Endorphinate® Science

Background

Endorphinate® is a proprietary and patent pending formulation based on the work of Dr. Stanley Crain, Professor Emeritus of Neuroscience at Albert Einstein College of Medicine, who spent more than 30 years researching opioid receptors. Dr. Crain's search for pharmaceuticals that could enhance the efficacy and reduce unwanted side effects of exogenous opioids (e.g., morphine, codeine) has led to the discovery of Endorphinate. Endorphinate is a unique and effective dietary supplement formulation that naturally enhances healthy adaptive emotional and physical responses to stress and injury by balancing neurotransmitter systems.

Dr. Crain has many issued patents for his methods to develop effective pain relieving drugs without aversive opioid side effects. Intellectual property in his pharmaceutical patents includes co-treating a subject with both an opioid and an agent that rebalances opioid receptor signaling. Preclinical studies with Dr. Crain's pharmaceutical formulations completed in mice were validated in a human Phase III FDA clinical trial with more than seven hundred chronic pain patients. (Webster et. al., Oxytrex Minimizes Physical Dependence While Providing Effective Analgesia: A Randomized Controlled Trial in Low Back Pain (The Journal of Pain, Vol. 7, No 12 (December), 2006: pp 937-946) .Two pending patents extend Dr. Crain's research with exogenous opioids (i.e. morphine, codeine) to endogenous opioids (endorphins). These pending patents opened the door to development of Endorphinate a nutraceutical formulation based on the complex interaction of endorphins and the opioid receptor system.

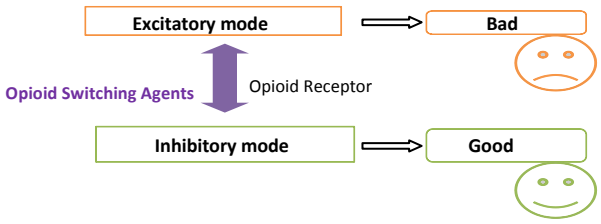
Endorphins are powerful natural opioids that act as signaling agents by binding to the opioid receptor. They are found in the cells of both the brain and the peripheral nervous system and resemble morphine and codeine in their ability to reduce pain and create a feeling of well-being. Endorphins are released when the body encounters any stimulus that requires an adaptive response (an appropriate reaction to an environmental demand). The adaptive response may be caused by negative stimuli such as pain and stress or rewarding stimuli such as love, orgasm and eating.

The Endorphinate formulation is based on Dr. Crain's groundbreaking discoveries:

1. Opioid receptors are unusually plastic protein molecules that can evoke inhibitory (good) or excitatory (bad) effects depending upon presence and concentration of specific biochemical molecules that regulate the structure of these receptors.

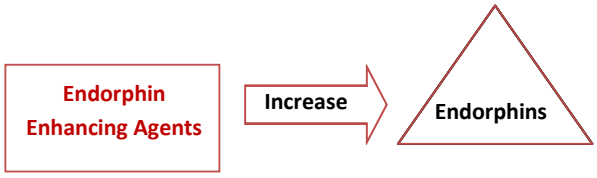
2. Certain molecules "switch" the structure of opioid receptors from excitatory to inhibitory mode. Certain molecules "switch" the opioid receptor from inhibitory to excitatory mode. (Figure A)

Figure A
Switching Agent Acts on Opioid Receptors



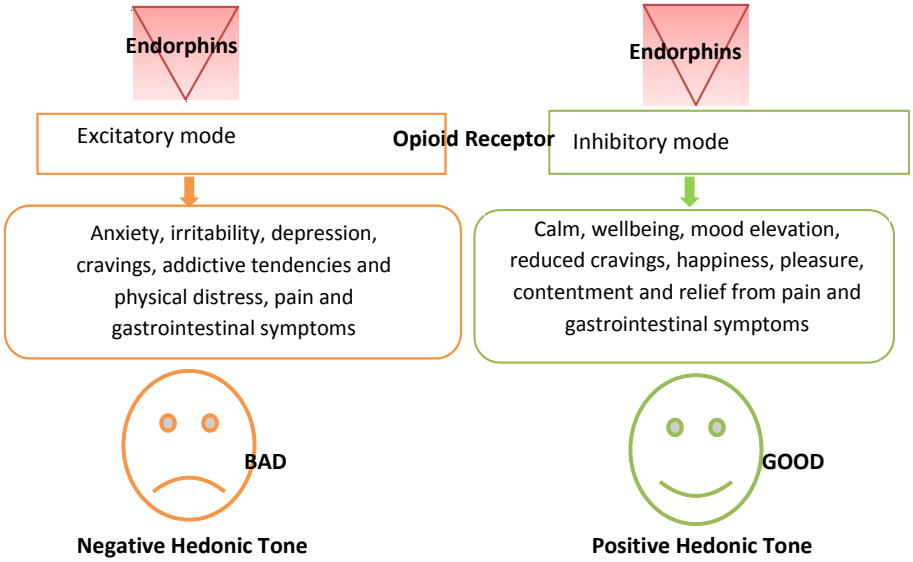
3. Certain molecules enhance the natural release of endorphins in the body. (Figure B)

Figure B
Endorphin Enhancing Agents



4. When endorphins are released, they bind to and trigger opioid receptor signaling and depending upon which mode the opioid receptor is in the response is fundamentally different (Figure C):

Figure C
The Binding of Endorphins to Opioid Receptor Results in Different Responses Depending on the Mode of the Opioid Receptor

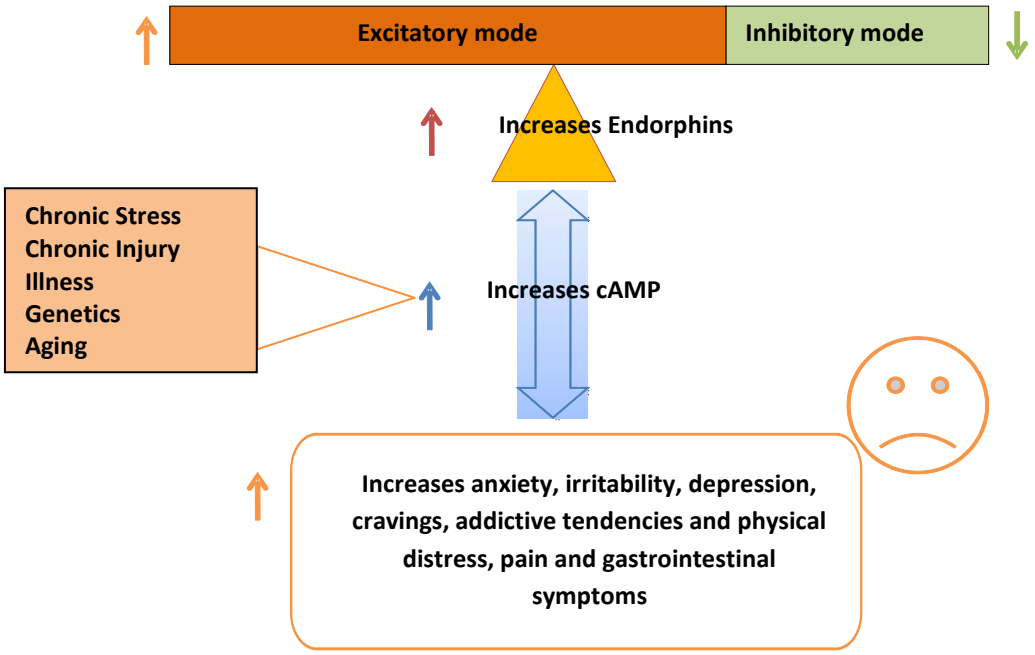


a. When the receptors are in the excitatory mode, endorphin signaling triggers a state of alert and perceived threat that produces emotional and physical distress including increased pain, anxiety, and urgent cravings for a way to relieve this distress (negative hedonic tone).
b. In contrast, when the receptors are in the inhibitory mode, endorphin signaling triggers a sense of reward and perceived safety in which pain is reduced and feelings of calm, wellbeing, happiness, pleasure, and contentment are produced (positive hedonic tone).

5. Unless there is a real and serious risk of imminent injury or harm that warrants acute excitatory signaling, the opioid receptors should generally be in the inhibitory mode so that endorphins maintain healthy positive hedonic tone.

6. For many people, an abnormal fraction of the opioid receptors are stuck in a protracted excitatory mode causing pain and anxiety when endorphins are released. (Figure D)

Figure D
Protracted Excitatory Mode



7. When specific agents that increase endorphins are combined with agents that re-balance opioid receptor signaling, the formulation enhances relief of pain and distress without having to resort to exogenous opioid narcotics.

8. When other specific agents are combined with agents that increase endorphins and agents that re-balance opioid receptor signaling the formulation has a further synergistic effect.

The Science

Opioid receptors are transmembrane proteins that bind endorphins, exogenous opioids, gangliosides, and specific amino acids. These receptors are found in high concentrations in the spinal cord, various brain regions, intestinal and immune acting cells.

GM1 gangliosides are naturally occurring molecules that bind to the opioid receptor and were unexpectedly shown to switch the opioid receptor from the inhibitory mode to the excitatory mode in response to injury or stress.

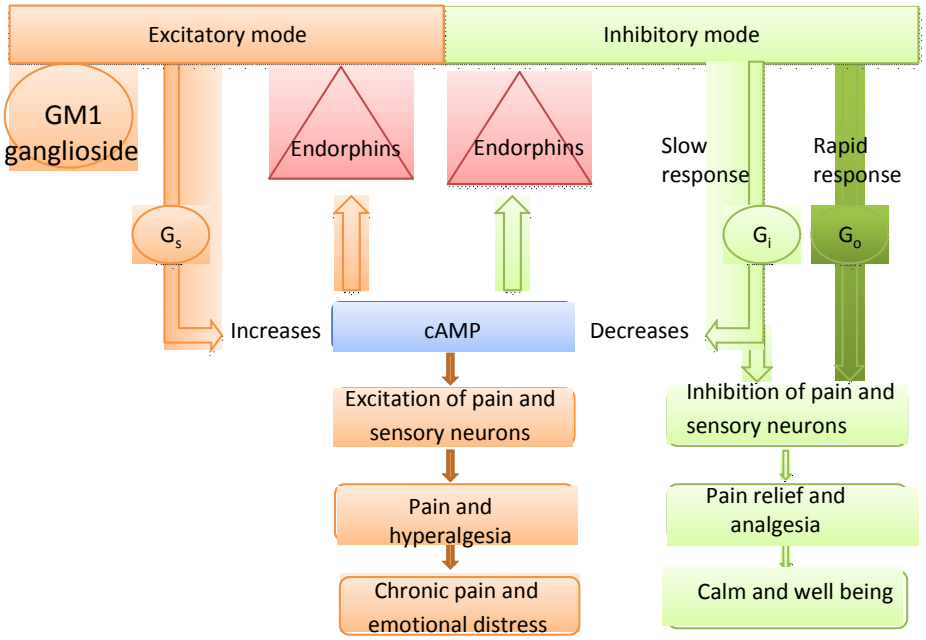
G Proteins (G_s, G_i and G_o) are guanine nucleotide-binding proteins that regulate the concentration of cyclic adenosine monophosphate (cAMP). cAMP regulates the concentration of endorphins. G_s is activated during the excitatory mode and increases

the production of cAMP and endorphins. G_i and G_o are activated during the inhibitory mode. G_i signals degradation of cAMP, decreasing its concentration and subsequently, the endorphin concentration. G_o effects the sensory neurons directly via ionic mechanisms to reduce pain.

Dr. Crain's discovery that the opioid receptor responds differently to endorphins and exogenous opioids depending upon whether the receptor is in the excitatory or inhibitory mode is known as the **bimodal operation of the opioid receptor**. The regulatory pathways and biochemistry associated with bimodal operation of the opioid receptor is very complex (Figure E). Each of the various pathways of the system will be discussed in further detail. The excitatory pathway is outlined in orange color and the inhibitory pathway in green.

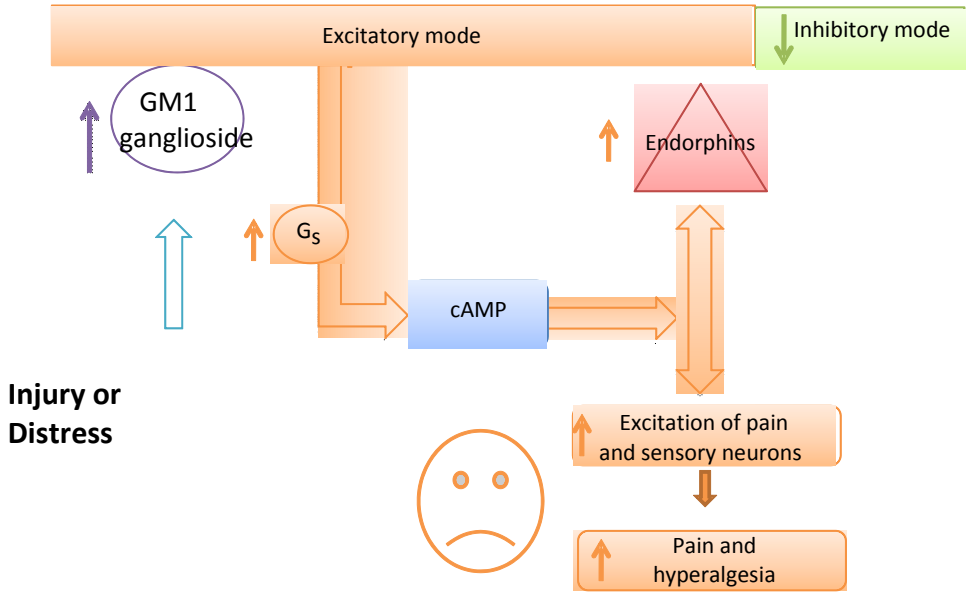
Figure E

Bimodal Operation of the Opioid Receptor: Biochemical Pathways



Excitatory Mode is used in order to adaptively respond to acute injury or stress. For example, when you touch something hot, the opioid receptors are involved in signaling you to remove your fingers quickly because it hurt to leave them there. The signaling pathway is illustrated in Figure F.

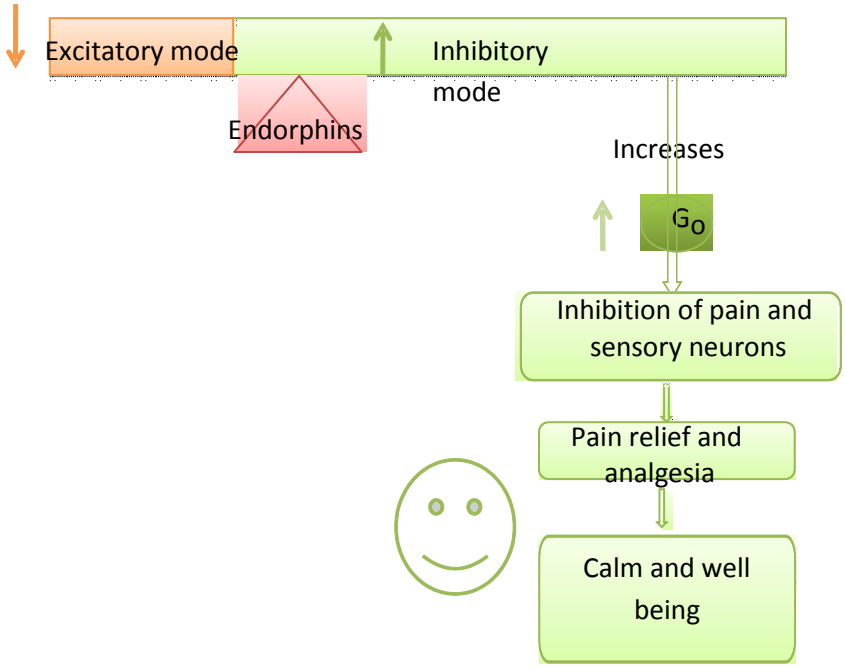
Figure F
Excitatory Mode of the Opioid Receptor



Injured cells release GM1 ganglioside that bind to the opioid receptor and switches the opioid receptor to the excitatory mode. When in this mode the stimulative G protein (Gs) acts as a transmembrane signaling mechanism activating adenylate cyclase. This enzyme synthesizes cAMP from adenosine triphosphate ATP resulting in increased cAMP levels. The increase in cAMP effects the concentration of another protein called kinase A, increasing Ca^{++} and decreasing K^{+} conductance, resulting in increased synaptic excitatory transmitter release by pain sensory neurons into the spinal cord. This triggers the sensation of pain as well as increased pain (hyperalgesia). The increased cAMP also enhances the release of endorphins that bind to opioid receptors and because the receptor are in the excitatory state, these endorphins maintain the pain and distress cycle until the distress stimuli are no longer a threat.

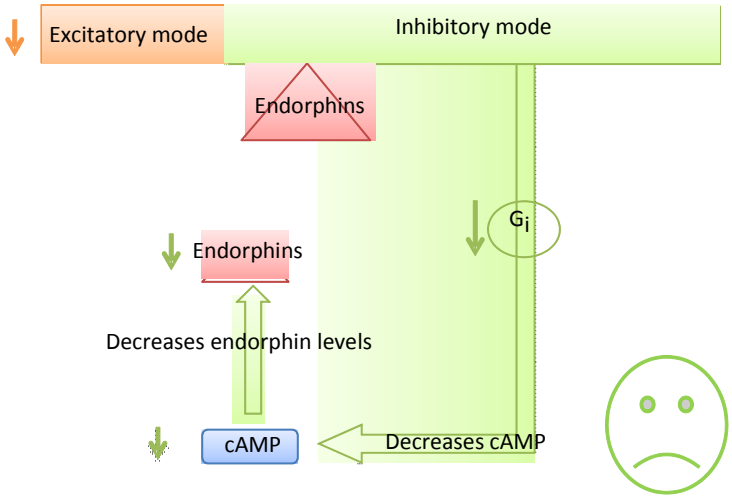
Inhibitory Mode begins as soon as the acute danger is reduced. Enzymes begin to reduce synthesis of GM1 ganglioside and its concentration drops, removing the stimulus for excitatory mode and allowing the receptors to switch back to their normal inhibitory mode. After the switch to the inhibitory mode, the binding of endorphins to the receptor triggers two different inhibitory G binding proteins. G_o rapidly decreases Ca^{++} conductance and increases K^{+} conductance in pain-sensory neurons, which triggers reduced sensation of pain, produces analgesia and feelings of wellbeing. This rapid response pathway is illustrated in figure G.

Figure G
Inhibitory Mode of the Opioid Receptor: Rapid Response



To return the endogenous opioid pain response system to **normal homeostatic balance mode**, a second G protein, G_i, simultaneously inhibits the action of the enzyme adenylate cyclase that synthesizes cAMP causing a decrease in intracellular cAMP concentration. The decrease in cAMP results in reduced endorphin levels, returning levels of pain relief and well being to normal levels. This pathway is illustrated by the excitatory mode slow response pathway in Figure H.

Figure H
Inhibitory Mode of the Opioid Receptor: Slow Response

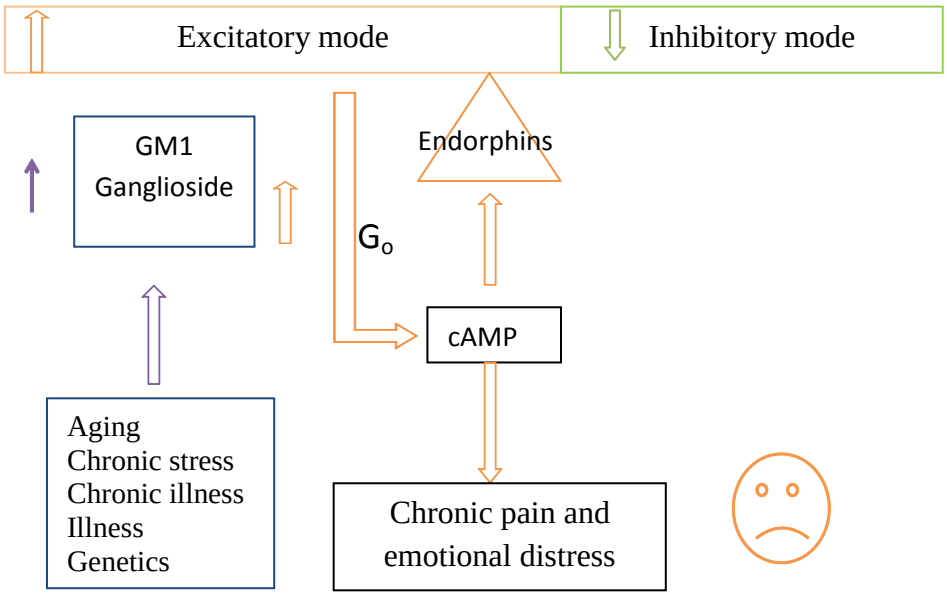


It would be nice to keep that “runner’s high” after exercise or “aura” after lovemaking but under normal conditions endogenous opioids are homeostatically maintained at concentrations that keep most of the opioid receptors in the inhibitory mode but the concentrations of endorphins fairly low. Pondera’s scientific discoveries overcome this feedback mechanism keeping endorphin levels high while in the inhibitory mode.

For many people, an abnormal fraction of the opioid receptors are in a **protracted excitatory** mode when endorphins are released. Aging, chronic stress and injuries, illness, and genetic factors can set opioid receptors in a protracted excitatory mode. The release of endorphins can be triggered by chronic stress, chronic injury, exercise, sex, caffeine and even meditation. In this protracted excitatory mode, endorphins mostly trigger excitatory signaling, resulting in chronic pain and hyperalgesia responses. This becomes a vicious cycle since excitatory signaling triggers increased cAMP and GM1 ganglioside levels, which produces elevated endorphins that trigger further excitatory signaling. This protracted dysfunctional condition triggers other pathways including serotonin, dopamine, and other neurotransmitter systems that result in further emotional and physical stress. While in protracted excitatory mode, an individual may experience anxiety, irritability, depression, cravings, addictive tendencies and physical distress, including pain and gastrointestinal symptoms. Protracted opioid receptor excitatory mode plays a major role in the symptoms associated with aging. In effect, the entire CNS system is “stuck” in a state of perceived threat, producing serious emotional and physical distress. The concept is illustrated in Figure I.

Figure I

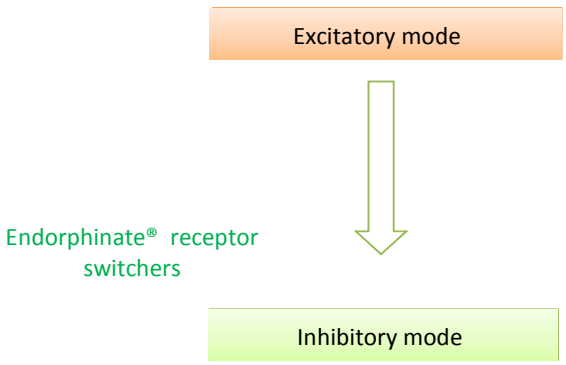
Protracted Excitatory Mode



The ingredients in Endorphinate® switch opioid receptors to a healthy inhibitory mode, ending the dysfunctional protracted excitatory mode often associated with physical and emotional pain and distress. The Endorphinate formulations contain several opioid receptor switchers, including the amino acids N-Acetyl-Cysteine and L-Theanine as well as Magnesium Sulfate and Magnesium Glycyl Glutamine. The concept is illustrated in Figure J.

Figure J

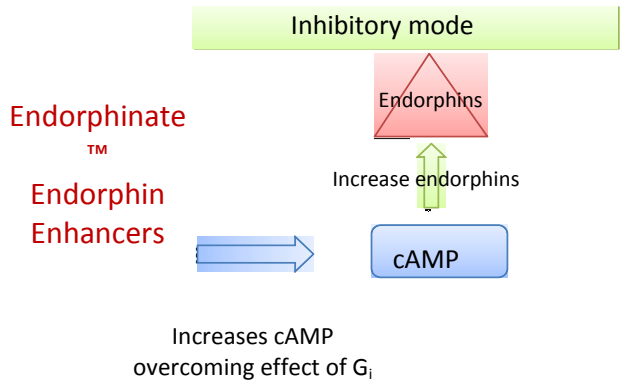
Endorphinate® Opioid Receptor Switching Mechanism



Dr. Crain identified certain molecules that when added to the diet, act as **endorphin enhancing agents**. These increase the concentration of endorphins by controlling the amount of cAMP present at the opioid receptor. In the body, there are several enzymes that are involved in the breakdown of cAMP. These enzymes are called phosphodiesterases (PDE). By inhibiting the action of PDE, cAMP levels remain high and subsequently endorphin levels remain high. Endorphinate® has several natural endorphin enhancers, including Guarana and Ginkgo Biloba. The concept is illustrated in Figure K.

Figure K

Endorphinate™ Endorphin Enhancing Agents



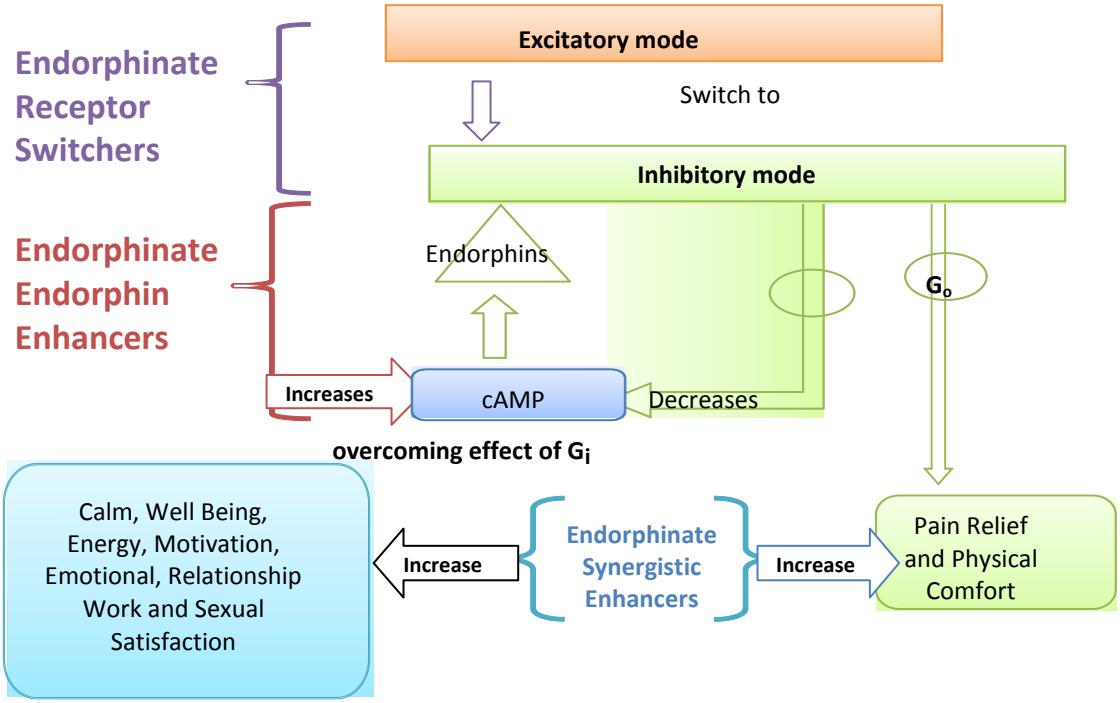
Dr. Crain established that when opioid receptors are in the excitatory mode and endorphin enhancers (as well as exogenous opioids) are administered alone, they are likely to signal an increase in pain as well as emotional and physical distress. However, when co-administered with an opioid receptor switcher, the increase in endorphin concentration created by endorphin enhancers leads to increased inhibitory signaling of the opioid receptor, resulting in relief from pain and distress and an elevation in mood.

Dr. Crain also identified S**ynergistic Enhancers** that facilitate the release of other stress-related neurotransmitters, including serotonin, GABA, glutamate, and dopamine. These agents have a synergistic effect with the endogenous opioid system through the G_i mediated metabolic pathways. The synergistic enhancer agents in our formulation work together with switching and endorphin enhancing agents to increase the effectiveness of the formula at relieving aches and pains and restoring positive mood. Endorphinate® contains various synergistic enhancers, including Ashwagandha, Lemon Balm, Magnesium Taurinate, and Ginger Extract as well as specific vitamins and minerals.

The patent pending formula for Endorphinate® contains endorphin enhancing agents, co-administered with opioid receptor switchers and synergistic enhancers to rebalance the signaling of opioid receptors from excitatory to inhibitory. The result is that Endorphinate® restores a healthy homeostatic balance to the endogenous opioid system, using the body's own endorphins to reduce pain, emotional and physical distress; restore calmness and well being; and make you feel younger and more vital.

Endorphinate® uniquely combines natural herbs and amino acids as well as vitamins and minerals that (1) restore natural endorphinergic balance to opioid receptors and enhance endorphin levels, reducing pain and emotional distress, (2) provide powerful anti-inflammatory effects to further reduce physical discomfort, and (3) enhance the synergistic functioning of other stress-related neurotransmitter systems, increasing a sense of calm, comfort, and well being. All Endorphinate® products include a scientifically developed formulation of Endorphin Enhancers, Opioid Receptor Switchers, and Synergistic Enhancers. By enhancing the body's pain and stress relieving system Endorphinate® is the most effective dietary supplement available for the relief of physical and emotional distress. The concept of how Endorphinate® ingredients function together synergistically as illustrated in Figure L.

Figure L
Endorphinate Science Summary



INGREDIENTS IN ENDORPHINATE®

Ingredients for Endorphinate® products are chosen from each of the following three functional groups, depending on the targeted indications.

OPIOID RECEPTOR SWITCHERS:

N-Acetyl-Cysteine (NAC) – an amino acid, which switches opioid receptor signaling from excitatory to inhibitory by producing sulfates which function as a neuraminidase inhibitor. NAC is also a powerful antioxidant with antiviral and detoxification capacities. Alone, NAC can help to reduce cravings, obsessions, and compulsions; when combined with endorphin enhancers, such as guarana and ginkgo biloba, the synergistic effect can help to produces pain and distress relief, reduction of anxiety and cravings, as well as enhanced mood and well being.

L-Theanine – an amino acid that is found naturally in green tea and functions as an opioid receptor switcher. L-theanine also increases GABA and dopamine levels, which can help to reduce anxiety and improve mood. Nature synergistically combines caffeine with L-theanine in green tea, in order to produce a unique blend of energy combined with calm and well being.

Magnesium Glycyl Glutamine – a stabilized form of the amino acid, glutamine, combines the natural opioid receptor switching power of the endorphin breakdown dipeptide product, glycyl-L-glutamine with the calming influence of magnesium. Glycyl-L-glutamine has been shown to help reduce the maladaptive noxious effects of both endogenous opioids (endorphins) and exogenous opioids (e.g, morphine).

Magnesium Sulfate – a natural compound that combines the potent opioid receptor switching effects of sulfate, a natural GM1 ganglioside blocker, with the calming influence of magnesium. Magnesium sulfate, or Epsom salt, has been shown to help relieve pain as well as reduce noxious side-effects of exogenous opioids.

ENDORPHIN ENHANCERS:

Guarana – a natural seed that contains caffeine, theophylline, and other components, which are endorphin enhancing agents. These are cAMP PDE inhibitors that prevent the metabolic breakdown of cAMP, enhancing the concentration of endorphins. Guarana releases endorphin enhancing agents more gradually than other sources and does not create "spikes" and other side effects, making it a natural source for prolonged release of endorphins in the Endorphinate® formulation.

Ginkgo Biloba – an herbal endorphin-enhancing agent that is also a cAMP PDE inhibitor. This inhibitor specifically targets cAMP within inflammatory and immune cells enhancing the release of endorphins within these cells. Ginkgo biloba is also a powerful antioxidant that helps to enhance energy, circulation, memory and concentration.

Glutamic Acid – an excitatory amino acid that directly enhances cAMP, which increases endorphin levels. When combined with opioid receptor switchers, glutamic acid has been shown to help produce analgesia.

SYNERGISTIC ENHANCERS:

Pyridoxal 5 Phosphate, Folic Acid, and Vitamin B-12. – vitamins that are critical cofactors in the production of endorphin, serotonin, GABA, dopamine and related neurotransmitters.

Magnesium Taurinate – naturally combines magnesium and an important inhibitory amino acid, taurine, which synergistically amplify their effects on calming anxiety, agitation, irritability, cravings, and hyperactivity. The addition of magnesium taurinate to the Endorphinate®™ formulation potentiates pain and distress relief, and enhances a sense of calm and well being as well as focus and motivation.

L-Theanine – a natural amino acid that enhances GABA and dopamine, thereby potentiating the calming and relaxing effects of the core Endorphinate® ingredients. L-theanine also functions as an Opioid Receptor Switcher (see above).

Lemon Balm – a natural herb that can help reduce anxiety and insomnia while also enhancing memory and attention. Lemon balm synergizes the calming effects of L-theanine and other Endorphinate® ingredients.

Ashwagandha – a natural herb can help reduce anxiety, pain, and insomnia and to help the mind and body respond effectively to stress. Ashwagandha has anti-inflammatory effects as well as benefits for the gastrointestinal and immunological systems. Ashwagandha is also known for its ability to improve energy, motivation, attention, and sexual functioning.

Ginger Extract – a natural herb that can help to reduce pain and inflammation. Ginger is also known for its health-promoting benefits for gastrointestinal functioning.

Green Tea Extract – an herb that naturally contains L-theanine, an opioid receptor switcher, and caffeine, an endorphin enhancer, thereby providing core components to produce endorphinergic balance and relief from emotional and physical distress. Green tea also contains health-promoting polyphenols, which can help boost the immunological system with powerful antioxidant benefits.

White Willow Bark – a plant extract that contains salicin and other natural components, which have pain and inflammation relieving benefits. White willow bark is a natural product that has been shown to synergistically enhance the pain and stress relieving effects of the core Endorphinate® formulation. People who are sensitive to aspirin should not use white willow bark.

5-Hydroxytryptophan (*5-HTP)* – a naturally-occurring amino acid, which is directly involved in the biosynthesis of serotonin and melatonin. By enhancing levels of serotonin and melatonin, 5-HTP naturally helps to produce a sense of calm, well being, and positive mood, which is synergistically potentiated when combined with Endorphin Enhancers and Opioid Receptor Switchers.

Acetyl-L-Carnitine (ALC) – a powerful antioxidant with neuroprotective functions that can help prevent the development of age-related conditions, including cognitive and other neurological impairments as well cardiac, neuromuscular, and sexual conditions. These benefits synergize with the core Endorphinate® formulations to potentiate the relief of aches and pains and other distress conditions.

Alpha Lipoic Acid (ALA) – an omega-3 fatty acid and a powerful antioxidant and anti-inflammatory that that can help prevent the development of age-related conditions, including arthritis, diabetes, neuropathy, and cardiovascular conditions.