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Is there a relationship between the (p)ppGppbacterial Alarmone systems and the Mammalian brain? pRpp, pRibosepyrophosphate and the mode of action of Lithium, and ketamine, in mood and related disorders

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Abstract

A newly identified P.aeruginosa enzyme toxin has been shown to rapidly strip rival recipient bacterial cells of their ATP(1, 2). This noveltoxin causes alethal drop in the target bacteria's ATP levels, the new enzyme was originally thought to synthesise guanosine tetra or penta-phosphate, known as (p)ppGpp from ATP, but actually forms an alternate, analogue, (p)ppApp(adenosine pentaphosphate), from ATP(1, 2, 3).This actionnot only depletes the target cells ATP,italso has the additionalaction of blocking the formation of fresh ATP, i.e., it â€˜doubly disablesâ€™ a normally protective system based on ppGpp, a prototypic bacterial â€˜alarmoneâ€™, this seems part of a pattern whereby certain bacteria have managed to subvert a usually protective system,to gain a competitive advantage.

Introduction

The nucleotides guanosine tetraphosphate (ppGpp) and guanosine pentaphosphate (pppGpp) collectively known as (p) ppGpp, are utilized as ‘alarmones’ during the stringent response (1,2). Stress conditions, mediated by amino acid starvation, iron,or fatty acid starvation, heat shock, and similar factors, can induce the so called ‘stringent response’ in bacteria and chloroplasts. The formation of these protective, ‘high energy‘, (p)ppGpp, type pyrophosphateshelps bacteria to survive starvation, during which cell division and RNA/DNA metabolism halts, and other nutrients, including amino acids, are used as alternative sources of energy.

The alarmone3’,5’-(bis)guanosine pyrophosphate (ppGpp) can shut down transcription in bacteria suffering nutrient deprivation. Recently Kamarthapu et al (4) showed that (p)ppGpp mediates bacterial adaptation to nutrient deprivation by conserving energy and altering the initiation properties of RNA polymerase, ppGpp couples transcription elongation to the nucleotide excision repair pathway, and by inhibiting DNA replication.

In bacteria,such pools of (p)ppGppare fully integrated, asone of 3 three sets of nucleotide-based secondary messengers, alongside cAMP and c-di-GMP (5).

The ppGpp-mediated stringent response has not been identified in eukaryotes.Instead eukaryoteshave a general amino acid control (GAAC) system (6),this is not homologous to this bacterial alarmonesystem,but exerts a similar function(6). Nonessential cellular contents are recycled by autophagyinstead (6).

It is suggested here that there may be a potentially somewhat similarsystem in mammals, with similar ‘vestigial’, function in mammals;but utilising a different, but related,high energy pyrophosphate-co-enzyme,pRibosepp

This link to adaptation to survival in conditions of bacterial ‘starvation’ has some resonance with ‘autophagy’ in mammalian systems, as this too can be induced by lack of nutrients,and which is now emerging (7) as somehow involved in the action of Lithium and related neuro-psychiatric disorders (8). The GAAC pathway modulates autophagy by regulating amino acid uptake and mTOR reactivation during serum/glutamine starvation(6).

The role of (p)ppGpp, highly phosphorylated substances, created in response toenergetic and metabolic crisis in bacteria,mirrors the ‘alarmone’ type role of PRibosePPthat emerges in a recent new ‘fail-safe’ model, of the mode of action of Lithium (9).

Lithium by competing with Mg++effectively mimics a potentially ‘low’cell [Mg++] Magnesium level, as so many cellular systems rely on Mg++ this would constitutes a form of metabolic crisis; potentially calling for an ‘alarmone’ type response.

Mg-ATP, grinding to a halt, and the mode of Action of Lithium: As 400-450 cell enzymes and many cell systems, rely on adequate levels of cell [Mg++], (including an interesting key group of Lithium sensitive and Mg++ requiring enzymes), including the IMPase thought to be acted on by Lithium.

The question one has to ask is; ‘what would happen if cell [Mg++] and hence [ATP]levels drop to a critically low level?

There would have to be some protective response-or the cell would grind to a halt.

The appearance of a critically low cell [Mg++] concentration is postulated to force the activation of a set of cellular 'fail-safe', alarm systems, pre-configured to mobilize against metabolic crisis conditions, most obviously during birth, and associated head injury- associated with a low cell [Mg++] and the associated low cell [ATP],and low nutrition levels.

The multifaceted cell protection afforded by these integrated cell protection systems, related to protecting the brain in circumstances of low cell [Mg++] is postulated (9) to provide the basis on which Lithium works to stabilize mood.

This much expanded model of Lithium action that emerges from this 'fail-safe concept' provides a much needed, newly integrated context to both the existing 'inositol depletion' and GSK-3 inhibition concepts, which were previously seen as separate models, and involves additional mechanisms including metal ion, particularly Mg++and zinc chelation, and Lithium's potential effects on key Ca++/Mg++ related TRPM7 type, 'signaling 'type, ion channels, also linked to immunity (10)and cell survival.

The new model hasat its core the critical importance of low cell [Mg++] and the loss of ATP, and also-in this case, particularly putatively PRibosePP, (and/or perhaps potentially similar high energy polyphosphate compounds),as pRpp is a Mg++ chelating agent, and also as a probable alternative competing substrate to inositol Phosphate for theIMPase, Inositol MonoPhosphosphatase.

This combined cytoprotective action, spread across several related enzyme systems-with a common core structure,providesa basis for multifaceted(brain) cell protection, (during crisis- most apparent in the most severe form of metabolic challenge- post head injury- with conditions of low cell [Mg++] and low cell [ATP]) very much at its core.

Perhaps not all aspects of this system would need to be utilised when Lithium acts, in the presumably less severe conditions, as a mood stabiliser; indeed it leaves open the question of which of the various mechanisms identified would be the most relevant.

The chelation of cell Mg++ by various sugar-phosphates, including Inositol-phosphates, would temporarily reduce the availability of essential Mg++ and similar cofactors,required by many enzymes, and would tend to inactivate unnecessary enzyme activity, conserving energy, reducing ATP consumption, particularly post head injury, similar to the above bacterial situation, as it would tend to shut down energetically costly protein synthesis.

The chelation of cell Mg++ would also imply a greater degree of inhibition of both the IMPase and GSK-3 than had previously been anticipated during Lithium therapy.

GSK-3 would be doubly inhibited- limited by the lower than anticipated, suboptimal [Mg++] levels, and by the direct inhibition by Lithium.This removes some doubt whether or not GSK-3 would actually be adequately inhibited by Lithium- for the inhibition of GSK-3 to be actually operational, during the doses used in Lithium therapy.

These enzyme systemsare also postulated to act to protect (brain) cells in energetic crisis- e.g., following excess oxidative stress, or the over-activation of DNA repair systems such as Poly (ADP-ribose) polymerase 1 (PARP1), which can lead to depletion of NAD(+) , and then to depletion of ATP, e.g., following stroke or high glucose levels.

Factors that cause the depletion (11,12) of cell ATPare proposed to be capable of resulting in a much increased level in PribosePP, which is also a candidate 'novel' (13) additional /alternative competing 'competitive' substrate for the IMPase,as a group of related, similar sugar-phosphates, such as G-6-P, and Ribose-phosphate,similar to inositol-phosphates, are potential additional competing substrates(see 9) for the IMPase, acomplex,and not very specific sugar phosphatase, one quirk of the mode of inhibition of this enzyme is that it is rather moreeffectivelyinhibited 'grid-locked' by Li+, if there is excess of its substrate(s).

Damage to brain cells causes a large drop in [ATP], this is paradoxical,(as ATP chelates a

great deal of cell ATP) this is accompanied by a large fall in cell [Mg++] and an impliedpostulated rise on PribosePP, (which would complex with, bind the Mg++ released from the ATP)and which, which, given the structural similarities, could then be construed in a similar protective role,as appearing similar to a mammalian equivalent to an alarmone, but one based on PribosePP, (9, 13) the parent substance for adenosine, ATP, GTP, and similar bases.

ADP-Ribose, a novel second messenger, also features in the PARP-1, DNA repair system; as the Lithium sensitive BPNase is bifunctional, as both a PAP phosphatase, and is also an IPPase-an inositol poly-phosphatase; an inositol -1,4-biphosphatase (16). TRPM2 calcium channel (13, 14)opening, in response to oxidative stress, is dependent on PARP-1 activation, but inhibition of the 3'-phosphoAdenosine 5'-phosphate (PARP-1) phosphatase activity by Li+(16) leads to increased levels of PAP, (3'(2')-phosphoAdenosine 5'-phosphate)(Note the similarity to ppApp), which helps inhibit PARP-1, helping to prevent harmful excess Ca++ entry(14, 15, 17, 18).PAP inhibits enzymes that use the similar molecule, 3'-phosphoAdenosine-5-phosphosulphate, and also inhibits RNA processing enzymes (16a).The properties of TRPM2 and TRPM7 (see below) are similar, and connected with (Ca2+) and (Mg2+) homeostasis, oxidative stress, mitochondrial dysfunction, and immune mechanisms, involved in neurodegeneration (16b).

In generating 'myo- inositol depletion' by inhibiting the IMPase, Lithium also has the effect of creating a functional counter-part; as 'inositol-phosphate enhancement', or 'sugar-phosphate''enhancement' – this creates a reservoir of protective Ca++ chelation, combined with Mg++ and other protective metal ion chelation activity; which also helps protect against, bufferingexcess Ca++ toxicity, and this extra chelation further helps reduce toxicfree radical formation from heavy metal ions, (19) and may help regulate zinc,and similarlyrelatedtoxic systems, during metabolic crisis.

It is interesting that Lithium had historically, from early on, been felt to have a link to purine metabolism, and to gout, although why this was so, had remained obscure.

Recently, in addition to the fact that uric acid is raised, as an apparent true state marker in mania(20), it has also appears(21,22) that raised uric acid may also be a marker for depression in bipolar disorder, as uric acid- the ultimate break down product of various purines, also tends to be raised in the depressed phase of bipolar; perhaps suggesting increased throughput, increase formation and flux of pRibosePP, the ultimate precursor for uric acid (13).

Activated Ribose-phosphate;5-phosphoribosyl-1-pyrophosphate:

Rpp, pRibosepyrophosphate, is a biosynthetic precursor of GTP, riboflavin, and tryptophan; essential, and limiting, for both the de novo and the salvage pathways of purine, pyrimidine, and pyridine (NAD+, NADP+) nucleotides(13,9), so that pRpp availability will influence NAD availability, as well as affecting the availability of related (including potentially excito-toxic) tryptophan products.The excito-toxic tryptophan product and, NAD precursor, quinolate can induce poly (ADP-ribose) polymerase (PARP) activation with subsequent intracellular NAD+ depletion and reduced ATP levels, in response to DNA damage, leading to negative effects of mitochondrial permeability and overproduction of superoxide and nitric oxide, pRpp is also used to “detoxify” quinolate to nicotinate mononucleotide.

Note that the potential strong chelation of Mg++ (by such likely chelating agents) as described would exert an inhibitory effect on the competing cells ability to stabilise RNA/DNA ribosome structure,(perhaps related to the higher inositol phosphates having a role in stabilising chromatin, and limit Mg++ requiring enzyme activity, so that this type of newly identified toxin may perhaps also utilizeadditional, metalchelating-type mechanisms(9, 19, 23).

On the mode of action of ketamine: There has been much recent interest in ketamine as an ‘antidepressant’.

It is still not clear how ketamine might lift mood, both Mg++ and ketamine share complex actions on glutamate receptors, ketamine may block a Mg++ relatedMNDA type ion channel, perhaps if extra cellular ATP- purinergic transmission is affected, it could alter the [Mg++] buffering and availability in the extra cellular compartment- with implications for the normal buffering- of this small tissue volume?

This provides an interesting link with ketamine and the NMDA system, mood disorders, and lithium’s action.

The eukaryotic elongation factor 2 kinase,eEF2 kinase, which is activated by AMP-kinase, confers survival during nutrient restriction by blocking translation elongation,(25) this is similar to the effects of (ppGpp) shutting down transcription in starving bacteria, which will tend to help conserve, ATP levels.

eEF-2 Kinase also influences Cross-Talk Between Autophagy and Apoptosis (24).

eEF2Kinase, a Ca2+/calmodulin dependent serine/threonine kinase, phosphorylates eEF2 and regulates the elongation step of protein translation, thisis claimed to mediate the rapid antidepressant effect of ketamine; which may thus help maintain of lift cell ATP levels.Monteggia et al. (25) have shown that ketamine-mediated suppression of resting NMDA receptor activity leads to inhibition of eEF2 kinase and the subsequent dephosphorylation of eEF2,withsomeaugmentation of BDNF synthesis (25).

eEFK2 kinase is an unusual enzyme, an alpha kinase.

This uncommon form of enzyme activity isalso expressed in the TRPM7ion channel, a PIP2 requiring, and major Ca++ and Mg++ channel-enzyme, involved in excess Ca++ related excito-toxic cell death, e.g., post head injury. (9, 26)

The related alpha kinase Gcn2 also controls amino-acid metabolism (29, 30)

TRPM (6) or TRPM7,as well as being Mg++ and Ca++ion channel-enzymes, with complex signaling properties(27,28,31,32,33)also emerge as being putatively linked to Lithium’s mode of action, as it isboth PIP2 and ATP sensitive, (31) TRPM7 encodes a serine-threonine kinase closely related to the eEF-2 kinase,acting mainly within α-helical loops; the full range of thevarious natural substrates for this activity remain unknown (27, 28).

Perraud et al.,(33) have shown that the (alpha)Kinase activity of the TRPM7 ‘channel-enzyme’ interacts with and can phosphorylate the eEFkinase at a (mouse-serine 77 site), in a manner that is specifically sensitive to the availability of Mg++; the combined TRPM7-kinase activity is acting as a sophisticated sensor of extra- and/or intracellular Mg++ availability

Perraud et al (33) demonstrate that when Mg++ levels are insufficient to sustain normal cell activity TRPM-7 kinase phosphorylates eFK-kinase- (-on serine 78, in human eEFK-k). this appears to stabilize eEF2-kinase, and results in increased inhibitory eEF2 phosphorylation.

The system would lead to an increased rate of protein translation when adequate Mg++ is available and decreased translation efficiency when local Magnesium is lacking.

These observations strongly link the action of Ketamine in lifting mood to the local availability of Mg++ (and its common ligand, Mg-ATP), mediated via TRPM7.

TRPM-7 is poised as a cell nutrient, cell Mg+ concentration sensor, which is able to use its special alpha-kinase function to ‘channel’ this information to other systems that need to adapt to altered [Mg++] and in this case, suboptimal Mg++ concentration results in elevated eEF2-k activity, and in increased eEf2-kinase proteinlevels (Perraud, 33),

The Ketamine-mediated suppression of resting NMDA receptor activity , described by Monteggia et al, (25) is the opposite to this; ketamine thus seems to mimic an ‘adequate [Mg++]’ signal’, and leads to inhibition of eEF2 kinase (and subsequent dephosphorylation of eEF2) and the augmentation of BDNF

synthesis- (that seems to translate into a short term lifting of depressed mood).

To further demonstrate the possible linkages between TRPM7 and glutaminergic transmission there is related evidence, related to zinc. Zinc is an allosteric modulator of NMDA receptors, the maintenance of Zinc levels within a physiological range is claimed by Simcock et al. (34) to be key for normal glutamatergic functioning.

Simcock et al (34) state that Zinc deficiency may increase neuronal stores of Ca++ and affect NMDA receptors whichthey postulate may lead to over-activation and upregulation of NMDA receptors, they claim it may facilitate high levels of glutamate, Ca++ influx withpotential excitotoxicity, altering synaptogenesis and plasticity (34)

Krapivinsky et al.(35)have shown that the alpha kinase section of TRMP7 can be cleaved to form a chromatin modifying kinase, transported to the cell nucleus- where it has major effects on zinc; cytosolic free [Zn(2+)] is TRPM7 dependent, TRPM7also senses oxidative stress to release Zn2+ from unique intracellular vesicles.(35,36).

Given that the eEF-2-kis also an alpha-kinase, it will be interesting to see what corresponding interactions itactivity might have?

Note that postulated increased pRpp levels might be expected to interact by chelating both cell Mg++ and Zn++.

The Lesch- Nyhan syndrome, a severe deficiency of HPRT, results in increased intracellular pRibosepp,it has never been clear why this is associated with severe compulsive self-mutilation. Ketamine acts as a form of 'dissociative anaesthetic', this profound alteration in pain perception and 'dissociation'– relevant to the broader phenomena of compulsive self-harm, e.g., in certain personality andeating disorders, might relate to particularly important alterations in Glutaminergic systems, connected to the role of Mg++ , Zinc, pRpp, and the important links to the TRPM7 type, alpha- kinase- eEF-2 signalling system; as identified by Perraud et al (33).

Conclusions

It seems possible that pRibosepp, and perhaps similar, e.g.,Ins-pyrophosphates-(not discussed here),mayhave retained a somewhat vestigial, parallel,alarmonetype role, in mammalian brain. The focusof bacterial alarmonesprovidessome conserved core principles;and may give some guide to the biochemistry of the core of mood disorders.

The bacterial alarmones, as bacterial second messengers arefundamentally fully integrated in bacterial cell function,and appear mostly concerned with adaptation to nutrient deprivation, energetics of DNA repair, and limitation of protein synthesis during nutrient deprivation.Alpha- kinase systems retain a link to resistance against bacteria (37).

The action of a newly identified bacterial toxin,(1,2,3) that can deplete [ATP], might suggest, given that in the brain these protective systems also seem to be geared up to protect against conditions of low cell [ATP], which in post-head injuryare then associated with a low cell [Mg++]; it leads to the slightly disturbing possibility that this form of bacterial toxin might at times be 'attacking' brain tissue?Or generating perhaps unexplained 'white matter lesions' often found in such patients, and perhaps possibly mood related symptoms the brain? This concept is supported by the suggestion by Proal et al., (38), that there may existlatent bacterial infections in humans (see also 39). An alternative enzyme toxin, if exists, and if it were capable of promoting an excess of the reaction of ATP+ Ribose, to PRPP +ADP+Pi, could have the effect of depleting cell [ATP].

What has the action of lithium got to do with the evolution of early life???

To generate life one needs a number of things.Some source of metabolic energy- power supply- usually assumed to be ATP.

But pRibosepp and similar high energy phosphates might be able to directly donate- phosphorylate in an ATP like fashion, and in any case the conversion of ATP to pRibosepp seems in equilibrium, inter-convertible, so that pRpp could act as a form of crude ATP prototype- or substitute.

One needs a form of information store, to build complex molecules- one also needs to be able to remember how to recreate them if they are successful.pRpp is unique as the precursor for all the RNA and (with the help of Selenium as catalyst) ultimately for deoxy-DNA bases, it looks as though Ribose as much as glucose must have been a most important 'sugar' early in evolution.

A less obvious – but interesting point; in order to maintain functional RNA and or DNA memory stores it requires the local regulation of [Mg++] concentrations (see the BBC website on the Origin of Life), similarly ATP also requires Mg++ as a cofactor/ stabilizer.

This relationship between energy systems- the potential for phosphorylation, memory storage- the ability to produce RNA precursor bases etc., and the ability to chelate- hence 'regulate' key Mg++ ions, puts p-Ribose-pyrophosphate in a unique position in respect of generating potential early 'life'.

'Life' perhaps now needs a little re-definition; at its simplest just some simple set of basic reactions starting with pRpp, that with precursors and some catalytic assistance potentially spews out a string of bases, that in some way then eventually, somehow assemble and produce RNA or eventually small peptides that may sometimes, by chance have some useful enzymatic activity; this is much simpler than the usual 'cell concept'; just a form of creative primal reaction 'soup'.

It might be possible to recreate it in vitro- put it throught its paces- start all over again!

It might already still be here, still chundering away- in some rock pool- if only we know what to look for. It makes the evolution of life – not dependent on chance, or sheer fluke, it makes it almost inevitable- forced by the Chemistry at this point, is so structured cannot stop itself from potentially aimlessly churning out these

ultimately, 'life yielding ' products. This cluster of IMPase type, Lithium and sensitive Mg++ requiring enzymes- are strangely coherent in their actions, often multifunctional, primitive and very versatile- show some aspects expected in early 'proto-enzymes'.

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