Medical Hypotheses

Medical Hypotheses (1988) 25, 125–129

The Role of the Primitive Sea in the Natural Selection of Iodides as a Regulating Factor in Inflammation

ORVILLE J. STONE

18700 Main Street, Suite 201, Huntingdon Beach, California 92648

Abstract — Iodides have many non-endocrine biologic effects, including a role they play in the physiology of the inflammatory response. Iodides when given systemically or applied locally increase the movement of granulocytes into areas of inflammation. They improve the phagocytosis of bacteria by granulocytes and the ability of granulocytes to kill bacteria. They alter native protein to make it more susceptible to enzymes produced by granulocytes. They increase glandular secretions and make mast cells more labile.

They concentrate around tumors and granulomas in man and animals. They also move into areas of tissue injury. When iodide is redistributing around sites of tumors or injuries there is decreased thyroid uptake and decreased renal excretion. The multiple effects of iodides have suggested that iodide may have a physiological role in inflammation. Iodides were once used widely in medicine, especially before a cure for syphilis. Understanding the many known effects of iodides requires crossing multiple fields.

The purpose of this paper is to propose that the rising iodide content of the primitive sea played a role in the natural selection of a system which helped the organism recover from tissue injury or invasion. As primative life forms underwent mutations those with a defense system more responsive to environmental factors, such as iodide, had the best chance of survival. It was important for a defense system to move to any point of surface injury. The diverse biologic effects of iodides suggest a very primative role. This effect was so important that it was later internalized so that today iodides are concentrated in the host around sites of injury or tumor growth.

For the purposes of this paper the effect of iodides on inflammation and the redistribution of iodides around sites of injury or tumor growth will be emphasized. Iodides' endocrine role is of undoubted great significance; so much so, that it has overshadowed other functions.

Effect of Iodides on Inflammation

In my first year of specialty training, I was told that the way by which iodides cured sporotrichosis was a mystery. The organism that caused the disorder could live in a significant concentration of the potassium iodide which was used therapeutically in small oral doses. I also read that iodides caused resolution or prevented formation of the gummas of syphilis and that they consistently aggravated acne and dermatitis herpetiformis. It appeared that some broad mechanism was involved.

I spent a year studying the effect of iodide on various models and eventually found iodide increased early cellular inflammation.[1] Then, on a more detailed review of the literature, I found I had only rediscovered what had been studied much more thoroughly by others.[2,3,4] I also found by review of other fields that iodide has multiple known non-endocrine biologic effects.[5] I believe the non-endocrine biologic effects of iodides have been overshadowed by iodides' endocrine role.

Iodides were repeatedly found to be pro-inflammatory. It seems to be inconsistent that a substance that increases granulocytic inflammation should be therapeutic for chronic inflammatory disorders. My reasoning was that increased granulocytic inflammation could clear certain chronic inflammation by speeding microdebridement of tissue.[1,5] I cannot find this explanation used in the past for sporotrichosis or gummas, but Kolmer et al[4] came close to this terminology in his description of iodides effect on the Luetin test, as discussed later. Today, twenty years after I published the concept, it is still basically ignored.

I showed that in humans iodides significantly increased inflammation when applied topically over sites of injections of dead bacteria.[1] It had been known for years that if humans were patch tested with iodides they occasionally developed a pustule in the patch test site.[6] This was known to be unrelated to allergy and just occurred sporadically and never consistently in the same patient. In my human model all test sites covered by potassium iodide became tender and developed more severe inflammation and induration over the sites by the end of 22 hours. None of the control sites became tender. The ointment caused no irritation of normal skin.

It appears that the pustular patch test that had occurred sporadically represented patch tests placed over sites of subclinical folliculitis or inflammation. The iodide patch test increased the reaction to form a clinical pustule.

Inflammation — Historical

In 1896, Unna[7] stated that the formation of pustular lesions in the skin of persons on iodides was so common and characteristic that "it is almost a physiological response." I believe he meant to imply pharmacologic. Hinz,[8] in 1899, stated that iodides make leukocytes more active.

It is important to realize that syphilis was a very significant disease in the early part of the century. Iodides were widely used for many disorders and within one year of the discovery of iodides it was reported to cause the resolution of gummas (the type of chronic granuloma that occurs in syphilis). In 1915, there was a much debated skin test for syphilis known as the Luetin test which consisted of the injection of agar and a spirochete antigen. A pustular reaction was considered positive. Since iodides prevented gummas from forming, most patients suspected of having syphilis had been placed on iodides. In 1915, Sherrick[2] showed that a pustular or nodular Leutin reaction could be obtained in 99% of all patients, irrespective of the presence of syphilis, by the administration of potassium iodide. The test determined whether the patient was on iodide therapy rather than whether he had syphilis. The next two papers by Kolmer et al[3,4] in 1961 and 1917, studied the phenomenon in far greater detail. They studied non-syphilitic human volunteers and also guinea pigs and rabbits. The 1917 paper stated, "Iodides apparently increase the purely inflammatory and suppurative phases of skin reactions. As many of the reactions influenced by potassium iodide become pustular with extensive infiltration of the tissues with polymorphonuclear leukocytes, it is possible that the iodide may influence the leukocytes and facilitate the phagocytosis of the injected foreign material."

They concluded that substances most likely to induce inflammatory reactions in the skin appear to be most influenced by iodides. They determined that the total and differential leukocyte counts showed no significant alteration.

In 1934, Sulzberger et al[9] gave oral iodides to patients with acne and a control group. After two to three days all of the acne patients developed flares of existing lesions and many new lesions. Only one of 21 controls developed a few small acne lesions.

As noted above, in 1967 Stone and Willis[1]

showed that iodides increased induced inflammation in both systemic and topical models.

Additional Non-endocrine Biological Effects of Iodides

Iodides can influence many chemical reactions, but I have attempted to describe only reactions that I think are of physiologic significance.

In 1913, Rothschild[10] published the idea that iodide stimulated phagocytosis. Kolmer et al also reported that the serum of persons and rabbits receiving iodides had increased power for facilitating phagocytosis. Persons on iodides had higher phagocytic and opsonic indices.

Gerasimova[11] studied the effect of iodides on normal and thyroidectomized frogs. The phagocytic activity of granulocytes for *Escherichia coli* was significantly increased. Klebanoff[12] described bactericidal mechanism involving small amounts of iodide in viable granulocytes.

Iodides cause marked increases in bronchial and salivary secretions and even lacrimation. This effect is widely appreciated and, therefore, will not be reviewed in detail. It was widely used in expectorants. Increased lacrimal and bronchial secretions can be beneficial. Some investigators believe that glandular secretions and inflammation have similar mediators.

In 1915, Jobling and Peterson[13] showed that larger doses of iodides inhibited the antitryptic (anti-enzyme) activity of serum. The paper reviews the various theories about iodides' biologic effects as they were interpreted in 1915.

In 1964, Lieberman and Kurnick[14] published on how iodides decrease the viscosity of sputum. The studies suggest that iodides interact with the native protein in purulent sputum and enhanced its susceptibility to proteolytic enzymes from granulocytes. To be consistent with the hypothesis being presented here one would state that iodinated native protein is more susceptible to proteolytic enzymes from granulocytes.

Effects on Granulomas

Iodides have been used to treat granulomas and gummas for well over 100 years. The effect has often been referred to as "fibrolytic" or "histiolytic." Iodides have decreased the size of sterile granulomas.[15]

Iodides and Infections

Iodides are excellent treatment for sporotrichosis even though the organism survives in medium containing 10% potassium iodide. They were also used in some forms of tuberculosis, but their use was complex.[16,17] They also had some therapeutic effects against deep fungal infections. Stone[18] has previously reviewed how all the known therapeutic effects of iodides could be beneficial in sporotrichosis.

Distribution of Iodides in the Body

Numerous articles reported on the distribution of iodides in the body in various disease states such as infections, granulomas, and tumors. Early studies depended on chemical analysis and pharmacologic amounts of iodides. Later studies used physiologic amounts of radioactive iodide. The studies have generally agreed that iodides are more concentrated in infected, granulomatous or necrotic tissues, but some authors related this to increased extracellular space. Sternberg et al[19] felt that in small amounts iodides were concentrated in experimental, infected, granulation tissue but they did not find a connection when large doses were given.

Plasma iodide levels are elevated in patients and animals with tumors. The distribution in the tissue is also altered.

Scott[20] has described a phenomenon referred to as "iodide trapping." When a small subcutaneous tumor is implanted in an animal there is a higher than normal I-131 uptake in the skin for up to 5 cm. With larger tumors the entire skin took up almost twice the amount of I-131 as normal. Rats with large tumors showed a progressive reduction of thyroid uptake and urinary excretion of I-131. The data suggested increased tissue binding and a reducted glomerular filtration.

Scott and Peng[21] found that injection, or release of, histamine or 5-hydroxytryptamine will prevent excretion of I-131 and induces the iodide trapping phenomenon as discussed with tumors. Injection of histamine or 5-hydroxytryptamine causes increased distribution of iodides to the skin which then increases the lability of mast cells. Cantin[22] showed that larger doses of iodides rupture mast cells.

The Trapping Phenomenon

The work of Scott and Peng[21] which showed that an injury of the animals skin caused a binding of physiologic doses of iodides in the surrounding area, made the mast cells in the area more labile, and also decreased thyroid uptake of iodide and decreased urinary output. This phenomenon

could be triggered in multiple ways. If one believes in inflammation as a generally beneficial response, iodides effects appear as a series of events that contribute to increased inflammation and thus host defense. In prior publications I published the concept that iodide might play a role in the physiologic regulation of inflammation.

Hypothesis — Role of Environmental Iodides

The system of "iodide trapping" and the many biologic effects of iodides is extremely complex to have occurred by chance. Admittedly, iodide is a very active chemical so it could have all these effects on a non-specific basis. However, the "trapping phenomenon" of localizing a substance at sites of injuries which in turn influence many therapeutic and physiologic responses seems unlikely to be chance. The purpose of this paper is to point out that the concentration of iodide in the sea was known to be gradually increasing at the time when primitive life forms were developing. Whenever injuries occurred to primitive life forms, the ones that responded to repair the best had the greatest chance of survival. Since iodides were gradually increasing in the environment, primitive life forms that developed mutations that were more sensitive in their response to injury to the iodide in the environment had the best chance of survival. It would almost be surprising if it did not play a role in natural selection. By the time primitive life forms moved into water with lesser iodide content (fresh water) or an amphibious stage this iodide mechanism had become so important that mutations that shifted internal iodide into injury sites had the best chance of survival. I do not know enough to try to incorporate endocrine function with these other non-endocrine biologic effects. I do not know if endocrine function became so important that an adequate dose of iodide for the thyroid was more than adequate to cover the normal non-endocrine biologic effects of iodides. However, extra iodides did cure sporotrichosis and remove gummas in persons who were not hypothyroid. The author still thinks that the non-endocrine biologic effects of iodides are of physiological importance. This is not to state that iodides by themselves are going to solve a large number of medical problems. Extensive human use of iodides occurred many years ago and it was even preceded by studies with burnt sponge. As we gradually learn to manipulate inflammation to host advantage, the role of iodides could be more important.

Allergy to Iodides

Stone[1,5] has previously reviewed the many known side effects of iodides. In his opinion iodide is no more a cause of allergic reactions than sodium, chloride, or potassium. It does cause adverse reactions but they are a consequence of physiologic or pharmacologic effects. Iodinated compounds are a completely different matter and allergic reactions certainly can occur. Proliferative inflammatory lesions are one of iodides known reactions. Stone[2,3] has recently explained the mechanism for this reaction based on the release of connective tissue — active peptides from granulocytes. Iodides would probably be more widely used, especially for pulmonary disease, if it were not for adverse effects.

Additional Comment

Iodides may be old fashioned medication but they play a definite role in the series of events that occur in response to injury, infection or tumors.

There is a vast, but old, literature on iodides that may contribute to better understanding. For example, the syphilologist realized if the patient developed excess tearing and secretions the symptoms could often be eliminated by increasing the dosage of iodides. This suggests that some of iodides' effects only occur in a specific dosage range.

Abstract

Iodides role in endocrine disorders is of great importance. However, iodides have many other non-endocrine effects. They initiate reactions that can be beneficial at sites of injury, infections, or tumors. One of iodides known functions is increased movement of granulocytes into areas of inflammation. They improve phagocytosis of bacteria by granulocytes and play a role in helping kill bacteria in granulocytes. They can change native protein to make it more susceptible to the enzymes released by granulocytes.

Iodides are redistributed in the body to concentrate in the area around tumors or injuries.

The fact that iodides concentrate around injury and act in multiple ways to promote host defense suggests that they play a physiologic role in inflammation.

This paper proposes that the increasing

concentration of iodides in the sea at the time of evolution of early life forms played a role in the natural selection of host defense mechanisms. This role became so important that it was internalized in more developed life forms that were no longer in an environment containing external iodides. The selective movement of iodides into sites of injury and their multiple beneficial effects on host defense seems to the author to be more than a coincidence.

Iodide was once a major medication and there is a vast store of empiric and experimental knowledge. Iodides can cure sporotrichosis and cause regressions of gummas of syphilis but they might also have an important clinical role in regulating physiologic inflammation.

References

1. Stone O J, Willis C J. Iodide enhance of inflammation-experimental with clinical correlation. Texas Rep Biol Med 25: 205, 1967.
2. Sherrick J W. The effect of potassium iodide on the leutin reaction. JAMA 65: 404, 1915.
3. Kolmer J A, Matsunami T, Broadwell S. The effect of potassium iodide on the luetin reaction. JAMA 67: 718, 1916.
4. Kolmer J A, Immerman S L, Matsunami T, Montgomery C M. The effect of certain drugs upon skin reactions. J Lab Clin Med 2: 401, 1917.
5. Stone O J. What are the non-endocrine biologic effects of iodides? Medical Times 99: 143, 1971.
6. Fisher A A, Chargin L, Fleishmajer R, Hyman A. Pustular patch test reaction. Arch Derm 80: 742, 1959.
7. Unna P G. The histopathology of diseases of the skin. pp 104. New York: 1896.
8. Heinz R., Ueber Jod and Jod-verbindungen. Virchows Arch F. Path Anat 155: 44, 1899.
9. Sulzberger M B, Rostenberg A Jr, Sher J J. Acneform eruptions. New York State J Med 34: 899, 1934.
10. Rothschild D. Der einfluss der jodmedikation auf die sputum-phagocytose der tuberkel bazillen. Deutsch Med Wchnschr 39: 404, 1915.
11. Gerasimova N F. Effect of iodide as a trace element on the phagocytic activity of leukocytes. Pat Fiziol Eksp Ter 10: 69, 1966.
12. Klebanoff S J. Iodination of bacteria: bactericidal mechanism. J Exper Med 126: 1063, 1967.
13. Jobling J W, Peterson W. The therapeutic action of iodide. Arch Int Med 15: 286, 1915.
14. Lieberman J, Kurnick N B. The induction of proteolysis in purulent sputum by iodides. J Clin Invest 43: 1892, 1964.
15. Sutter M D, Adjarian R, Haskell A R. Observations on the therapeutic activity of cuprous iodide. J Amer Vet Med Assoc 132: 279, 1958.
16. Woody E Jr, Avery R C. The combined effect of potassium iodide and streptomycin on established tuberculosis in guinea pigs. Science 108: 501, 1948.
17. Editorial. Potassium iodide and streptomycin for tuberculosis. New Engl J Med 240: 664, 1949.
18. Stone O J. How iodides cure sporotrichosis by increasing inflammation. Texas Medicine 65: 53, 1969.
19. Sternberg T H, Newcomer V D, Steffen C G, Fields M, Libby R L. The distribution of radioactive iodide (I-131) in experimental coccidiodomycosis and sporotrichosis. J Invest Derm 24: 397, 1955.
20. Scott K G. The mast cell, its amines, and tumor growth in rodents and man. Ann N Y Acad Sci 103: 285, 1963.
21. Scott K G, Peng C T: Tumor-host studies, the physiological and pharmacological action of an iodide trapping substance formed in tumor-bearing animals. Univ of Calif Publ Pharmacol 2: 345, 1955.
22. Cantin M. Study of a generalized erythema induced by iodides. J Invest Derm 48: 560, 1967.
23. Stone O J. Proliferative iodo derma. Int J Dermatol 24: 565, 1985.