 2018). Keep in mind that a mild fever is considered a body temperature above 100.4°F (38°C), while a dangerous fever is a body temperature of 104°F (40°C) or higher. However, the debate of whether the benefits of fever outweigh its risks remains unresolved. Despite evidence and research on the benefits of mild fever (below 104°F), the majority of physicians still look at fever as more dangerous than beneficial and prescribe medications to alleviate fever whether it is mild or not, especially in children because they are highly susceptible to seizures, brain damage, and even death (Radhi, 2012).

The Magic Number: 98.6°F (37°C)

Normal body temperature for humans can range from 97°F (36.1°C) to 99° F (37.2°C). Differences in body temperature within normal range depend on sex, stress, site of measurement, environment, activity, time of day, body chemicals, fitness, and age (Ogoina, 2011). The origin of average body temperature at 98.6°F (37°C) can be traced back to the work of Becquerel and Breschet in the 19th century, and the more well-known work of Carl Reinhold August Wunderlich. Wunderlich measured axillary temperatures of 25,000 patients multiple times using a thermometer that took about 15-20 minutes to give a reading and then averaged the temperature readings that resulted in 98.6°F (37°C). Many other studies have recently measured temperatures of a large group of people to determine the accuracy of Wunderlich's readings. The recent studies found that the average body temperature of participants was 98.2°F (36.8°C). Reasons for the differences in average body temperature between the studies include that Wunderlich's thermometer is considered less accurate then today's thermometers, Wunderlich's sample size was much larger than the recent studies, and Wunderlich's measurements included both sexes, while some of the recent studies measured and averaged body temperature using male or female participants only, and different sites of measurement. Both averages for normal body temperature reported in Wunderlich's studies and recent studies are still within the normal body temperature range of 97°F (36.1°C) to 99°F (37.2°C), and that normal body temperature is now looked at as a range instead of a single number (Kelly, 2006).

The studies showed how the normal range of body temperature was established, but not why it is within that range. According to Bergman & Casadevall (2010), the normal range for human body temperature is considered an intermediate temperature which is high enough to prevent fungal infection, yet optimal enough to maintain regular metabolism. The study also shows that the number of fungal species that can infect a host declines by 6% for every 1.8° F (1°C) rise in temperature.

The Role of Fever in Immunity

An increase in body temperature during infection has been observed in both invertebrates and vertebrates (both warm-blooded and cold-blooded beings). According to (Evans et al., 2015), pyrogenic cytokine interleukin-6 (IL-6) induces fever when an infection is detected by changing the set point temperature by sending signals to the hypothalamus to alter thermoregulation and the set point temperature. This in turn leads to increased mobilization of lymphocytes which either release antibodies (B lymphocytes), send signals to other inflammatory cells (helper T cells), or destroy the pathogen. Increasing body temperature not only induces immune response, but the response of high temperature itself also helps eliminate pathogens due to the lack of ability to survive at certain temperatures. Increasing the set point temperature results in actual body temperature being below this new set point. In order to increase core temperature to reach the new set point, adaptive behavioral modifications such as shivering, vasoconstriction, and changing environments have helped maintain such temperature.

However, fever also has some evolutionary draw backs. For example, shivering and maintaining a higher core body temperature requires a 12% increase in metabolic rate per 1˚C, which can shift energy usage from other important bodily processes (such as cellular respiration, DNA replication, DNA repair, and mental activity) to energy usage for increasing metabolic rate and increasing body temperature. Other organisms with infections such as animals may expose them to predators when moving to warmer environments (Singh & Hasday, 2013). To further look at the relation between fever response and behavioral change, Boltaña et al. (2013) conducted a study on zebrafish in a manipulative experiment that used simulated viral infection to determine the effect of maintaining a certain body temperature on survival. The zebrafish exhibited what is known as behavioral fever, in which the fish relocate to a warmer environment to reach a certain body temperature. It was observed that fish that were not able to find the optimal environmental temperature to express behavioral fever showed decreased survival under viral infection. Maintenance of the fever response over generations and across multiple organisms indicates an evolutionary advantage and positive selection for fever response despite some negative effects that are associated with this response.

Recent research is exploring the possibility of using fever to treat cancer by using combined pathogen associated molecular pattern (PAMP) substances to induce fever in cancer patients. Using PAMP to induce fever in this study to treat cancer has replaced traditional treatments, such as chemotherapy or radiation that suppress the immune system. Fever therapy requires 4-5 weeks of treatment with a frequency of 2-3 times per week. Fever therapy can be a future treatment for cancer because cancer cells are more susceptible to high heat than normal cells. Not only does fever induction affect cancer cells in terms of heat, but also further induces and extends normal activation of B lymphocytes, T lymphocytes, and tumor infiltrating lymphocytes in response to cancer. Fever therapy is considered less expensive than traditional cancer treatment, with less adverse effects (other than the effects felt by fever which depends on concentration of treatment given, higher concentrations resulted in stronger response), and reported as safe when PAMP injections are given in the correct route and when fever is settled (Reuter et al., 2018).

According to Reuter et al. (2018), results from using fever therapy to treat cancer included a patient diagnosed with prostate carcinoma in 2009, who underwent traditional cancer treatment of prostectomy and hormone therapy. However, in 2011, this patient's PSA was rising and reached 387mmol/L in 2012. Elevated prostate-specific antigen (PSA) is an indication of an abnormal condition in the prostate such as cancer. Between 2012 and 2014, the patient received 15 fever inductions, which decreased PSA levels to 1 mmol/L in 2014 (Figure 1). This showed that fever induction can be a less expensive treatment and complete remission of cancer that traditional therapy cannot always achieve without suppressing the immune system and without the negative effects of chemotherapy or radiation treatment. The time it takes for fever therapy to clear a patient from cancer or a tumor might be improved once more research is done on fever therapy and becomes more widely considered as cancer treatment. Keep in mind that most chemotherapy takes about 3-6 months to clear cancer and may take up to 18 months, depending on how effective it is and on the cancer itself.

Risks of Uncontrolled Fever

Body temperatures that reach 104°F or higher can be dangerous and lead to organ damage, tissue damage, brain damage, seizures and death; especially in children. This risk of fever in children refers to the children themselves having an uncontrolled fever. However, Zerbo (2013) published a study at UC Davis that discusses the association between fever and Autism spectrum disorders. The study compared mothers who reported not having fever during pregnancy, mothers who reported fever during pregnancy and not taking medications to reduce fever, and mothers who reported fever during pregnancy and taking medication to reduce fever. It was found that influenza during pregnancy was not associated with Autism spectrum disorders or developmental delays, and that influenza was only a confounder. Results of the study showed that mothers who did not have fever had low risk for having children with Autism or developmental delays, which had similar results to mothers who had fever and took medication to reduce it. Risk for children with Autism or developmental delays was higher for mothers who had fever and did not take medications to reduce it. Mothers of children with Autism were more likely to report fever during pregnancy compared to mothers with normal developing children.

The mechanism at which fever during pregnancy can increase the risk of having children with developmental delays is related to the release of cytokine interleukin-6 (IL-6), lymphocytes, cytokines, and other inflammatory cells during fever; which is the same in non-pregnant individuals who have fever. However, IL-6 and cytokines can cross the placenta and enter amniotic fluid and the fetal environment. These cells then have the ability to alter the release of neurotransmitters such acetylcholine, dopamine, serotonin, and norepinephrine in the brain leading to decreased brain development that causes developmental delays and behavioral abnormalities seen in Autism spectrum disorders.

Another population at risk for fever is patients with brain injury, head trauma, stroke, and cardiac arrest. According to the study Liu et al. (2012) had conducted on rats, the switch from fever to hypothermia during induced systemic inflammation was observed. Hypothermia was also observed in rats during non-induced (natural) severe systemic inflammation. The study proposed that the advantages of hypothermia are due to the switch in later stages of severe systemic inflammation after fever in earlier stages. This was related to the study's results that the hypothermic rats died earlier than those with fever, although mortality rate was lower in the hypothermic rats. These results could be explained by when the switch from fever to hypothermia was induced, in which earlier stages of systemic inflammation should be fought with high body temperatures due to its advantage in immunity. If inflammation proceeds and becomes severe, then the switch to hypothermia occurs to protect the organism from the harms of prolonged elevation in body temperature. Inducing hypothermia in the rats too early or too late in the inflammatory stages might have been a possible cause in earlier deaths in some of the hypothermic rats. Advantages of hypothermia during severe systemic inflammation include decreased abdominal organ dysfunction (kidneys, liver, and pancreas), suppressed oxidative stress, conservation of mitochondrial and calcium homeostasis; which reduced overall mortality rates.

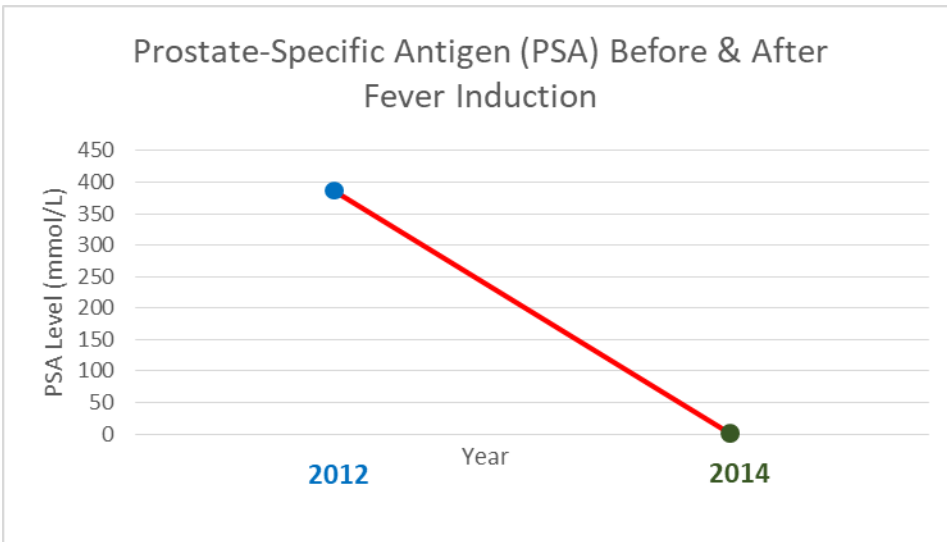
The same induced reduction in body temperature for patients that have suffered brain injury, head trauma, and stroke is performed in the Intensive Care Unit (ICU) in the form of either normothermia or hypothermia. Which patients need an application of normothermia or hypothermia is still to be further studied, but applying either one was considered more beneficial than leaving the patient with a fever because reducing body temperature in such cases improves brain metabolism, improves brain physiology, and reduces intracranial pressure after brain injury, head trauma, and stroke (Bohman & Levine, 2014). According to the Maekawa et al. (2015) study, reducing a fever after cardiac arrest can prevent severe brain damage. The Kim et al. (2014) study also showed that induced hypothermia after cardiac arrest improved resuscitation and brain recovery. Studies that looked into induced hypothermia after brain injury or cardiac arrest had similar results in that reducing fever lead to better patient outcomes and increased mortality. However, the studies' limitations include the necessity of further research to understand which patients need normothermia and which need hypothermia. Another limitation includes which method of induced body cooling, such as intranasal cooling, cold intravenous fluid, and others, would provide the best outcome.

Conclusion: Fever Could be an Evolutionary Trade-Off

It is possible that fever has been positively selected by evolution because the benefits outweigh the risks if the raise in body temperature is still within a safe range and under control. The evolution of fever might be an intermediate adaptation for survival similar to sickle cell anemia heterozygotes protected against malaria. Even with much research on the benefits of fever in natural immune response, fever is still looked at negatively by physicians and the general public because letting a fever run its course is not for everyone. This is possibly due to that fact that physicians don't want to increase the risk of fever's adverse effects in certain patients such as children and pregnant mothers. More research is needed to better control fever in terms of not completely alleviating it while keeping it in a safe range, such as looking into genetic modifications that can alter hypothalamus thermoregulation, less energy usage to raise body temperature, and immune sensitivity required to raise temperature to be considered beneficial and outweigh its risks. In the future, it might become a doctor's order to not take anything for fever as long as it is within the safe range to speed up recovery from infection under certain circumstances and for certain patients. Further studies can look at whether an evolutionary change or evasion of pathogens to the optimal fever temperature cause an increase or decrease of the optimal temperature response to fight infection. Future studies can also look at the possibility of the appearance of new immune responses to fight infection.

Figures

Figure 1: Comparison of Prostate-Specific Antigen (PSA) Levels Before and After Treatment with Fever Induction. Higher PSA levels are indicative of cancer of the prostate. In 2012, a patient had a PSA level of 387mmol/L, which decreased to 1 mmol/L in 2014 after 15 fever inductions. The decrease in PSA level within two years suggests the ability of pathogen associated molecular pattern substances (PAMP) to induce fever, which could be a possible alternative to treat cancer.



Glossary

Pyrogenic – A polypeptide substance released by bacteria into the blood that induces fever and inflammatory response.

PAMP – Pathogen Associated Molecular Pattern Substances. Molecules that are shared among related groups of microbes and are identified by the immune system.

Normothermia – Normal body temperature ranging from 97°F to 99°F.

Hypothermia – A body temperature below 95°F, which is considered dangerous and could cause death.

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