Interaction between Mg and Stress Hormones in Stress

A Short Review

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Zusammenfassung

Besonders während Streß wird der enge Zusammenhang zwischen Mg Metabolismus und Catecholamin Wirkung deutlich. Der Grund ist vorwiegend der beachtliche Mg Verlust, der mit Streß einhergeht und die Ursache für die überaus wirksame Mg Prämedikation ist. Deshalb verhinderte auch rechtzeitige MAH Substitution den streßinduzierten Leberglykogenverlust, was auch die Auslösung zusätzlicher Adrenalinsekretion verhinderte. Darüber hinaus vermindert eine solche prä-Streß MAH Substitution direkt die modulläre Adrenalinsekretion und in sehr deutlichem Maße den Cortiol-Output.

Regulatoren der vom Mg Status beeinflußten CA Wirkung und des, von CA beeinflußten Mg Umsatzes, sind CA Rezeptoren, wobei die quantitative Beteiligung der alpha- und beta Rezeptoren noch nicht abgeklärt ist. Sie könnte sich durchaus mit Gewebeart, Spezies und Situation ändern.

Die Zeit, die für die Rückregulation solcher Rezeptoren gebraucht wird, ist eine wesentliche Determinante der Empfindlichkeit des Systems. Diese gewisse Trägheit macht es für plötzliche Streßereignisse möglich, ihre gesamte Mg depletierende Wirkung zu entfalten, während bei chronischer CA Erhöhung die Gewebeempfindlichkeit durch Rezeptorrückregulation vermindert ist.

Summary

During stress, the close relationship between Mg metabolism and catecholamine action becomes evident. The reason is mostly the considerable Mg loss which goes hand in hand with stress and makes the effects of substitutive MAH premedication most obvious. Therefore timely MAH substitution prohibited stress induced liverglycogen depletion which in turn cannot trigger additional adrenalin secretion. Moreover, pre-stress MAH substitution directly diminishes medullar adrenaline secretion as well as drastically curbs cortisol increase.

The regulators of Mg influenced catecholamine action and catecholamine influenced Mg turnover seem to be the catecholamine receptors, whereby the quantitative participation of alpha and beta types is not yet decided and may well depend upon tissue, species and situations.

The time needed for downregulation of those receptors is an important determinant of the sensitivity changes of the system. It allows sudden stresses to unfold all their Mg depleting power, while during long term catecholamine increase tissue sensitivity is diminished by receptor backregulation.

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Résumé

Au cours d'un épisode de stress, le métabolisme du magnésium se montre étroitement corrélé à l'action des catécholamines, essentiellement en raison de la déplétion considérable en Mg liée à ce type d'épisode, qui rend évidents les effets d'un prétraitement substitutif par le MAH (chlorhydrate d'aspartate de magnésium).

L'administration bien programmée d'un traitement de substitution par le MAH s'est opposée à la déplétion en glycogène hépatique induite par le stress, empêchant celle-ci de déclencher à son tour une sécrétion supplémentaire d'adrénaline. De plus, le traitement par le MAH avant un stress exerce un effet direct de diminution de la sécrétion médullaire d'adrénaline et infléchit considérablement l'augmentation du taux de cortisol. Les récepteurs des catécholamines semblent être les régulateurs de l'action magnésium-dépendante des catécholamines et du renouvellement également Mg-dépendant de celles-ci.

La participation quantitative des récepteurs alpha ou bêta n'est pas élucidée et dépend peut-être du tissu, de l'espèce ou de la situation.

Le temps nécessaire pour la contre-régulation de ces récepteurs est un déterminant important des modifications de sensibilité du système. Il permet au stress subits de développer tout leur potentiel de déplétion magnésienne alors qu'au cours d'une augmentation prolongée des catécholamines, la sensibilité tissulaire diminue à la suite d'un rétrocontrôle des récepteurs.

1. The liver as a Mg sensitive catecholamine regulator

Liver glycogen loss during longer stress exposition is well known in man and a great variety of mammals (*Epple* et al. 1989, *Porta* et al. 1989). Occasionally the loss of glycogen becomes so drastic, that even hypoglycemia may ensue, which is described i. a. in cases of neuroses and psychoses in man and also in laboratory animals (*Porta* et al. 1979). This resulting hypoglycemia has been blamed to be the trigger of additional epinephrine output of the liver. It seemed always a little strange to us that a very dangerous and irregular event like hypoglycemia should be regarded as a regulatory tool.

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Recently we could show, that the triggering command for epinephrine release of the adrenal medulla is already given before hypoglycemia occurs. Epinephrine secretion increases greatly if liver glycogen levels fall drastically and swiftly below a certain niveau near the 1 g/100 g mark, while the blood sugar is still in normoglycemic regions (*Porta* et al. 1990). The resulting medullar epinephrine secretion is obviously not needed for further increase in glycogenolysis, but to quickly increase gluconeogenesis and replenish liver reserves by the direct gluconeogenetic action of epinephrine β effects and by the indirect epinephrine induced increase in gluconeogenesis by low insulin and high cortisol levels. Even glycogen synthesis during high epinephrine and low insulin levels is possible in a severely glycogen depleted liver, because of the special situation of glycogen synthase in glycogen lack (*Nazar* et al. 1989, *Danforth* 1965).

Thus the increased epinephrine levels which were triggered by glycogen depletion indirectly increase glycogen reserves again. This epinephrine induction by glycogen downfall, probably via afferent capsaicine sensitive fibres and the well known efferent splachnic pathway begins only to operate-as mentioned above-if glycogen falls swiftly below a certain mark. A 10 days pretreatment with different doses of Magnesium Aspartate Hydrochloride (MAH, Verla Pharm. Tutzing, BRD) had significant influences upon the stress induced Mg depletion of the liver.

Five groups of rats were treated with food containing five different concentrations of MAH. It turned out, that stress induced downfall of liver glycogen was inhibited by pretreatment with higher MAH concentrations in a dose dependent manner. Thus MAH pretreatment prohibited liver glycogen depletion beyond the point of epinephrine triggering and therefore also additional epinephrine secretion (*Porta* et al. 1990).

2. Direct action of MAH upon epinephrine secretion

Not only via carbohydrate-catecholamine regulation systems does an increased Mg level suppress catecholamine secretion, but also seemingly by direct action upon the medulla. This could be shown by checking the remaining epinephrine content of the adrenal medulla of differently MAH pretreated animals (see above) after standardized stress. The higher the dose of the Mg pretreatment, the more epinephrine remained in the gland after stress. Also here MAH pretreatment inhibits epinephrine secretion in a dose dependent manner (*Porta* et al. 1992). Not only in animals, but likewise in man a moderate pretreatment with MAH (see below) prohibited short term-stress induced total (free and bound) Norepinephrine increase in plasma of normoglycemic people.
However, it is still not known, whether this direct effect is connected with the indirect epinephrine secretion suppressing action via the liver. The fact, that a clear increase in residual medullar epinephrine after stress could be seen already after lower MAH pretreatment than that which inhibited liver glycogen downfall, indicates that both mechanisms may play a role under different conditions.

3. Direct action of MAH upon corticosteron (Cortisol) secretion in Rat and Man

An unusually clear effect concerning the reduction of stress hormone levels by MAH premedication is the curtailing of corticosterone (rat) and cortisol (man) plasma concentrations during stress. Pretreatment experiments in the rat according to the same systems which have been used in the preceding chapters revealed a striking and also dose dependent suppression of corticosterone levels during stress (*Porta* et al. 1992). It turned out, that already a moderate increase of MAH concentrations during the 10 days of pretreatment totally suppressed stress induced corticosterone increase which raised in hypomagnesemic animals and in those treated with normal Mg levels to 100 % above normal. But not only in animals, but also in man a moderate 10 days pretreatment of 2 times 5 mM MAH per day was astonishingly effective. A five minutes' exhaustive step test followed by an hours rest and a second step test increased cortisol plasma levels of placebo treated probands doublefold. MAH pretreated persons did not show any significant increase (*Porta* et al. 1992). If one bears in mind the catecholamine inducing properties of increased cortisol production (*Axelrod* 1965) as well as a possible influence of the ongoings in the adrenal medulla upon the cortex (most recent observations of *Epple* 1992, in print) then the two sided impact of MAH upon the inhibition of both medulla and cortex as interactive systems is impressive.

4. The other way round: Action of catecholamines upon Mg turnover and its regulation by catecholamine receptors

One of the most striking events hitting the Mg homeostasis is its removal from so called soft tissue organs like liver and heart during stress. It is estimated by different authors between 30 % and 60 %, depending upon in vitro or in vivo techniques used. The loss is quick – minutes in vitro and hours in vivo – and can therefore not be replenished fast enough by the slower Mg liberation from the bones.
This exactly is the situation, when an individual Mg deficit occurs, temporary of course, but with the very same symptoms as a classic Mg deficiency like e.g. in diabetic electrolyte loss. What happens is, that increased catecholamine levels during stress increase Mg output from tissues. Since on the other hand a constant Mg loss per se induces catecholamine secretion, a vicious cycle seems easily imaginable. But it does not occur, because Mg loss – as a mentioned above – is mediated via catecholamine receptors, whose numbers are backregulated by persi-

stently increased agonist levels. Thus Mg depletion is regulated via hormone (catecholamine) receptors.

Experiments to that effect were carried out by our group. A 10 days Mg depletion by Mg deficient food resulted in permanently higher plasma catecholamines and therefore in an about 30 % downfall of β receptors in the liver at the end of the treatment. A subsequent 20 hours stress did not elicit significant Mg depletion (as it did in normally fed controls) because of the backregulated receptor number. When medullectomized animals, who had no chance of increasing their plasma adrenaline were treated in exactly the same way, the additional stress exposition led to the same expressed Mg depletion from the liver as in controls, because those animals had a normal number of receptors, not backregulated by increased adrenaline plasma concentrations. The quantitative importance of the role of alpha as well as that of β receptors is still discussed (*Jacob* et al. 1989, *Romani* and *Scarpa* 1990, *Porta* et al. 1992, *Rauter* et al. 1992). The important point in this context is, that backregulation takes some time, so that sudden stress rushes its catecholamines upon the cells and takes them by surprise with a large number of receptors expressed on their membrane surface, while stress induced catecholamine increase lasting for some days is able to induce receptor backregulation. This seems to be an efficient system for counteracting the Mg depleting effects of cumulating stresses, but does not affect sudden stress action. Theoretically, more and more stresses during a certain time may lead to less and less Mg losses, unless of course there are sudden peaks in between, which is not at all unlikely.

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