Title: NEUROTRANSMITTER BALANCE CHEMOTHERAPY

Abstract: A protocol for modulating neurotransmitter balance so as, for example, to prevent Alzheimer’s disease onset is described. The protocol involves stimulating the implicit memory, followed by continuing such stimulation in conjunction with psychological treatments followed by continuing said stimulation of the implicit memory and, in addition, stimulating the explicit memory.
NEUROTRANSMITTER BALANCE CHEMOTHERAPY

Technical Field

[0001] The invention relates to restoring or maintaining neurotransmitter balance in a subject, using a combination of chemotherapeutic assistance and psychological counseling. More specifically, it relates to a three-stage protocol for effecting this balance, thus having a positive effect on the immune system and preventing dementia.

Background Art

[0002] A large number of pharmacological agents that affect neurotransmitter balance is known. Perhaps one of the best known is the combination Fen-Phen used for many years to exert an anorectic effect to treat obesity. This combination of phentermine and fenfluramine was available until recently when the cardiopulmonary side effects of this medicament were considered unacceptable. Both of these components are related to amphetamines and are epinephrine analogs which can be used to combat fatigue and drowsiness. The use of, for example, donepezil to treat the symptoms of Alzheimer’s disease is also known. In short, a variety of agents known to affect the central nervous system have been used in various contexts to treat a number of indications related directly or indirectly to behaviors.

[0003] At present, however, there appears to be no established treatment that is adaptable generally to assuring appropriate neurotransmitter balance. The present invention provides such a protocol.

[0004] The protocol of the present invention restores the normal balance of the various neurotransmitters mediated by norepinephrine, dopamine, serotonin and acetyl choline. By virtue of the imbalance in the behavior of these neurotransmitters, chronic conditions such as cancer and Alzheimer’s disease may occur. Therefore, by restoring the balance, the protocols of the invention operate as preventative for these conditions.

Disclosure of the Invention

[0005] The invention protocol relates to a method to prevent the onset of chronic conditions such as Alzheimer’s disease and cancer by restoring appropriate neurotransmitter balance. The capacity of the protocol to prevent cancer may be mediated by a positive effect on the immune system.
[0006] The invention relates to a three-stage protocol the length of which will vary with the nature of the subject treated.

[0007] The first stage comprises acute treatment with effective amounts of compounds that augment the activity of and generally affect the amine neurotransmitters that are associated with the sympathetic nervous system and which influence implicit memory. This treatment may be supplemented with specific aids as dictated by the condition of the subject.

[0008] The second stage involves maintaining chemotherapy with these amine neurotransmitter augmenting compounds but adds a component of psychology/supportive therapy. The third stage comprises administering an acetylcholinesterase (AChase) inhibitor along with the compounds described above with respect to stages I and II. The third stage mimics the psychological condition of rapid eye movement (REM) sleep.

[0009] The protocol may be supplemented by a superimposed treatment whereby diurnal variation is mimicked by administration of a corticosteroid, such as prednisone.

Modes of Carrying Out the Invention

[0010] The subjects for which the invention protocol is intended are human subjects who would be benefited by modification of, or maintenance of, neurotransmitter balance.

[0011] An important component of the intended balance involves implicit memory. In general, the habitual behavior is controlled by “implicit memory.” “Implicit memory” includes the unintentional recall of events or activities that influence behavior. The implicit memory is highly overlapped with all implicit cortical function. The implicit cortical function spectrum includes all sensory input, the transfer of that input to the metabolic cortex, and the function of the metabolic cortex. The metabolic cortex controls all metabolic function: digestion/nutrition, immune function, neuroendocrine function, all major organ systems, and surveillance of body homeostasis to initiate change. The protocol herein is based on supporting implicit function (memory/cortical) and thus allowing the “normalization” of implicit cortical functioning. Implicit memory is controlled by amine neurotransmitters, most prominently serotonin, norepinephrine, and dopamine. Implicit memory is brought to bear in behaviors that are permanently available and relatively unconsciously
controlled. Exemplary behaviors of this type often include a physical component.
Motor skills such as riding a bicycle, skiing, swimming, ice skating and the like, once
learned, are essentially permanent. Conscious mechanisms are not required to bring
them to recall.

[0012] On the other hand, "explicit memory" as defined herein relates to a conscious
and deliberate recall of recent events and volitional behavior. In general, this type of
memory is controlled by a single neurotransmitter, acetylcholine. In stage III of the
protocol described herein, the explicit memory is stimulated along with the implicit
memory, thus mimicking the transfer of elements from explicit to implicit memory
similar to that which occurs in REM sleep. This transfer, in general, permits
replacement of a good result which has been implanted in the explicit memory into the
realm of the implicit memory. Thus, the information and behavior patterns explicitly
learned in stage II of the invention protocol are transferred into the implicit memory in
stage III.

[0013] By improving implicit function, an improvement an innervation of explicit
memory/cortical function is accomplished since the sensory input prepares the implicit
cortex for the appropriate metabolic changes necessary to run the body. Only after that
has been done does the explicit cortex receive the appropriate signal from the implicit
side, which can then feed the appropriate signals. The improvement in explicit cortical
function on a long-term basis prevents the chronic isolation of the explicit cortex.

[0014] Thus, the protocols of the invention can be used to restore appropriate
neurotransmitter balance in anyone where imbalance occurs. It is believed that
imbalance in neurotransmitters negatively affects the immune system, which in turn
lowers the resistance of the individual to the onset of malignancy and that this
imbalance also contributes to the onset of Alzheimer's disease.

[0015] Adult onset allergies and complaints of sinusitis have been identified and
treated, and the protocols herein have been associated with an improvement or
sometimes resolution of these problems. Chronic asthma universally improves, not in
the acute exacerbation and treatment but in the chronic stable state with an association
of fewer medications needed to maintain that stability.

[0016] Explicit cortical function (cognitive function) has been seen to improve in
nearly all cases. This has been associated with less confusion, better word finding,
fewer "senior moments", improved letter grades.
[0017] The cancer rate in the thousands of people treated as described herein is with low. The incidence of cancers in the treated patients over the 18 years using these protocols is extremely low. Furthermore, the few cancers have been well differentiated ones (a less aggressive cell type) and it appears all patients are in a “no evidence of disease” state at this time.

[0018] As set forth above, the method of the invention is a protocol that involves three stages of treatment. The first stage, initial therapy, is designed to activate the implicit memory to make the these neurotransmitters available for modification. The pharmacological agents useful in this stage are compounds that stimulate amine neurotransmitters of the sympathetic nervous system. In general, these compounds are amines which are related to the three major neurotransmitters, serotonin, norepinephrine, and dopamine. Included among these are compounds related to norepinephrine such as ethylnorepinephrine, metaraminol, tyramine, hydroxyamphetamine, methoxamine, albuterol, metamphetamine, benzphetamine, phenylpropanolamine, phentermine, fenfluramine (Pondamin) and dextfenfluramine (Redux), diethylpropion, phentraizine and phendimetrazine. Preferred among these is a combination of phentermine (Ionamin, Adipex) and fenfluramine (Pondamin).

[0019] Also useful in stage I is administration of a selective serotonin reuptake inhibitor (SSRI) such as citalopram (Celexa), fluoxetine HCl (Prozac), fluoxamine maleate (Luvox), paroxetine HCl (Paxil) and sertraline HCl (Zoloft). Also useful are drugs which affect dopamine receptors, such as apomorphine and its derivatives.

[0020] The dosage of the compounds administered to stimulate the sympathetic nervous system and implicit memory will depend on the specific pharmacologic agent chosen, the condition of the subject, and the judgment of the physician. However, for the combination of phentermine and fenfluramine, preferred dosage ranges are approximately 10 mg fenfluramine and 15-30 mg of phentermine daily. Typical dosages of citalopram are of the order of 10 mg daily.

[0021] In addition to the general implicit memory stimulators of the types set forth above, supplemental medication may also be indicated. Where the subject shows severe dependency, or is desirous of modifying a multiplicity of habits, an adrenergic agonist selective for the α2 receptor is also desirable. These compounds are typically imidazolines and are typified by clonidine. The effects of clonidine appear to result from activation of the α2 receptors in the lower brain stem region, and clonidine has
been used previously in treating subjects addicted to drugs, alcohol and tobacco, which may themselves adversely affect the balance. Clonidine is considered to help ameliorate adverse sympathetic nervous activity associated with withdrawal from these agents. If clonidine is used, typical dosage levels are on the order of 0.1 - 0.4 mg orally, daily. It can also be administered as a patch.

**[0022]** Other supplementary medications which are employed in stage I are specific for particular addictions. Thus, a nicotine patch may be useful where the subject is addicted to smoking; a low-dose nicotine patch which provides 7 mg is typical, alternate dosage levels can also be used. If the habit to be shed is alcoholism, a supplementary dose of benzodiazapine may also be helpful.

**[0023]** For treatment of obesity due to overeating, the subject is generally placed on a low-calorie or very-low-calorie diet. One such diet is marketed as Nutrimed which is a high-protein, low-carbohydrate, semistarvation fast. The standard protocol for providing Nutrimed regimens utilizes five “milkshake” like compositions per day to supply 420 kcal. It is helpful to modify this regimen to include, as a substitute for one or two of the “shakes,” a small meal so that the subject can experience the social interaction associated with dining. The inclusion of this modification has been helpful in ensuring compliance. The use of this regimen, modified or unmodified, is also sometimes helpful in subjects who are not obese and inclusion of this regimen in the therapeutic protocol has been found successful in a number of instances.

**[0024]** In general, very low calorie diets generally successfully block hunger driven by habit rather than by appetite. Such habit-driven hunger is an example of behavior controlled by implicit memory but governed by an external metabolic agent. Used in conjunction with therapies for treating external habits, very low calorie diets can supplement the effectiveness of these therapies.

**[0025]** In addition, if the subject has other physiological conditions that aggravate possible side effects of the stimulators of the implicit memory, offsetting medications such as β-blockers, which reduce heart rate, lower blood pressure, and ameliorate hypertension may be added to the protocol. Typical β-blockers which may be provided to ameliorate hypertension include atenolol (Tenormin), usually in dosages of 12.5-50 mg.
With regard to hypertension, however, a preferable treatment may include vasodilators such as amlodipine besylate, marketed as Norvasc® and nifedipine marketed as Procardia® or Adalat®.

Thus, stage I involves, in general, stimulation of the implicit memory using appropriate compounds that stimulate amine neurotransmitters associated with the sympathetic nervous system supplemented with additional medications if desirable. The duration of stage I will vary from subject to subject. It may be as short as 1-3 weeks but may extend longer.

Stage II, which provides the basis for long-term control, continues the administration of stimulators of the implicit memory as done in stage I. The dosages and protocols for administration of these stimulators may be identical to that of stage I or may be modified according to the response perceived in the subject. In addition, medications which are used to control adverse effects of the primary effectors of implicit memory activity may also be used. Thus, for example, for hypertension, the administration of β-blockers may be continued.

Stage II differs from stage I in that a component of psychological and supportive therapy is added. Most auxiliary medicaments are typically dropped. Conventional psychological and supportive treatment modalities are employed. These modalities are designed to affect the explicit memory and provide the basis for the deliberate recall of recent events that will be employed in stage III to result in more permanent balancing of neurotransmitter activity. The psychological and supportive therapy may be as simple as consultations with the attending physician or may be more formal in nature, such as psychiatric treatment. Generally a professional will provide this psychological and supportive therapy, although this could also be achieved through group counseling or intervention with respect to a care provider or other individual or individuals who routinely or often or sporadically interact with the subject of treatment.

The duration of stage II is also variable, but is typically several months to more than two years, most typically approximately 4-8 months. This stage is most susceptible to external influences, and the duration and intensity of the psychological and supportive component will vary depending in the case of human subjects, on the other circumstances in which the subject finds himself or herself. There is no theoretical upper limit to the duration of this stage, and Stage III can begin at any time, provided the effect of Stage II has been accomplished.
[0031] In stage III, the transfer of the behavior and effects placed into explicit memory in stage II into the implicit memory occurs. In stage III, stimulation of the implicit memory is continued as in stage II, with suitable variation in dosage and regimen if indicated. Stage III involves the addition of administration of an acetylcholine esterase (AChase) inhibitor such as donepezil. Other currently available AChase inhibitors include tacrine and pyridostigmine bromide. Also available are rivastigmine tartrate, marketed as Exelon® and galantamine hydrobromide, marketed as Reminyl®. Any AChase inhibitor or combination is within the scope of the invention. In stage III, both the implicit and explicit memory are stimulated, thus mimicking REM sleep. During this stage, the replacement of the learned behavior and effects from stage II into the implicit memory is accomplished. The duration of stage III also varies from subject to subject, but is typically on the order of 6-12 months; stage III is continued until successful results are achieved.

[0032] Once the three stages are completed, the protocol is successful in assurance of proper neurotransmitter balance.

[0033] As will be apparent from the foregoing, the timing of stage I, stage II and stage III is quite variable depending on factors not necessarily under the control of the practitioner. The duration of any particular stage is dependent on, for example, the level of social support available to the subject, whether or not there are multiple addictions, the presence or absence of physical or psychological problems, and the like. Thus, although suggested durations are provided above, it is anticipated that such times will vary widely. Determination of the appropriate timing for each stage is well within ordinary skill of the practitioner.

[0034] Optionally, superimposed on the above protocol at any stage or at more than one stage is treatment to mimic diurnal fluctuations in metabolism by administering a corticosteroid. Typical protocols include administering 5 mg of prednisone at 7 a.m. and 3 p.m. for the first month in which this aspect of the treatment is employed, and later reducing the dosage regimen to 5 mg at 7 a.m. and 2.5 mg at 3 p.m.

[0035] The examples below illustrate typical protocols useful in the invention. In addition, the following dosages are typical as a preferred embodiment:

for phentermine (Adipex-P 37.5) one-half pill or one pill daily; this product contains 30 mg phentermine per pill;

for fenfluramine, one-quarter, one-half, or (rarely) one pill daily of a 20-mg
tablet;

for citalopram (Celexa), one-fourth or one-half pill daily of a 20-mg tablet (if
the subject indicates use of a serotonin uptake inhibitor, one pill daily may be
prescribed);

for donepezil (Aricept), one-fourth to one-half pill daily as a 5-mg tablet.

[0036] The following examples are intended to illustrate but not to limit the
invention.

Example 1
Protocol for Preventing Alzheimer’s

[0037] The following protocol is suitable for a subject of normal size and weight not
suffering from hypertension or heart failure.

[0038] Stage I: 10 mg fenfluramine plus 30 mg phentermine daily for 2 weeks. The
administration of these drugs is accompanied by a daily administration of 10 mg
citalopram and 0.1 - 0.4 mg clonidine. The clonidine is administered as a transdermal
patch.

[0039] Stage II: 10 mg fenfluramine/30 mg phentermine daily plus 10 mg
citalopram daily for 6 months. Stage II also employs weekly 1-hour sessions with a
psychotherapist. The duration of stage II is 12 months.

[0040] Stage III: 10 mg fenfluramine/30 mg phentermine plus 10 mg citalopram
daily plus 2.5 mg donepezil daily. This regimen is continued for 6-12 months.

Example 2
Protocol for Enhancing Immune Function

[0041] The following protocol is suitable for a subject of normal size and weight not
suffering from hypertension or heart failure.

[0042] Stage I: 7 mg fenfluramine plus 25 mg phentermine daily for 3 weeks. The
administration of these drugs is accompanied by a daily administration of 15 mg
citalopram and 0.4 mg clonidine. The clonidine is administered as a transdermal patch.
The subject is also provided a low dose of benzodiazapine.
[0043] **Stage II:** 7 mg fenfluramine/25 mg phentermine daily plus 15 mg citalopram daily for 6 months. Stage II also employs weekly 1-hour sessions with a psychotherapist. The duration of stage II is 4 months.

[0044] **Stage III:** 7 mg fenfluramine/25 mg phentermine plus 15 mg citalopram daily plus 3.0 mg donepezil daily. This regimen is continued for 6-12 months.
Claims

1. A method to modulate neurotransmitter balance in a patient which method comprises
   a) administering to said subject an effective amount of at least one medicament that stimulates implicit memory for a time period sufficient to stimulate said implicit memory; followed by
   b) administering to said subject at least one medicament which stimulates implicit memory along with treating said subject with or causing said subject to be treated with psychotherapeutic or psychological support stimuli for a period sufficient to affect the explicit memory of said subject so as to learn a desired behavior or provide a desired effect; followed by
   c) administering to said subject an effective amount of at least one medicament that stimulates the implicit memory of said subject and at least one medicament which stimulates the explicit memory of said subject for a period sufficient to transfer the behavior learned from or effect achieved by, step b) from the explicit memory into the implicit memory,

whereby the neurotransmitter balance is modulated.

2. The method of claim 1 wherein said modulation results in prevention of Alzheimer’s disease onset.

3. The method of claim 1 wherein said modulation results in a level of protection against cancer.

4. The method of claim 1 wherein said modulation results in amelioration of asthma, allergies or sinusitis.

5. The method of claim 1 wherein said at least one medicament to stimulate the implicit memory comprises phentermine, fenfluramine and citalopram.

6. The method of claim 1 wherein the medicament to stimulate the explicit memory comprises donepezil, rivastigmine tartrate or galantamine HBr.
7. The method of claim 1 wherein the patent is at risk or is suffering from tachycardia and step a) further includes administering to said subject a β-blocker; or the subject is at risk or is suffering from hypertension and step a) further includes administering a vasodilator.

8. The method of claim 7 wherein the β-blocker is atenolol or the vasodilator is amlodipine besylate or nifedipine.

9. The method of claim 1 wherein the duration of step a) is about 1-3 weeks, of step b) is about 4-8 months, and of step c) is about 6-12 months.

10. The method of claim 1 which further comprises administering a corticosteroid to regulate diurnal metabolism during at least a portion of stage I and/or stage II and/or stage III.