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Draft Abstract for Long-Term Memory: Mechanisms, Types and Disorders

Title: A Molecular Mechanism Integrating Adenylate Cyclase Responsiveness to Metabolic Control on Long-Term Emotional Memory and Associated Disorders

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The physiological relationships of fat cells and liver releasing free fatty acids, and glucose and ketone bodies respectively, are integrated into a sensor response of red cells, releasing O_2 to match glucose uptake by brain. The molecular level reveals an integrative axis of in common metabolic feedback control of a requirement for free Mg^{2+} of:

Enzymes Responsiveness to Neurotransmitter Signaling

- Noradrenaline dependent activation of Adenylate cyclase (AC) of brain is fully dependent on free Mg^{2+}, in excess of MgATP.
- In brain, the Na^+ pump consumes ATP^{4-} for the propagation of nerve impulses, releasing free Mg^{2+}. The event increases AC responsiveness because ATP^{4-} has a much higher binding constant for Mg^{2+}, than ADP^{3-} and AMP^{2-}.
- AC of brain, liver, and fat cells as well than insulin receptor tyrosine-kinase (IRTK) show 3 differentiable sites as a function of free $[Mg^{2+}]$.
  a) An active site for the formation of the enzymes substrate complex: MgATP.
  b) A basal site(s) activatory: for free $[Mg^{2+}]$ saturation and by decreasing saturation with $[ATP^{4-}]$.
  c) A free $[Mg^{2+}]$ requirement for the hormonal-receptor sites.
- The computation separable saturation curves, of the 3 sites, yields a joint saturation response with a cooperative value of about 2.6 resulting of the sum of activatory sites for MgATP and for Mg^{2+}, plus desaturation of one inhibitory site for $[ATP^{4-}]$.
- The affinity for O_2 of the Heme Prosthetic Group of Hb, is mutually inclusive for the binding of free Mg^{2+} or Zn^{2+}, at the R-groups of interphase $\beta_2\alpha_1$: His$\beta_2$143, His$\beta_2$92, Cys$\beta_2$93, His$\alpha_1$87 and for the respective R-groups in $\beta_1\alpha_2$. Moreover, these bindings are mutually exclusive of the H^+ and 2,3-DPG binding. Hence, the pO_2 saturation curve of Hb by inclusion of the activators Mg^{2+} plus O_2 binding and exclusion of inhibitors shows a cooperative value of about to 2.6 (Biomed. Biochim. Acta, 46 No 2/3, 314-319 (1987)).
- At the organismal level, the fight or flight reaction releases adrenalin in blood activating AC. Adrenalin in liver increases glucose level in blood and adrenalin plus other hormones in fat cells releases free fatty to produce in liver ketone bodies.
- An action or hormone dependent increase of glucose in blood results in an increase in sugar phosphates within the red cell decreasing free Mg^{2+} and Hb releasing O_2 that diffuses into the cerebrospinal fluid (CSF).

- The glia cells support minimal aerobic glycolysis. The activation effect on the membrane receptors of brain, by increasing free Mg^{2+} by the conception of MgATP by AC and Na^{+} pump, requires a sudden increase of aerobic glycolysis to regenerate MgATP. The Mg^{2+}-dependent cooperative increase in neuronal activity, needs to be match by the promptness of the cooperative responsiveness of Hb deoxygenation, adjusting the supply of O_2 to that of G in CSF. This allows the sudden 10 times increment of the rate of aerobic glycolysis at the activated neuronal circuits.
- Hence, a metabolic-ionic feedback for metabolic integration rests in a hemoglobin sensor role.
- **Long-term memory:** is involved into the affirmative process associated with emotional experiences. Is sensitive a beta-blocking of the noradrenalin of AC receptor of AC. Persistence of an activate state of AC may allow significant activation by cAMP of kinase-A, which by phosphorylation modifies the responses of enzymes and proteins within neuronal pathways.
- Additionally, free Mg^{2+} is required for binding of oxytocin to if receptor. AC dependent emotional intelligence, could also involves, oxytocin favoring attachments which involves a response to reward and the desire to obtain it.
- **Short-term memory:** the release of Ca^{2+} inhibits AC, allowing completion of a neuronal transmission impulse
- The pulse of endogenous generated cAMP controls Ca^{2+} fluxes.
- The nerve impulse releases Ca^{2+} for Ca^{2+}-actin formation regulating *Microtubule* Self-Assembly. ATP^{4-} binds Ca^{2+} releasing actin.
- cAMP activate calmodulin binding free Ca^{2+} and allows its return to the endoplasmic reticulum.
- cAMP is consumed by phosphodiesterase enzymes, sensitive to inhibition by caffeine, prolonging cAMP action.
- In short term memory a high uptake of G versus a low oxygenation may affect the turnover of the Na^{+}-pump dependent cyclic fluctuations of ATP^{4-} level. A possible explanation for after meals sensation of mental slowdown.

Dysfunctions

- Over-exposure noradrenalin inactivates AC during stress inducing psychosomatic pathologies. Hence, it could be inferred a physiological protection mechanisms leading to attenuate the emotional response to the input of adrenalin secretion, at first inducing anxiety. However, if the synthesis of new AC could not match the rate of inactivation, a pathological depressive state develops.
- The degree of comfort prevents the avoidance mechanisms which relates to the need to escape from the fight or flight reaction.
- Positron emission tomography reveals that diseases may not only activate differentiable brain areas, but also the intensity of metabolic processes, for example in schizophrenia.
- The optimization effect of caloric restriction increasing the life-span of experimental animals involves a decrease of sugar in blood, allowing in many tissues a more equilibrated responsiveness of IRTK, to hormones an AC.

- The corporal to limbs pH-axis allows that a decrease of insulin increases the red cell concentration of sugar phosphates and ATP^{4-}, leading an early discharge of O_2, inducing anoxia in the limbs of untreated diabetics. Insulin treatment allows to decrease blood sugar and the red cell decreases in anaerobic glycolysis decreases sugar phosphates increasing free Mg^{2+}. Hence, allowing Hb to retain enough O_2 to discharge at the limbs level.
- Anorexia nervosa characterized by brain starvation by insufficient glucose uptake shows the need for an adequate caloric balance to preserve intellect.

Attachments

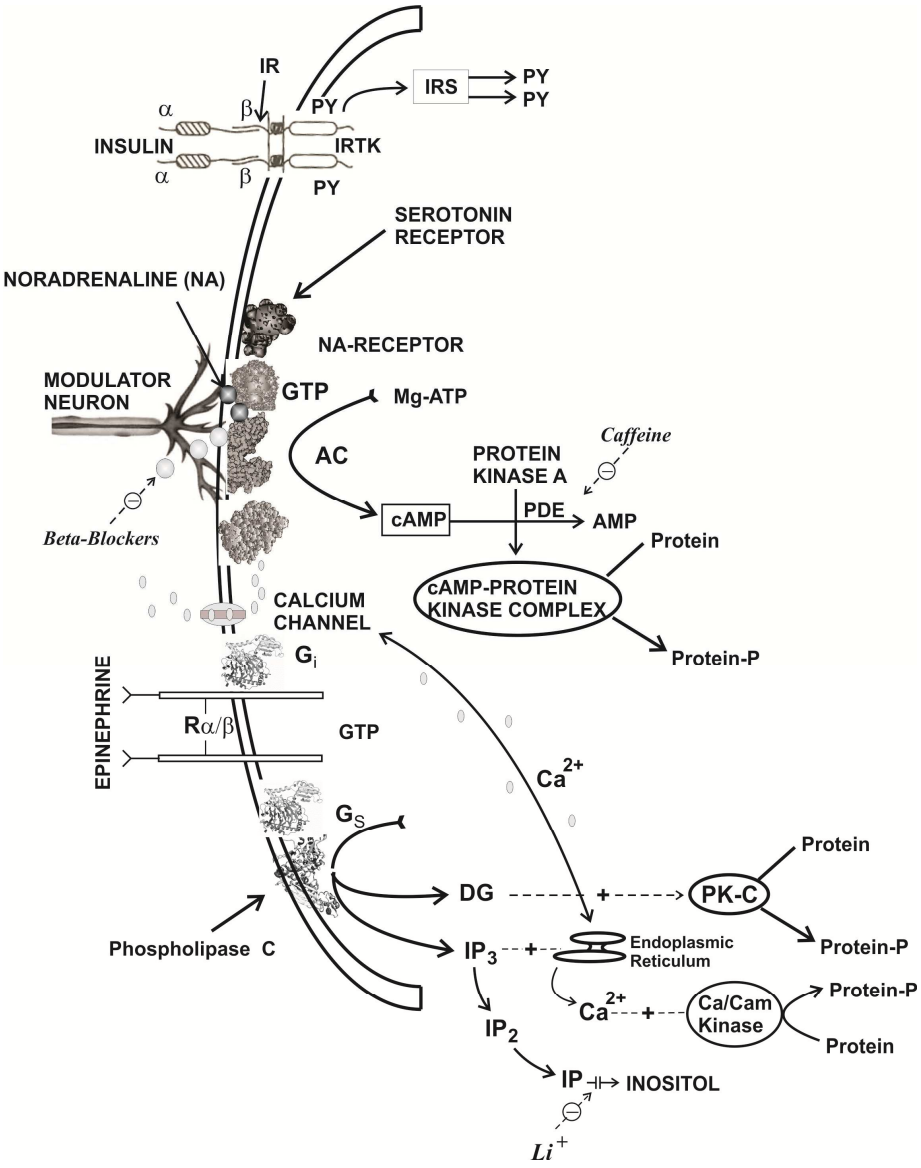

Fig.1. Integrative ionic-metabolic feedback controls: The figure illustrates ionic-metabolic signal transduction control over hormonal responsiveness of different proteins, subject to modification by phosphorylation depending on the hormonal signal and tissue.