USING ALTERNATING ELECTRIC FIELDS TO INCREASE PERMEABILITY OF THE BLOOD BRAIN BARRIER

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims the benefit of US Provisional Application 62/722,100, filed August 23, 2018, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Ordinarily, cerebral microvessels strictly regulate the transfer of substances between the blood and the brain tissue. This regulation by cerebral micro-vessels is called the blood–brain barrier (BBB), and is due to intercellular tight junctions (TJs) that form between brain capillary endothelial cells. In cerebral capillaries, TJs proteins are expressed 50–100 times more than in peripheral microvessels. TJs are formed by an intricate complex of transmembrane proteins (claudin and occludin) with cytoplasmic accessory proteins (ZO-1 and -2, cingulin, AF-6, and 7H6). By linking to the actin cytoskeleton, these proteins form a strong cell–cell connection. Brain endothelial cells, which form the endothelium of cerebral microvessels, are responsible for about 75–80% of the BBB's resistance to substances, and other cells such as astrocytes and pericytes provide the remainder of the resistance.

[0003] The BBB consists of tight junctions around the capillaries, and it ordinarily restricts diffusion of microscopic objects and large or hydrophilic molecules into the brain, while allowing for the diffusion of hydrophobic molecules (transcellular instead of paracellular transport).

[0004] In healthy people, the BBB serves a very important function because it prevents harmful substances (e.g. bacteria, viruses, and potentially harmful large or hydrophilic molecules) from entering the brain. There are, however, situations where the action of the BBB introduces difficulties. For example, it might be desirable to deliver large or hydrophilic drug molecules to treat a disease in the patient's brain. But when the BBB is operating normally, these drugs are blocked from entering the brain by the BBB.

SUMMARY OF THE INVENTION

[0004a] According to an aspect of the present invention, there is disclosed an apparatus for treating a tumor in a subject's body and facilitating delivery of a substance across a blood brain barrier of the subject's body, the apparatus comprising:

an AC voltage generator having a control input and being configured to output an alternating electric field at a first frequency when the control input is in a first state and a second frequency when the control input is in a second state; and

a controller programmed to (a) place the control input in the second state so that the AC voltage generator outputs the alternating electric field at the second frequency, (b) accept a request to switch the AC voltage generator to output the alternating electric field to the first frequency, (c) upon receipt of the request, place the control input in the first state so that the AC voltage generator outputs the alternating electric field at the first frequency for an interval of time, and (d) after the interval of time has elapsed, place the control input in the second state so that the AC voltage generator outputs the alternating field at the second frequency, wherein the first frequency is between 75 kHz and 125 kHz and the second frequency is between 150 kHz and 250 kHz, and wherein the interval of time is at least 24 hours.

[0005] There is disclosed a method for delivering a substance across a blood brain barrier of a subject's brain. In this first method, the relevant

substance can be delivered across a blood brain barrier of a subject's brain by applying an alternating electric field to the subject's brain for a period of time. Application of the alternating electric field to the subject's brain for the period of time increases permeability of the blood brain barrier in the subject's brain. The substance is administered to the subject after the period of time has elapsed, and the increased permeability of the blood brain barrier allows the substance to cross the blood brain barrier.

[0006] In some instances of the first method, the period of time is at least 48 hours. In some instances of the first method, the alternating electric field has a field strength of at least 1 V/cm in at least a portion of the subject's brain. In some instances of the first method, the alternating electric field is applied at a frequency between 75 kHz and 125 kHz, the period of time is at least 24 hours, and the alternating electric field has a field strength of at least 1 V/cm in at least a portion of the subject's brain.

[0007] In some instances of the first method, the administering of the substance is performed intravenously. In some instances of the first method, the administering of the substance is performed orally. In some instances of the first method, the subject's brain is tumor-free.

[0008] In some instances of the first method, the substance comprises a drug for treating a disease. Examples of these instances include a cancer treatment drug, an infectious disease treatment drug, a neurodegenerative disease treatment drug, or an auto-immune disease treatment drug, an anti-epileptic drug, a hydrocephalus drug, a stroke intervention drug, or a psychiatric drug. In some instances of the first method, the substance is used for monitoring brain activity. Examples of these instances include a brain dye, a reporter, or a marker.

[0009] In any of the instances of the first method noted above, discontinuing the application of the alternating electric field may be done to allow the blood brain barrier to recover.

[0010] There is also disclosed a method for delivering a substance across a blood brain barrier of a subject's brain. In this second method, the relevant substance can be delivered across a blood brain barrier of a subject's brain by applying an alternating electric field at a first frequency to the subject's brain for a period of time,

WHAT IS CLAIMED IS:

1. An apparatus for treating a tumor in a subject's body and facilitating delivery of a substance across a blood brain barrier of the subject's body, the apparatus comprising:
an AC voltage generator capable of generating an alternating electric field having a control input, wherein the AC voltage generator is configured to output the alternating electric field at a first frequency when the control input is in a first state and a second frequency when the control input is in a second state; and
a controller programmed to (a) place the control input in the second state so that the AC voltage generator outputs the alternating electric field at the second frequency, (b) accept a request to switch the AC voltage generator to output the alternating electric field to the first frequency, (c) upon receipt of the request, place the control input in the first state so that the AC voltage generator outputs the alternating electric field at the first frequency for an interval of time, and (d) after the interval of time has elapsed, place the control input in the second state so that the AC voltage generator outputs the alternating electric field at the second frequency, wherein the first frequency is between 75 kHz and 125 kHz, and the second frequency is between 150 kHz and 250 kHz, and wherein the interval of time is at least 24 hours.

2. The apparatus of claim 1, further comprising:
a set of electrodes configured for affixation to the subject's body; and
wiring that connects an output of the AC voltage generator to the set of electrodes.

3. The apparatus of claim 1, wherein the second frequency is between 190 kHz and 210 kHz.

4. The apparatus of claim 1, wherein the alternating electric field has a field strength of at least 1 V/cm in at least a portion of the subject's brain.

5. The apparatus of claim 1, wherein the interval of time is at least 48 hours, optionally at least 72 hours.

6. The apparatus of claim 1, wherein the interval of time comprises a single uninterrupted interval of time that is at least one week long.

7. The apparatus of claim 1, wherein the controller is further programmed to, subsequent to the receipt of the request, switch the control input back and forth between the first state and the second state.

8. The apparatus of claim 1, wherein the AC voltage generator is capable of generating the alternating electric field at at least one additional frequency between 50 kHz and 500 kHz and configured to output the at least one additional frequency when the control input is in at least one additional state, and the controller is programmed to cycle the control input through the second state and the at least one additional state prior to receipt of the request, and cycle the control input through the second state and the at least one additional state after the interval of time has elapsed.

9. The apparatus of claim 1, further comprising:
a user interface, wherein the request is accepted via the user interface; or
wherein the request is accepted via RF.

10. The apparatus of claim 1, wherein the substance has a molecular weight of at least 4 kDa, optionally at least 69 kDa.

11. The apparatus of claim 1, wherein the substance comprises a drug for treating a disease, optionally the drug comprises a cancer treatment drug, an infectious disease treatment drug, a neurodegenerative disease treatment drug, an auto-immune disease treatment drug, an anti-epileptic drug, a hydrocephalus drug, a stroke intervention drug or a psychiatric drug.

12. The apparatus of claim 1, wherein the substance is used for monitoring brain activity, optionally the substance is a brain dye, a reporter or a marker.