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COMMENTARY

ADRENAL STEROID INFLUENCES ON THE SURVIVAL OF HIPPOCAMPAL NEURONS

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Whereas the selective and programmed destruction of nerve cells plays an important role in nervous system development [1], the preservation of nerve cells from destruction is an important aspect of the mature nervous system. The factors which mediate cell survival and death are of particular interest for our understanding of neuronal development, maintenance and aging. A variety of chemical factors have been shown to influence cell death developmentally and in response to injury. For example, nerve growth factor [2] is able to retard or prevent loss of basal forebrain neurons following surgical lesions to their target sites. On the negative side, circulating glucocorticoids exacerbate neural damage associated with transient ischemia [3] and with aging [4, 5], and possibly also as a result of severe social stress [6]. However, the role of glucocorticoids in neuronal survival is not uniformly negative. A recent report indicated that adrenalectomy (ADX) of rats results, within 3–4 months, in massive loss of nerve cells in the dentate gyrus of the hippocampal formation [7]. This loss can be prevented by maintaining the ADX rats on low levels of corticosterone in the drinking water [7]. One of the puzzles from these findings is that one-third of the ADX rats did not show any gross evidence of massive neuronal loss within the dentate gyrus [7]. These differential effects are particularly surprising because pyramidal cells of Ammon's horn and granule cells of the dentate gyrus express both Type I and Type II adrenal steroid receptors [8, 9]. The apparent paradox of adrenal steroid protection of the dentate gyrus and glucocorticoid potentiation of cell loss in the Ammon's horn demands that we understand more about underlying mechanisms by which nerve cells die or survive. In fact, there are multiple mechanisms and agents involved in neuronal destruction or survival, and this article reviews some of the principal mechanisms and discusses them in relation to the contrasting effects of adrenal steroids on cell survival.

Adrenal steroid protection of dentate gyrus neurons from destruction

The report by Sloviter *et al.* [7] showed that ADX of young (150–175 g) male rats results, in approximately two-thirds of them, in massive loss of neurons in the dentate gyrus 3–4 months later. This loss can be prevented by replacing the rat's natural glucocorticoid, corticosterone, in the drinking water at a low concentration, 20 μg/mL. An unusual feature of this experiment is that all ADX rats received corticosterone replacement during the first 3 weeks after surgery, and this procedure protected ADX rats from subsequent death even when the hormone replacement was discontinued for an additional several months.

The approximately two-thirds of the ADX rats which showed the extensive loss of dentate gyrus neurons had lower serum sodium and higher serum potassium levels than ADX rats in which cell loss was not evident [7]. It should be noted that actual counts of dentate gyrus neurons were not reported, and thus it cannot be ruled out that there was some loss of neurons in ADX rats in which large scale reduction of the dentate gyrus was not evident. It is also noteworthy that neuronal loss in the dentate gyrus was not uniform and was higher in the lateral end of the dorsal blade and greater in the septal and middle third of the dentate gyrus than in the temporal third.

What is the most likely explanation for the partial nature of these effects? As far as the regionality of neuronal loss in the dentate gyrus, it is interesting that more cell loss was noted in the rostral portion of this brain region, which contains neurons that were born later than those in the caudal portion of the dentate gyrus [10]. Thus, the relative degree of maturity may play some role in the determining the susceptibility of a neuron to ADX. In addition, the granule neurons located in the rostral dentate gyrus appear to be more densely packed than those of the caudal dentate gyrus and exhibit a greater degree of convergence onto their target cells, the CA3 pyramidal neurons [10]. If competition for target sites plays a role in mediating cell survival in this brain region, it is possible that more densely packed rostral dentate gyrus neurons are particularly vulnerable to ADX because they are more in competition with each other for target-derived trophic factors. In this connection, levels of nerve growth factor have been reported to decrease in the hippocampal formation following ADX [11]. The possible significance of this observation will be considered further at the end of the article.

With regard to an explanation for the one-third of the rats in which the dentate gyrus did not diminish in size, there is accessory adrenal tissue to be considered. Rats are known to have accessory adrenal

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tissue which can grow following ADX and provide some replacement of adrenal steroids [12], and low levels of corticosterone and aldosterone from such accessory nodules may not produce readily detectable blood levels. The animals in which neuronal loss was evident may have been those in which accessory adrenal tissue was not present after ADX and in which insufficient residual adrenal steroids were present to maintain serum sodium and potassium levels or to protect the dentate gyrus. It is noteworthy that three other studies employing long-term adrenalectomy gave either corticosterone [4] or periodic injections of mineralocorticoids [13, 14] to maintain animal health after ADX and did not see signs of dentate gyrus neuronal loss.

Neuronal death in the dentate gyrus within several days after adrenalectomy

Because of the 3- to 4-month time interval in the ADX effects of the Sloviter *et al.* [7] study, these experiments are very cumbersome and time-consuming to perform in search of a possible mechanism. Demonstrating ADX-induced dentate gyrus neuronal loss in a shorter time interval would add support to the notion that the ADX effect is directly related to adrenal steroids and that it may have some role in physiology or development. With this in mind, we conducted quantitative observations of the hippocampal formation 3 and 7 days after ADX and were surprised to find that every ADX rat examined showed a substantial, though somewhat variable, increase in the number of dying (i.e. pyknotic) granule cells at both time intervals [15]. There was no indication of neuronal death in Ammon's horn. The distribution of dying neurons within the dentate gyrus was not uniform and approximated the pattern of cell loss found by Sloviter *et al.* [7]. That is, cell death was noted exclusively in the dentate gyrus and was concentrated more heavily in the rostral and lateral aspects of this neural region. Moreover, the loss could be prevented by low doses of corticosterone in the drinking water [15], and we now have data indicating that moderate doses of aldosterone and dexamethasone also prevent dentate gyrus neuronal death (Gould E, Woolley CS, Sakai R and McEwen BS, unpublished observations) (see also Fig. 1). The ease and speed of these experiments will allow a rapid and detailed pursuit of the cellular mechanisms involved.

We do not know whether the short-term increase in cell death after ADX leads to a net loss of neurons. Alternatively, it is conceivable that it represents an acceleration of cell turnover, with ADX also producing a compensatory increase in neurogenesis. This possibility, which is currently under investigation in our laboratory, is not unreasonable, given the fact that the dentate gyrus of the rat continues to show neurogenesis for more than 1 year after birth [16, 17], and ADX is known to increase cell division in the developing brain [18]. It is also possible that increased cell turnover yields a net loss of neurons [19]. That is, if dentate gyrus neuroblasts have a finite number of cell divisions, then eventually the number of dying cells may exceed the number of newly generated cells. As an initial step in studying these possibilities, we are currently investigating whether older rats show the short-term increase in dentate gyrus neuronal death when they are adrenalectomized after the active period of dentate gyrus neurogenesis has subsided. Our preliminary results indicate that the intensity of neuronal loss in the dentate gyrus is markedly, but not completely, reduced in 9- to 12-month-old rats compared to 58-day-old rats (Gould E, Woolley CS and McEwen BS, unpublished observations).

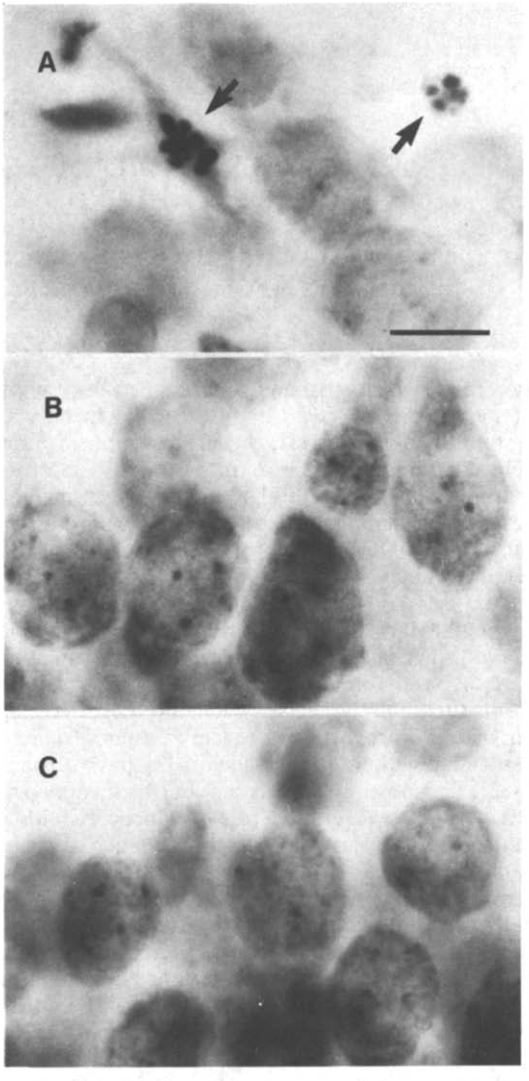

Fig. 1. Photomicrographs showing pyknotic dentate granule cells in 60-day-old rats adrenalectomized for 7 days (A) and the sparing effects of aldosterone (1 μg/hr in Alzet minipump) (B) and dexamethasone (10 μg/mL in drinking water) (C) during 7 days after ADX. Scale bar: 10 μm.

Glucocorticoid exacerbation of neuronal loss in aging, ischemia and after excitotoxin treatment

We do not know yet at the cellular level why dentate gyrus neurons die, and we must look for clues in other situations in which glucocorticoids are involved in neuronal death or survival. Contrasting with the cell death occurring in the dentate gyrus

after ADX is the effect of glucocorticoids in potentiating neuronal loss after transient ischemia [3] and during aging [4, 5] or after exposure to exogenous excitotoxins [20, 21]. Before this information was available, glucocorticoids were first shown to cause pyknosis and neuronal loss in the hippocampus and diencephalon when given over 21 days to guinea pigs [22]. Age-related loss of hippocampal neurons has been shown to be retarded by ADX in mid-life [4], and age-related changes could be mimicked by a course of 12 weeks of corticosterone injections of young adult rats [23]. We have found recently that a 21-day course of daily injections of corticosterone at this same dose (40 mg/kg) causes neurons in Ammon's horn to become less branched and smaller, as if they were in a catabolic state [24]. These effects are noted in the pyramidal cells of the CA3 region and they are not evident in the dentate gyrus [4, 23]. In studies of transient ischemia and excitotoxin administration, ADX had the effect of attenuating neuronal loss, and elevated glucocorticoids potentiate neuronal loss [3, 20, 21, 25].

A common denominator of this type of neuronal loss appears to be the involvement of excitatory amino acids. Excitatory amino acid levels are increased by transient ischemia in the hippocampus [26], and the hippocampus is particularly rich in excitatory amino acids and their receptors [26–29]. In the hippocampus, glucose and other metabolizable sugars retard the damage produced by exogenous excitotoxins both *in vivo* [30, 31] and *in vitro* [32], leading to the suggestion that energy supplies may be the rate-limiting step through which glucocorticoids exert their damage-potentiating effects [30]. In support of this notion, glucocorticoids appear to inhibit glucose uptake *in vivo* [33] and in neurons and glial cells of the hippocampus in primary culture [34]. Even though the inhibition of glucose transport is not large, it may be enough to restrict energy generation when neurons are heavily stimulated by excitatory amino acids [30, 34, 35]. It is noteworthy that seizure-induced damage, which is also thought to involve excitatory amino acids, results in death of CA3 pyramidal cells but not dentate gyrus granule cells [36], suggesting that there is a fundamental difference in the survival requirements of these two different neuronal populations.

It is also possible that glucocorticoid-induced degeneration of CA3 pyramidal neurons is the result of indirect was well as direct effects on this neuronal population. Since ADX causes decreased cell survival as well as decreased electrical activity in the dentate gyrus [7], it is likely that increased levels of glucocorticoids have the opposite effect on granule cells, namely, to increase cell survival and increase neuronal activity. If increased glucocorticoids result in increased granule cell activity, the postsynaptic sites of these neurons would be subjected to increased release of excitatory neurotransmitters, including excitatory amino acids. Because they receive a major input from the dentate gyrus, it is likely that CA3 neurons may be gradually and adversely affected by the extra excitatory amino acids released by an overactive dentate gyrus. This possibility is summarized in Fig. 2. While only a speculative possibility at this stage, such an indirect mechanism could explain why CA3 and not CA1 neurons die as a result of prolonged glucocorticoid exposure, since rostral CA1 neurons receive no input from the dentate gyrus.

How do excitatory amino acids cause neuronal destruction?

If excitatory amino acids are the primary cause of neuronal damage associated with ischemia and possibly also with aging, what is it that they set in motion which kills cells? There are at least three types of recognition sites by which excitatory amino acids produce effects on neural tissue; the kainate, quisqualate and *N*-methyl-D-aspartate (NMDA) receptors [29]. However, as noted in Fig. 3, although the agonists kainic acid and quisqualate can trigger neurotoxicity, it is not clear whether they do so totally via the so-called kainate and quisqualate receptor sites independently of the NMDA receptors [37–39]. Excitatory amino acids are linked to the entry and mobilization of calcium ions via ion channels and the phosphoinositol pathway [40]. However, as is shown in Fig. 4, there are multiple control mechanisms mediating calcium ion homeostasis [35, 39, 40]. As far as ischemic damage to nerve cells is concerned, the principal villain appears to be the NMDA receptor [41] which mediates calcium entry (Fig. 3). This receptor is modulated by other agents, such as glycine, glutamine and magnesium ions. Magnesium ions attenuate traumatic brain damage [42] and may do so in part by blocking the NMDA receptor [43], whereas glycine and glutamine both potentiate NMDA-mediated damage [44–46]. The phencyclidine (PCP) binding site on this receptor enables drugs such as MK-801 and phencyclidine to attenuate ischemic and traumatic brain damage [47–50]. Hypoglycemic damage to neurons in cell culture is mediated by NMDA receptors [51], strengthening the connection noted above between glucose deprivation and the potentiating effects of glucocorticoids.

Quisqualate produces a delayed neurotoxicity [38], and kainic acid causes neurotoxicity which, however, appears to involve NMDA receptors as well [37]. Nevertheless, quisqualate also inhibits neurotoxicity caused by kainate [52], perhaps because of its ability to antagonize the kainate receptor at high concentrations [53]. Inhibition of kainate toxicity is also produced by high levels of calcium ions [52]. Since calcium ions are otherwise implicated as mediators of NMDA-induced toxicity, this observation indicates that there are additional levels of complexity which must eventually be considered in probing the mechanisms by which glucocorticoids or any other agent promotes or protects from neuron destruction. In spite of the antagonistic effects of quisqualate toward kainate actions, quisqualate, kainate and NMDA are all capable of elevating free Ca^{2+} in hippocampal neurons in primary culture [54]. However, it is not clear whether these effects represent primary actions via the quisqualate, kainate and NMDA receptors, respectively, or are secondary effects mediated finally by the NMDA receptor.

Besides glutamate and the synthetic excitatory amino acids, there are endogenous metabolites of

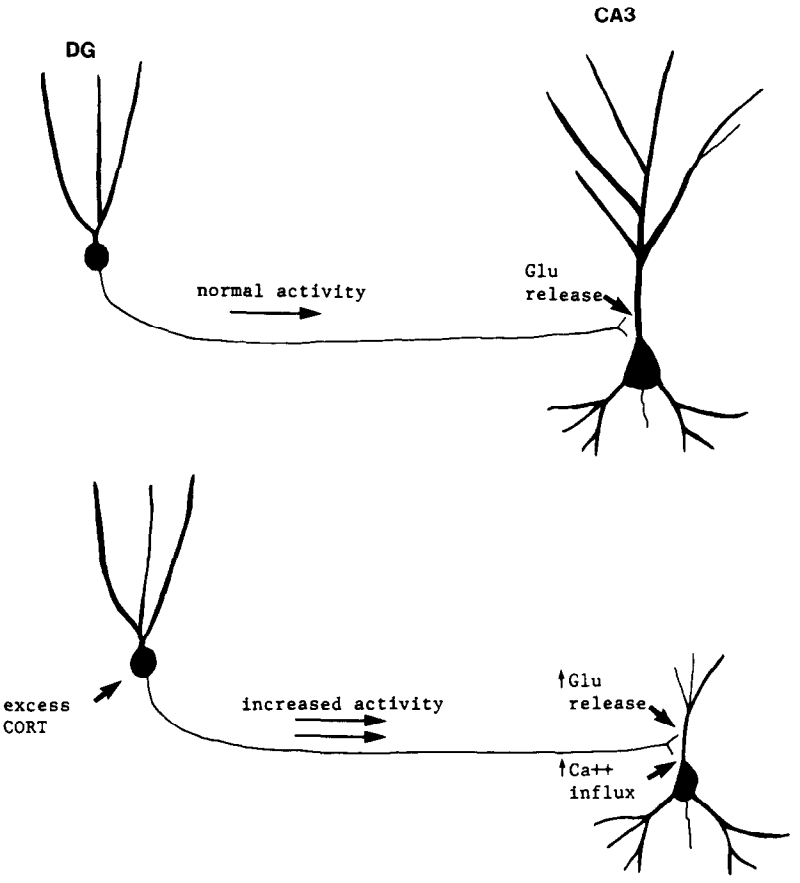

Fig. 2. Schematic representation of a possible mechanism whereby chronic corticosterone (CORT) administration could affect adversely CA3 pyramidal cells by altering dentate gyrus (DG) granule cell activity. Excess glucocorticoids could increase the release of glutamate (Glu) on to their target sites; the increased Glu of the CA3 pyramidal cells would result in an increase in Ca^{2+} influx which would result in pyramidal cell degeneration.

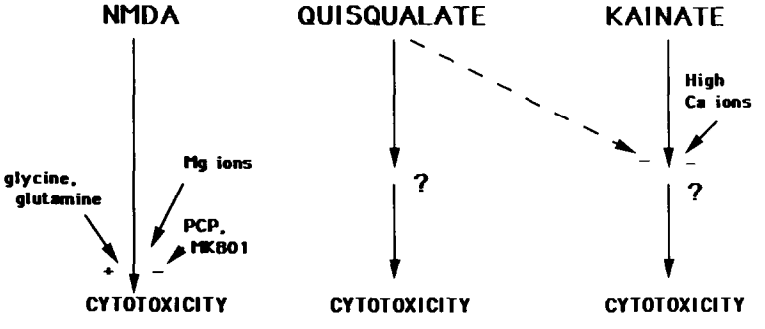

Fig. 3. Depiction of three types of excitatory amino acid receptors which are defined by three agonists: *N*-methyl-D-aspartate (NMDA), quisqualate and kainate. Whereas NMDA receptors are clearly involved in mediating cytotoxicity in which calcium ions are implicated, the abilities of quisqualate and kainate to produce cytotoxicity exclusively via their own specific receptor types are unclear. Instead their cytotoxic effects may be dependent, at least in part, on the participation of NMDA receptors. See text for details.

tryptophan which have potent effects toward excitatory amino acid receptors, namely, quinolinic acid and kynurenic acid. Quinolinic acid is a potent excitotoxin [55, 56] which acts via NMDA receptors to cause cell death in the hippocampus and other brain regions [44, 57]. Kynurenic acid is an antagonist of excitatory amino acid receptors which can block the damaging effects of quinolinic acid [38, 44]. Because

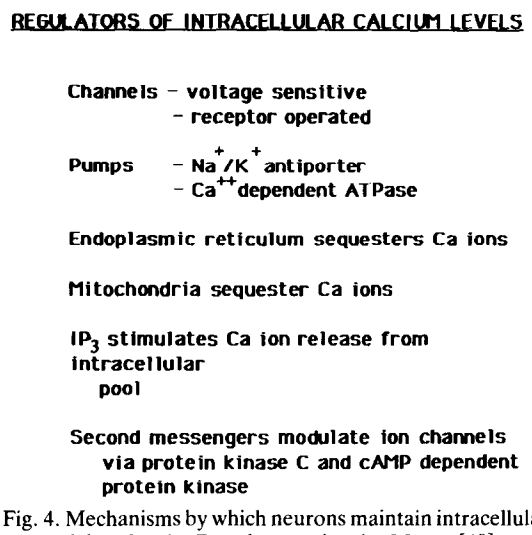

Fig. 4. Mechanisms by which neurons maintain intracellular calcium levels. Based on review by Meyer [40].

both metabolites are present in the brain and certain of their biosynthetic enzymes are present in brain as well [55, 58], the ratio of quinolinic to kynurenic concentrations is an important consideration with regard to excitotoxicity. It is, therefore, of particular interest that brain damage by excitotoxins leads to increased levels of quinolinic acid [59]. On the other hand, in Huntington's disease brains, in which excitatory amino acids are presumed to play a primary role in neuronal destruction, there is reported to be an increase in kynurenic acid levels, which may represent some form of compensation [60].

What is the role of elevated calcium ions in neuronal death?

How do elevated levels of Ca eventually contribute to cell destruction? A key element appears to be the generation of oxygen free radicals which cause lipid peroxidation [61] and damage to DNA [62] (see Fig. 5). One way in which increased calcium causes increased free radical formation is by activating a protease which converts xanthine dehydrogenase, a major enzyme for degrading purines, into xanthine oxidase which reacts directly with oxygen to generate superoxide, the oxygen free radical [64] (see Fig. 4). Another important event, involving glutamate, is the competitive inhibition of the cellular uptake of cystine [65, 66]. In the absence of cystine, cellular levels of glutathione, an antioxidant, decline and oxidative stress ensues [65, 66]. As is summarized in Fig. 5, excitatory amino acids have two synergistic effects leading to cell death, namely, increasing calcium levels and decreasing cystine and glutathione levels. In addition, osmotic damage results from failure of ionic homeostasis (Fig. 5), induced by too much excitatory amino acid stimulation.

With regard to the damaging effects of excitatory amino acids on CA3 pyramidal neurons but not dentate granule cells [36], it is interesting to note that both cell types undergo Ca^{2+} influx in response to excitatory amino acids [54, 67]. Despite this commonality, granule cells, but not CA3 pyramidal cells, express calcium binding protein [68], presenting a possible mechanism whereby granule cells can avoid excitatory amino acid-induced death.

Glucocorticoid involvement in the excitatory amino acid-calcium cascade

Let us return to consider the places in which glucocorticoids intervene in cellular destruction. From our still rather limited knowledge, it is nevertheless possible to see that the effects of glucocorticoids are not uniformly negative (Fig. 6). On the negative side, we have already noted the ability of glucocorticoids to inhibit the cellular uptake of glucose, an event which can compromise cellular energy generation, but to a limited extent because the effects of glucocorticoids on glucose transport are not large ones [33, 34]. On the positive side, glucocorticoid treatment reduces brain levels of quinolinic acid [69], although nothing is known about changes in kynurenic acid levels which may also follow high glucocorticoid treatment. Another potentially positive effect of glucocorticoids is their ability to reduce the number of recognition sites for glutamic acid in hippocampus [28]. This reduction involves both chloride-sensitive and chloride-insensitive forms of binding as well as the quisqualate-sensitive component [28]. Although these changes are not large, they represent a potential mechanism for retarding the impact of excitatory amino acids on the hippocampus. Another action of glucocorticoids (Fig. 6) is to induce glutamine synthetase, the enzyme which converts glutamate to glutamine in astroglial cells [70, 71]. However, the significance of this induction for excitotoxicity is not clear: whereas glutamine is not an excitotoxin, it is a potentiator of agonists which act via the NMDA receptor and, therefore, is capable of potentiating NMDA receptor-mediated neurotoxicity [45, 46]. Thus, elevated levels of glutamine appear to potentiate the actions of excitatory amino acids rather than representing an inactive pool. Finally, glucocorticoids act by an unknown mechanism to inhibit damage related to lipid peroxidation, and this has led to the development of a class of steroids lacking in classical glucocorticoid potency which nevertheless act to inhibit lipid peroxidation and also to improve recovery after head trauma [72, 73].

What is impressive about the pathways summarized in Figs. 5 and 6 is that there are so many other potential sites through which circulating glucocorticoids may effect excitotoxicity positively or negatively. These include possible effects on calcium entry, which have been reported in neural tissue and synaptosomes [74, 75], as well as possible effects on free radical levels via regulation of free radical generation (e.g. xanthine oxidase) or destruction (e.g. superoxide dismutase; levels of glutathione). It is clear that the multiple, positive effects of glucocorticoids are more compatible with the view that glucocorticoids are generally protective against effects of stress and promote adaptation and re-establishment of homeostasis [76, 77].

Another feature of the multiple interactions between excitatory amino acids and neurons is the various ways in which destructive processes interact with each other both positively and negatively. As

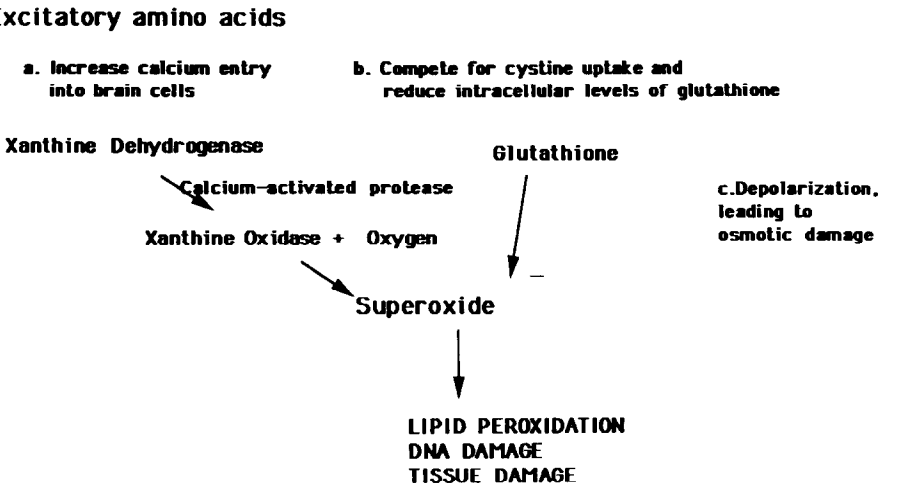

Fig. 5. Schematic summary of the interacting ways in which excitatory amino acids bring about increased oxidative stress which leads to cytotoxicity and tissue damage. (a) One way to increase intracellular calcium ions intracellularly, which can, if not buffered by the mechanisms summarized in Fig. 3, lead to activation of a protease which converts xanthine dehydrogenase into xanthine oxidase, an enzyme which reacts with molecular oxygen to generate superoxide. (b) A parallel effect of excitatory amino acids is to compete for cystine entry into cells and thereby cause depletion of intracellular glutathione levels. Because glutathione is an antioxidant, this reduction exacerbates the oxidative stress. (c) Excitatory amino acids also cause depolarization-induced influx of ions which can lead to osmotic damage [39, 63].

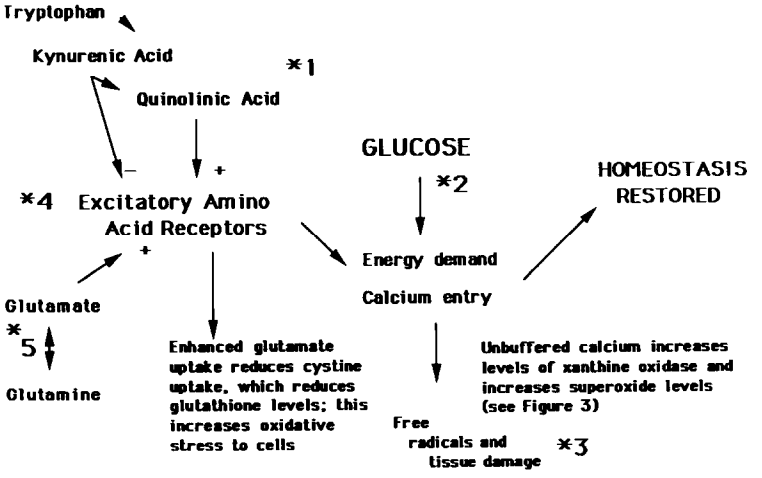

Fig. 6. Schematic summary of the interactions described in the text between excitatory amino acids and cytotoxicity, showing control points at which glucocorticoids have been shown to have positive or negative effects on cytotoxicity. (1) Glucocorticoid treatment reduces quinolinic acid levels in brain. (2) Glucocorticoids inhibit glucose uptake. Note that if sufficient energy is supplied via glucose, the cell is able to reestablish calcium homeostasis, thus reducing the deleterious effects of unbuffered calcium. (3) Glucocorticoids retard cellular damage related to lipid peroxidation. (4) Glucocorticoids decrease levels of recognition sites for glutamate, particularly in the hippocampus. (5) Glucocorticoids induce glutamine synthetase; glutamine potentiates effects of glutamate acting via NMDA receptors. See text for details.

noted above, lesioned neural tissue produces more quinolinic acid than non-lesioned tissue [59], and this has the potential to exacerbate damage. However, as noted, Huntington's disease brains, which are thought to be very sensitive to the destructive effects of excitatory amino acids, generate increased levels of the inhibitor, kynurenic acid [60], and this may represent a form of compensation. Another type of potentially destructive interaction derives from the report that elevated levels of superoxide, generated by exogenous xanthine oxidase, lead to enhanced release of excitatory amino acids [78]. However, glucocorticoids, as noted above and in Fig. 6, are capable of reducing the levels of certain excitatory

amino acids (quinolinic acid) as well as the binding of glutamate to its recognition sites. Furthermore, the glucocorticoid, methylprednisolone, inhibits the damaging effects of free radicals on lipid peroxidation-induced neural damage [72, 73]. Thus, the interacting system of chemical agents and processes which can cause neuronal destruction has an inherent set of checks and balances as well as the potential for hysteresis.

Other mechanisms for cellular destruction

It is important to recognize that there are other mechanisms by which neurons die, aside from those involving excitatory amino acids and free radicals. Developing neurons, which are frequently produced in excess, die at a particular stage of development by what is known as "programmed cell death" [1]. Among the factors involved in cell death are believed to be the failure to gain access to sufficient growth factors which promote cell survival [79]. Aside from peptide growth factors [80], steroid and thyroid hormones also appear to mediate cell death in some systems. For example, in the sexually dimorphic SNB nucleus of the spinal cord, testosterone prevents cell death in the male rat [81]. In contrast, the timed release of some hormones appears to trigger cell death, as exemplified by the actions of thyroid hormone in tadpoles [82, 83] and ecdysone in insects [84]. A non-neural case of hormonally-induced cell death is the destruction of lymphocytes triggered by glucocorticoids acting genomically [85, 86] which results in the activation of nucleases which cleave DNA [87]. This mechanism does not appear to operate with regard to glucocorticoid-facilitated destruction of hippocampal neurons [88]. It is presently unknown whether glucocorticoids mediate naturally occurring cell death in the developing hippocampal formation. It is likely that an understanding of the factors which influence developmental cell death in the dentate gyrus and Ammon's horn will shed considerable light on the mechanisms by which glucocorticoids can protect or harm these neurons in adulthood.

Conclusions: how can glucocorticoids both promote neuronal destruction and protect neurons?

We have examined the protective role of glucocorticoids towards survival of dentate gyrus neurons against a background of effects in which glucocorticoids promote neuronal destruction in Ammon's horn via a mechanism involving excitatory amino acids, calcium ions and free radicals. To explore whether there is a possible commonality of underlying mechanisms, we have also discussed other mechanisms by which neurons are protected or destroyed and also noted that the known effects of glucocorticoids within the excitatory amino acid cascade are not uniformly negative. Can we now make some predictions as to possible mechanisms by which adrenal steroids protect dentate gyrus neurons?

One possibility, independent of the excitatory amino acid cascade, is that glucocorticoids may positively regulate trophic factors necessary for neuronal survival. This possibility is supported by the report the nerve growth factor (NGF) activity declines after adrenalectomy in the rat hippocampus [11]. A decline in NGF activity was found in dentate gyrus as well as in Ammon's horn, to which dentate gyrus neurons project [11]. Thus, because the density of neurons is highest in areas of the dentate gyrus showing the greatest loss after ADX (see above), competition for trophic factors such as NGF may be particularly intense in this region. Although NGF receptors have not been reported in the adult dentate gyrus [89], the observation that NGF antibodies can cause dentate gyrus cell death [90] suggests that NGF may play some role in the survival of these cells. It is also possible that other adrenalectomy-sensitive trophic factors having similar effects as NGF could exert an influence over hippocampal neurons. In addition, electrical activity has been shown to mediate developmental cell death [91, 92], and it is intriguing that both ADX and glucocorticoid administration affect the electrophysiological activity of the dentate gyrus and Ammon's horn [7, 93–95]. Further experimentation will be required to determine the extent to which these factors mediate ADX- and glucocorticoid-induced cell death.

Another possibility is that the dentate gyrus may be a site in which some of the beneficial effects of glucocorticoids, cited above, outweigh the negative effects. Glucocorticoid effects which are positive or potentially beneficial toward cell survival include the inhibition of damage related to lipid peroxidation [72, 73] and reduction in sensitivity of excitatory amino acid recognition elements [28]. Considering the vast number of interacting steps discussed above and summarized in Figs. 5 and 6, there are many as yet unexplored potential sites of regulation by adrenal steroids, involving such important features as the levels of the individual excitatory amino acid receptor types and excitatory amino acid transporters, the generation and metabolism of kynurenic acid, calcium transport and sequestration, and the levels of xanthine dehydrogenase and the calcium-activated protease which governs its conversion to the free radical generator, xanthine oxidase. Until we explore these possibilities as well as the effects of glucocorticoids on granule cell division and brain growth factor levels, it will not be possible to pinpoint clearly how glucocorticoids work. Only then will we know whether the protective and destructive effects which they exert represent extremes of a continuum or totally separate and distinct cellular and molecular actions.

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