METHODS, COMPOSITIONS AND ARTICLES OF MANUFACTURE FOR ENHANCING SURVIVABILITY OF CELLS, TISSUES, ORGANS, AND ORGANISMS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is continuation of U.S. patent application Ser. No. 11/408,734, filed Apr. 20, 2006 which claims the benefit of U.S. Provisional Patent Application No. 60/762,462, filed Jan. 26, 2006; 60/731,549, filed Oct. 28, 2005; 60/713,073, filed Aug. 31, 2005; 60/673,037, filed Apr. 20, 2005; and 60/673,295, filed Apr. 20, 2005. Each of which is hereby incorporated by reference in its entirety.

[0002] The government may own rights in the present invention pursuant to grant number GM048435 from the National Institute of General Medical Sciences (NIGMS).

TECHNICAL FIELD

[0003] The present invention relates generally to the field of cell biology and physiology. More particularly, it concerns methods, compositions and apparatuses for enhancing survivability of and/or reducing damage to cells, tissues, organs, and organisms, particularly under adverse conditions, including but not limited to hypoxic or anoxic states, using one or more substances, including those that compete with oxygen. In certain embodiments, the present invention includes methods, compositions and apparatuses for treating, preventing, and diagnosing diseases and conditions by exposing a subject to an oxygen antagonist, protective metabolic agent, or other chemical compound discussed herein, or a precursor thereof, that can achieve its stated goal (collectively referred to as "active compounds").

BACKGROUND

[0004] Stasis is a Latin term meaning "standstill." In the context of stasis in living tissues, the most common forms of stasis relate to the preservation of tissues for transplant or reattachment. Typically, such tissues are immersed in a physiologic fluid, such as saline, and placed in the cold to reduce biochemical processes leading to cellular damage. This stasis is incomplete and cannot be relied upon for extended periods. In fact, the success of organ transplant and limb reattachment is inversely related to the time the organ or limb is out of contact with the intact organism.

[0005] A more extreme version of stasis involves placing an entire organism into what is known colloquially as "suspended animation." Though still considered largely within the realm of science fiction, some notoriety has been achieved when wealthy individuals have sought to be cryopreserved after death, in the hope that future medical breakthroughs will permit their revival and cure of their fatal ailments. Allegedly, more than one hundred people have been cryopreserved since the first attempt in 1967, and more than one thousand people have made legal and financial arrangements for cryonics with one of several organizations, for example, Alcor Life Extension Foundation. Such methods involve the administration of anti-ischemic drugs, low temperature preservation, and methods to perfuse whole organisms with cryosuspension fluids. It has not yet been substantiated that this form of organismal stasis is reversible.

[0006] The utility of inducing stasis in biological matter as contemplated by the compositions, methods, or articles of manufacture described herein, is characterized by induction or onset of stasis followed by a period of time in which the stasis is maintained, followed then by reversion to a normal or near normal physiological state, or a state that one skilled in the art would recognize as a state that is better than the state of the biological matter had it never undergone stasis, in whole or in part. Stasis can also be defined as what it is not. Organismal stasis is not any of the following states: sleep, comatose, death, anesthetized, or grand mal seizure.

[0007] There are numerous reports of individuals who have survived apparent cessation of pulse and respiration after exposure to hypothermic conditions, usually in cold-water immersion. Though not fully understood by scientists, the ability to survive such situations likely derives from what is called the "mammalian diving reflex." This reflex is believed to stimulate the vagal nervous system, which controls the lungs, heart, larynx and esophagus, in order to protect vital organs. Presumably, cold-water stimulation of nerve receptors on the skin causes shunting of blood to the brain and to the heart, and away from the skin, the gastrointestinal tract and extremities. At the same time, a protective reflex bradycardia, or slowing of the heart beat, conserves the dwindling oxygen supplies within the body. Unfortunately, the expression of this reflex is not the same in all people, and is believed to be a factor in only 10-20% percent of cold-water immersion cases.

[0008] Compositions and methods that do not rely fully or at all on hypothermia and/or oxygen may be useful in the context of organ preservation, as well as for tissue or cell preservation. Cells and tissue are currently preserved using hypothermia, frequently at temperatures substantially below freezing, such as in liquid nitrogen. However, dependence on temperature can be problematic, as apparatuses and agents for producing such low temperatures may not be readily available when needed or they may require replacement. For example, tissue culture cells are often stored for periods of time in tanks that hold liquid nitrogen; however, these tanks frequently require that the liquid nitrogen in the unit be periodically replaced, otherwise it becomes depleted and the temperature is not maintained. Furthermore, damage to cells and tissue occurs as a result of the freeze/thaw process. Thus, improved techniques are needed.

[0009] Moreover, the lack of ability to control cellular and physiologic metabolism in whole organisms subjected to traumas such as amputation and hypothermia is a key shortcoming in the medical field. On the other hand, the anecdotal evidence discussed above strongly suggests that if properly understood and regulated, it is possible to induce stasis in cells, tissues and whole organisms. Thus, there is a great need for improved methods for controlling metabolic processes particularly under traumatic conditions.

SUMMARY

[0010] Therefore, the present invention provides methods, compositions, articles of manufacture, and apparatuses to induce stasis in cells, tissues and organs located within or derived from an organism, as well as in the organism itself. Such methods, compositions, articles of manufacture, and apparatuses can be employed to protect biological matter, as well as to prevent, treat, or diagnose diseases and conditions in the organism. In addition, such methods may directly induce stasis themselves, or they may act indirectly by not inducing stasis themselves, but by enhancing the ability of biological matter to enter stasis in response to an injury or