Type 1 diabetes, glucocorticoids and the brain: a sweet connection

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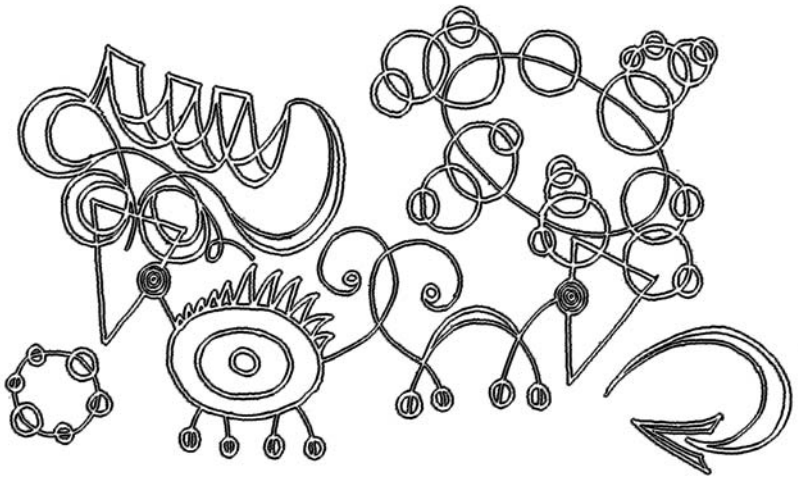
CHAPTER 6

GENERAL DISCUSSION



Outline

THE OBJECTIVE of the studies described in this thesis was to elucidate if glucocorticoids circulating in excess in mice suffering from type 1 diabetes enhance vulnerability to cerebral damage and cognitive impairment. For this purpose we have used two animal models, i.e. a pharmacological model, the streptozotocin (STZ)-treated mouse, and a genetic model the NOD mouse, which spontaneously develops type 1 diabetes. These models were used to test the hypothesis that the onset of diabetes induces first dysregulation of the HPA axis and subsequently hypersecretion of glucocorticoids which then renders the brain more vulnerable to metabolic insults causing damage and concomitant cognitive disturbances. Alternatively it also is possible that hyperglycemia and aberrant insulin levels cause deterioration of brain structure and function.

Main findings

The NOD model revealed a surge in ACTH release which likely preceded the onset and progression of diabetes marked by adrenal hyperreponsiveness and hypersecretion of corticosterone. To our surprise we found in the STZ model that not the initial ACTH surge was the most proximal cause of hypercorticism in diabetes, but rather the induction of adrenocortical ACTH receptors *per se*. At no time point after STZ administration ACTH levels did rise reinforcing the notion that hyperresponsiveness of the adrenals to ACTH may occur independent of the mitogenic activity of the peptide. In the same model, excess glucocorticoids rather than glycemia and insulin appeared causal to cerebral damage and mild cognitive impairment. These deficits in hippocampal function induced by high glucocorticoid concentrations were readily ameliorated by a brief treatment with the glucocorticoid receptor antagonist mifepristone.

HPA axis in a spontaneous T1D model, the NOD mouse

In the nonobese diabetic (NOD) mouse, a model of autoimmune type 1 diabetes (T1D), central nervous system alterations involve: (i) astrogliosis in the hippocampus during pre- and full-blown diabetes; (ii) decreased cell proliferation after diabetes onset, (iii) increased expression of hypothalamic arginine-vasopressin and oxytocin mRNAs and peptides in diabetes; and (iv) increased levels of circulating glucocorticoids. These results indicate hippocampal dysfunction and activation of the hypothalamus-pituitary-adrenal (HPA) axis in diabetes. Therefore, Chapter 2 tested the hypothesis that an altered HPA axis regulation in NOD mice may signal the onset and progression of the disease. Hence, we examined molecular markers of the hippocampal-HPA axis in diabetic and non-diabetic littermates. The results demonstrate that while the pre-diabetic phenotype seems to be characterized by adrenal hyporesponsiveness in view of high ACTH vs. low glucocorticoids levels, the opposite is observed in long-term diabetes. During full-blown T1D glucocorticoids are elevated and ACTH is significantly lower as compared

to non-diabetic littermates, a condition suggesting hyperresponsiveness of the adrenals to ACTH. Moreover, downregulation of the glucocorticoid receptor in the hippocampus and hypothalamus suggests that the capacity to suppress the HPA axis is disrupted. Such an impaired negative feedback would further promote hypercorticism.

The activation of ACTH release found in a subgroup of non-diabetic mice rises the question whether it precedes full-blown diabetes. Therefore, non-fasting C-peptide levels were determined, a measurement of residual beta-cell functionactivity, which is secreted in equimolar concentrations with insulin and is an appropriate outcome measure for T1D. We observed that the subgroup of non-diabetic mice exhibiting high ACTH levels also showed higher concentration of C-peptide as compared to the non-diabetic littermates with normal ACTH levels. In view of these results, it seems likely that the group of mice with elevated C-peptide might develop T1D. This indicates that ACTH release may precede the cascade of endocrine events triggered by the destruction of insulin-producing cells.

As mentioned above, ACTH hypersecretion occurs in a face of unaffected corticosterone levels, suggesting adrenal hyporresponsiveness and/or impaired function. This could facilitate the progression of autoimmunity. Cytokine levels, as an index of autoimmunity, can affect the HPA axis elevating CRH levels and destroying the adrenal glands. Although lymphocyte penetration of adrenals was established in NOD mice, no signs of immune destruction nor changes in corticosterone levels were found (Beales *et al*, 2002). Therefore, the idea that the lack of adrenal responsiveness is due to immune destruction of the adrenals in the subgroup of pre-diabetic NOD mice with high ACTH concentration can be discarded although a shift in the local cytokine balance cannot be excluded. However, our results from plasma cytokine concentrations (IL-1, IL-6 and TNFα) did not reveal an immune response neither at the time of the pre-diabetic ACTH surge nor during full-blown diabetes.

HPA axis alterations in type 1 diabetic mice

Type 1 diabetes is characterized by hypercorticism and lack of periodicity in adrenal hormone secretion. Our NOD mice data resemble the reported effects of food deprivation observed in young male mature rodents (Dallman *et al*, 1999). After food deprivation there is an immediate burst in ACTH possibly to sensitize the adrenals, subsequently hypercorticism is maintained in the face of very low circulating levels of insulin and ACTH suggesting a significantly enhanced adrenal responsiveness under these conditions. The hypercorticism reinforces catabolic activity and enhances the expression of peptides such neuropeptide Y which reinforce the drive for food seeking behaviour (Dallman *et al*, 1999). Likewise pups deprived from maternal care and feeding show a rapidly enhanced adrenal hyperreponsiveness which can be readily ameliorated when feeding is reinstated (Van Oers *et al*, 1998).

In Chapter 3 the data show that the expected rise in blood glucose levels induced by

STZ treatment preceded the surge in corticosterone secretion, which took place one day after diabetes onset. Surprisingly, there was no initial ACTH after STZ treatment. ACTH levels were below control levels during the first day after diabetes onset and remained low until day 11 during hypercorticism. These results suggest that in the STZ model sensitization of the adrenal glands to ACTH rather than the increase in circulating ACTH level characteristic for NOD mice is the primary event leading to hypercorticism. In support of this assumption, adrenal cell cultures of diabetic mice secrete higher amounts of corticosterone compared to controls, in response to ACTH (but not to vasopressin) and the adrenal glands increased expression of ACTH receptors (MC2 and MC5) in the adrenal glands.

To understand the regulation of the hypothalamic-pituitary-adrenal (HPA) axis activity that might lead to the adrenal hypersensitivity in diabetes, molecular markers were analyzed at different time points. We found that AVP mRNA expression in the paraventricular nucleus (PVN) of the hypothalamus was increased from the day of diabetes onset. Hippocampal MR mRNA was initially up-regulated at the day of diabetes onset, but downregulated at day 11 of the disease. The decreased MR expression suggests that as a consequence the disrupted inhibitory regulation of the HPA axis contributes to the observed chronic hypercorticism. This result implies that a time-dependent adaptation to the new metabolic condition had occurred. Whether this adaptation in T1D leads to a more fragile state of the brain in which glucocorticoids excess may enhance the potential for damage and attenuate protective mechanisms, thus facilitating cognitive dysfunction and impairing the ability to respond to stress, is addressed in Chapters 4 and 5.

Discrepancies between the findings described above and published reports in relation to the HPA axis regulation have been found in different models of T1D. In a STZ-rat model Chan *et al* (2002) showed a profound activation of the HPA axis characterized by a marked increase in ACTH and corticosterone levels at 8 days after STZ injection. Moreover, AVP and CRH mRNAs expression in the hypothalamus and MR mRNA in the hippocampus were enhanced. Based on these results, the authors suggested that there is an increase in the central drive to the HPA axis that overrides the inhibitory influence of a negative feedback action by corticosterone. These authors and others (Scribner *et al* 1993) also showed that adrenal sensitivity is not increased in uncontrolled STZ-diabetic rats. No rise in corticosterone levels was found in diabetic animals after stimulation with low dose of ACTH.

Variability of the animals models used among studies could explain these disagreements: 1) STZ-rats and mice largely differ in survival (STZ-rats up to 8 months, STZ-mice few months); 2) severity of diabetes and routes of STZ administration and dosages (due to species variation in response to the drug). In particular in the studies from Chan *et al*, 10% sucrose in drinking water was given to the animals the first 24 hours following the STZ injection to prevent hypoglycemia, rendering moderately reduced fasting insulin levels. In our model, no sucrose was administered, which results in a condition characterized by hyperglycemia and low insulin levels at fasting and fed states.

In our mouse STZ model of T1D, the HPA axis readily reached a new setpoint characterized by high circulating corticosterone, low ACTH levels and enhanced adrenocortical sensitivity. The upregulation of ACTH receptors in the adrenal glands of STZ-induced diabetic mice might explain, at least in part, how hypercorticism is triggered and maintained. Moreover, the enhanced AVP mRNA in the PVN and decreased MR mRNA in the DG also may be considered manifestations of a profound disturbance in HPA axis regulation. A better understanding of these mechanisms may explain how diabetic pathophysiology causes adaptations in the CNS that may lead to an increased potential for damage and cognitive impairment

Hippocampal alterations in type 1 diabetic mice

Previous studies have demonstrated in models of type 1 diabetes (nonobese diabetic and streptozotocin (STZ)-treated mice), a marked astrogliosis and neurogenesis deficit in hippocampus and an increased expression of hypothalamic neuropeptides. In Chapter 4 the results are shown of a study designed to analyze the alterations of astroglia and neurons in the hippocampus of mice 1 month after STZ-induced diabetes. The STZ-diabetic mice presented: (a) increased number of astrocytes positive for apolipoprotein-E (Apo-E), a marker of ongoing neuronal dysfunction; (b) abnormal expression of early gene products associated with neuronal activation, including a high number of Jun positive neurons in CA1 and CA3 layers and *dentate gyrus*, and of Fos-expressing neurons in CA3 layer; (c) augmented activity of NADPH-diaphorase, linked to oxidative stress, in CA3 region. These data support the concept that uncontrolled diabetes leads to hippocampal pathology, which adjoin to changes in other brain structures such as hypothalamus and cerebral cortex.

Increased apolipoprotein-E astrocytic reactivity reflects an incipient damage as part of the rescue program to counteract neurodegeneration. Increased early gene expression proteins indicate emerging neuronal derangement in the hippocampus of diabetic animals. Elevated NADPH-diaphorase immunoreactivity indicates increased nitric oxide levels, which at high concentrations can cause neuronal death. These data indicate that hippocampal astrocytes and neurons are strongly activated one month after diabetes induction, exhibiting also higher oxidative stress. The results identify the hippocampus as a crucial brain structure sensitive to T1D disturbances. However, these findings also raise new questions: (i) are these changes indicators of damage caused by glucocorticoids, and (ii) do they lead to hippocampal dysfunction?

Glucocorticoids action on molecules and cognition in type 1 diabetes

A fundamental question in the central neuropathophysiology of T1D raised in Chapter 4 is whether glucocorticoid aggravate the morphological signs of hippocampal

neurodegeneration that herald the onset of cognitive impairment. Since hypercorticism *per se* can evoke a neurodegenerative cascade similar to the one observed in T1D, the role of glucocorticoid excess in STZ- diabetic mice in relation to morphological indices for neuronal viability and cognitive performance is described in Chapter 5. STZ-diabetic mice exhibit increased glucocorticoid secretion, hippocampal aberrations such as astrogliosis, increased c-Jun expression and decreased cell proliferation already 11 days after the onset of diabetes. At this time, retention and reversal learning in the water maze, retention in the forced swim task and emotional parameters in the elevated plus maze were not affected in diabetic mice. However, cognitive deficits became obvious in an exclusively hippocampal-dependent test, the novel object-placement recognition task. We showed that the continuous blockade of glucocorticoid action by treatment with the glucocorticoid receptor (GR) antagonist mifepristone (200 mg/kg p.o.) for 4 consecutive days (from day 7 to 10 of STZ-diabetes) prevented some of the hippocampal aberrations and reversed others. The decreased cell proliferation observed at day 6 was further decreased at day 11, but restored to control levels upon GR blockade. The prevention of hippocampal astrogliosis and increased neuronal activation showed that mifepristone treatment also can interfere directly with the progression of hippocampal alterations observed in diabetic mice. Moreover, when glucocorticoid action is inhibited by mifepristone administration, the cognitive deficits observed at day 11 were ameliorated. Surprisingly, the diabetic animal treated with mifepristone performed even better than the untreated controls.

The results presented in Chapter 5 provide evidence that glucocorticoid excess and the concomitant continuous activation of the GRs are responsible for molecular changes and hippocampal dysfunction at the behavioral levels at the early stages of diabetes. However, other factors altered in T1D might also be involved. Imbalance of glucose metabolism may be of importance in modulating the brain disturbances induced by diabetes. Some studies have described that hyper- and hypoglycemic episodes can cause acute cerebral dysfunction in diabetic animals (Biessels, *et al* 1994; Cryer, *et al* 1994). In the STZ-induced mouse model of T1D, GR antagonist normalized hippocampal functions regardless the hyperglycemic state, which is not altered in diabetic mice treated with mifepristone. Therefore, it is unlikely that hyperglycemia *per se* accounts for the hippocampal disturbances observed. These findings are in agreement with a recently published report (Stranahan *et al* 2008), in which corticosterone replacement of the adrenalectomized at physiological concentrations restored hippocampal dysfunctions, while glycemia remained elevated. However, the possibility of an effect of glucocorticoid excess on hippocampal glucose metabolism in T1D can not be discarded.

Furthermore, cerebral dysfunction in type 1 diabetes can also be as a result of insulin deficiency. Although published studies describe a central role of insulin in several animal models of diabetes (Sima and Li, 2005; Inouye, *et al* 2005; Chan, *et al* 2005; McNay, *et al* 2006), a recent report revealed that hippocampal impairments are not determined by changes in insulin production (Stranahan *et al*, 2008). The authors present evidence of normalization of hippocampal dysfunction with corticosterone replacement despite

profound differences in insulin levels (elevated insulin in a type 2 diabetes animal model, the db/db mice; and insulin deficiency in STZ-rats). Nevertheless, it is likely that the negative effect of diabetes on hippocampal plasticity may be attributable to an interaction between elevated glucocorticoids and insulin receptor signaling.

In Chapter 5 is described that astrogliosis, c-Jun expression and cell proliferation are normalized after GR blockade. Astrocytic functions suggest that astrogliosis emerges as a response to a brain damage and challenges to glucose homeostasis. Therefore, in a context where excess glucocorticoids have lost their function in restoring homeostasis and have become damaging to the brain, hippocampal astrogliosis can be viewed as an index for neuronal suffering. At the same time, increased Jun-positive cells indicate emerging neuronal derangement in the hippocampus of diabetic animals. These data together with the strong reduction in cell proliferation of diabetic animals indicate that disruption of hippocampal integrity may likely lead to the observed cognitive impairments. The normalization of these disturbances after a short treatment with the GR antagonist, demonstrates that excess glucocorticoid acting through GR causes the deficits in hippocampal function.

GR interact with MR in the hippocampus and both receptors mediate in a co-ordinate manner a differential and often antagonistic action of corticosteroids (Oitzl and de Kloet, 1992; Oitzl *et al*., 1995; Joëls, 1997; de Kloet *et al*., 1998). Therefore, MR and GR operate in balance in control of homeostasis and health. As a consequence of GR blockade the effect mediated by the higher affinity MR becomes more prominent. Hence, RU486 treatment blocks the 'damaging' excessive stimulation of GR in hippocampus, sparing protective MR-mediated actions underlying the enhanced cognitive performance (Oitzl *et al*, 1998).

Taken together, a new concept in diabetes has evolved from the data presented in this thesis and from a recent paper by Stranahan *et al* (2008): In this concept glucocorticoids play a causal role in diabetes neuropathology. Moreover, we revealed that the receptors for the glucocorticoids are crucial for the mechanism that underlies the disruption of hippocampal integrity and the impairment of cognitive performance. At the same time these receptors appear an excellent target for a therapy aimed to normalize the disturbed hippocampal functions characteristic for diabetes neuropathology.

Perspectives

Functional studies on human subjects have revealed that type 1 diabetic patients have a mild to moderate slowing of mental speed and diminished mental flexibility (Brands *et al*, 2005). From these studies, it has become evident that not all cognitive domains are equally affected. Diabetic humans show accelerated decline on tasks that require episodic memory and rapid information processing, whereas attention and language abilities are unaffected (Messier *et al*, 2005). Because episodic memory mainly requires temporal lobe structures, and language and attention primarily recruit other cortical and

prefrontal regions, these data suggest that the hippocampus is particularly vulnerable to the negative consequences of diabetes.

Some reports suggest that cognitive function in unstressed conditions is hardly affected by T1D (Jacobson *et al*, 2007). However, even mild cognitive defects can impact everyday activities in more demanding situations. In a pioneering study the role of cortisol in diabetes-induced cognitive deficits was investigated in humans (Sandeep *et al*2004). The authors showed an improved cognitive performance in diabetic humans after reduced bio-availability of excess cortisol through blockade of the enzyme 11β-Hydroxy-steroid-dehydrogenease type 1 which regenerates cortisol from its bio-inactive precursor. Sandeep *et al* concluded that hypercortisolism in diabetic patients may contribute to their hippocampal dysfunction.

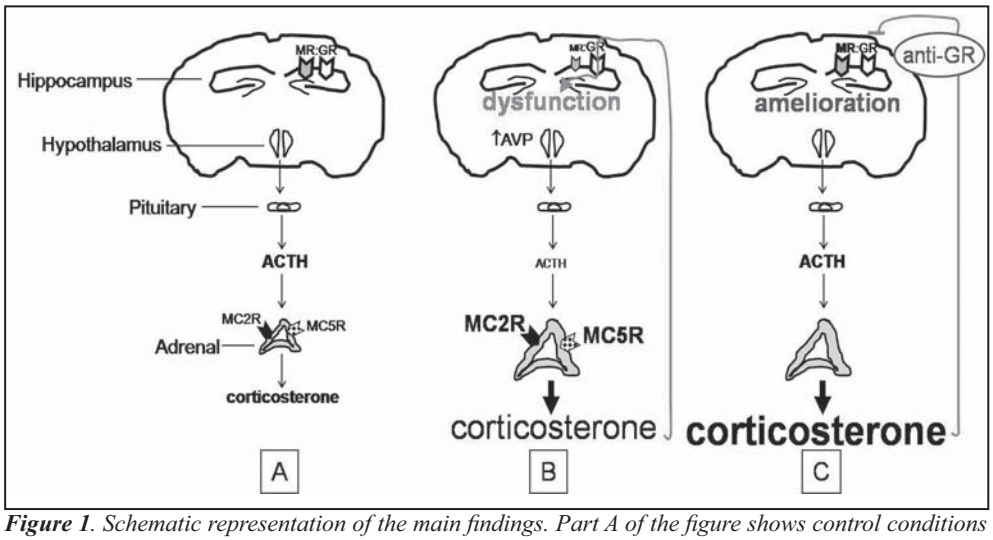


Figure 1. *Schematic representation of the main findings. Part A of the figure shows control conditions of the hippocampal-HPA axis. Part B summarizes the effects of STZ-induced diabetes: (i) hippocampal dysfunction characterized by alteration of molecular markers of hippocampal plasticity and cognitive impairments in a spatial memory task. (ii) Increased AVP mRNA expression. (iv) Significant decrease of ACTH levels. (v) Adrenal hypertrophy and increased ACTH receptors (MC2 and MC5R). (vi) Excessive corticosterone concentrations. These alterations indicate deteriorating hippocampal function leading to cognitive impairments, adrenal hypersensitivity to ACTH and HPA axis dysregulation. Part C illustrates the underlying mechanism of the hippocampal dysfunctions observed. Four days of anti-glucocorticods (mifepristone) treatment ameliorates hippocampal integrity and cognition. It is proposed that the mifepristone blockade of excessive hippocampal GR activation during diabetes restores the MR:GR balance underlying recovery from cognitive deficits. Anti-GR: anti-glucocorticods (mifepristone).*

In the current thesis two striking discoveries are described which both relate to glucocorticoids. Based on these findings we propose the following conceptual framework for the role of glucocorticoids in central pathology of type 1 diabetes (Figure 1).

First, while in NOD mice the expected pre-diabetic ACTH surge occurs, in the STZ model to our surprise the hypersecretion of glucocorticoids appears to be triggered by enhanced responsiveness of the adrenals to ACTH rather than that it depends on rising ACTH levels as primary event. In the STZ model he induction of ACTH receptors parallels the enhanced secretion of glucocortioids, while there is no rise in ACTH involved, which minimizes a role for the HPA axis as trigger. Second, we and others (Stranahan *et al*. 2008) have now clearly established that the onset and progression of cerebral damage and cognitive decline is due to the excess glucocorticoids circulating in diabetes. These signs of a damaged hippocampus function can be rapidly ameliorated with a brief anti-glucocorticoid treatment.

Since the intervention in corticosterone secretion and action now may become a treatment option it is essential to unravel the underlying mechanism of corticosterone action in the diabetic brain. One of the approaches is to study differentially regulated gene patterns in type 1 diabetes. The rationale would be that the action of circulating glucocorticoids in hippocampus is a key feature of stress as well as diabetes. However, there will be similarities and differences in genes turned on in either stress or diabetes. The differences may be related to reduced neuroprotection and increased damage-related gene expression, while in spite of the central role of glucocorticoids in diabetes also the action of insulin and glucose may be implicated; similarities will reflect overlap of structural remodeling of dendrites and suppression of neurogenesis that occur in both conditions and the fact that glucocorticoid actions are involved in both situations. To tip the protection/damage balance towards more severe impairment and degeneration in the hippocampus we will expose type 1 diabetic animals to daily stress. The outcome of these studies may lead to a conceptual framework explaining how type 1 diabetes may produce a more fragile state of the brain in which high levels of glucocorticoids enhance the potential for damage and attenuate a protective mechanism, which in concert would compromise adaptation and thus facilitate impairment of cognitive functions.

Another approach involves the evaluation of the hippocampal function in humans. It could be of interest to examine *post mortem* brains from male type 1 diabetes patients in comparison to aged match healthy individuals. Neurodegenerative markers similar to the ones used in rodents can be tested by immunocytochemistry and *in situ* hybridization. In addition, functional magnetic resonance imaging (fMRI) to measure the haemodynamic response related to neural activity in the brain, and behavioral tests to estimate cognitive performance in male patients and healthy subjects can be assessed. These results will make possible to understand better the impact of type 1 diabetes in the human brain and will allow us to proof the concept found from diabetic animals.

Conclusions

1) In a spontaneous model of type 1 diabetes, the NOD mouse, a surge in ACTH release may precede the onset of the disease. The subsequent HPA axis adaptations continue in overt diabetes with adrenal hypersensitivity leading to hypercorticism and poor shut-off of the stress response

2) In the STZ-induced diabetes mouse model hyperresponsiveness of the adrenal glands to ACTH, rather than an increase in circulating ACTH level, is the primary event leading to hypercorticism.

3) Type 1 diabetic mice show hippocampal pathology suggesting mild neurodegeneration and reactive nerve cell processes. Therefore, the hypercorticism observed in diabetic animals might enhance the vulnerability of brain areas with a high degree of plasticity such as the hippocampus.

4) Glucocorticoid excess is responsible for hippocampal disruption and cognitive impairment at the early stages of diabetes.

5) A brief treatment with GR-antagonist normalizes the markers for hippocampal dysfunction and hippocampus – related cognitive performance observed in T1D, indicating that the continuous GR activation is the likely mechanism by which glucocorticoids exert brain damage.

6) This action exerted by glucocorticoids and blocked by the GR antagonist involved blockade of GR activation, a process which makes the neuroprotective MR-mediated actions more prominent.

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