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Review

Diabetes-, stress- and ageing-related changes in synaptic plasticity in hippocampus and neocortex — The same metaplastic process?

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Abstract

Learning and memory in the brain likely occur through activity-dependent, long-lasting changes in synaptic transmission. Two opposite activity-dependent synaptic modifications have been identified so far, long-term potentiation and long-term depression. In many brain areas including hippocampal CA1 and neocortex, the level of postsynaptic depolarization controls the magnitude and sign of plasticity: long-term depression is obtained after low depolarizations, whereas long-term potentiation requires stronger ones. Synaptic plasticity also depends on prior synaptic activity. Activity-dependent modulation of subsequent induction of synaptic plasticity, termed "priming" or "metaplasticity", is due, at least in part, to concomitant opposite shifts in the levels of postsynaptic depolarization needed to elicit synaptic plasticity: in previously activated or potentiated synapses, induction of long-term potentiation requires a larger depolarization and that of long-term depression a smaller one compared with naïve synapses – i.e. potentiation is inhibited and depression promoted – and *vice versa* in depressed synapses. Many species including humans express cognitive deficits during ageing, diseases (diabetes mellitus, ...) and psychological insults (stress, ...). Interestingly, diabetic, stressed and aged rats show robust long-term depression and long-term potentiation. But, as in metaplasticity, induction of long-term potentiation requires a larger postsynaptic depolarization and that of long-term depression a smaller one compared with young control animals. Moreover, diabetes- and activity-dependent modulation of synaptic plasticity exhibit occlusion. This suggests that diabetes, stress and ageing act on synaptic plasticity through common mechanisms with metaplasticity. Such persistent inhibition of long-term potentiation and facilitation of long-term depression might lead to activity-dependent synapse weakening and contribute to cognitive impairments.

Keywords: Long-term potentiation; Long-term depression; Metaplasticity; Diabetes mellitus; Stress; Ageing

Contents

1. Introduction

Memory impairments, which occur regularly across species as a result of normal ageing, disease (diabetes mellitus, ...) and psychological insults (for example, stress), constitute a useful

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area for investigation into the neurobiological basis of learning and memory. Because synaptic plasticity is thought to support cognition, changes in synaptic plasticity or cellular alterations that directly affect its mechanisms have received much attention.

It is becoming increasingly apparent that during many experiences with cognitive deficit, for instance during diabetes mellitus (reviewed in Gispen and Biessels, 2000), stress (reviewed in McEwen, 1999; de Kloet et al., 1999; Kim and Diamond, 2002) and normal ageing (reviewed in Foster 1999, 2002; Burke and Barnes, 2006), the very mechanisms of up- or downregulation of synaptic strength are not impaired, that is, robust increase or decrease in synaptic strength can still be obtained. Rather, the levels of postsynaptic depolarization to elicit these synaptic variations are shifted. This review summarizes the diabetes-, stress- and ageing-related changes in synaptic plasticity to highlight the conclusion that they are actually the same: a facilitation of long-term depression and, conversely, an inhibition of long-term potentiation. It is proposed that these changes involve a persistent bias in activity-dependent modulation of synaptic plasticity, or metaplasticity. The mechanisms of metaplasticity might therefore represent potential targets for therapeutic agents to treat experience- – including diabetes-, stress- and ageing- – dependent cognitive disturbances.

2. Induction of use-dependent synaptic plasticity in hippocampus and neocortex

A generally accepted hypothesis in neurobiology is that, at the cellular level, memories are stored, at least in part, as long-term alterations in the strength of synaptic transmission. The discovery of long-term potentiation (Bliss and Lømo, 1973), whereby brief high-frequency stimulation of a neural pathway can induce long-lasting increases in synaptic efficacy, provided a phenomenon that incorporates most of the features expected for a form of synaptic modification appropriate for learning and memory (for review see Bliss and Collingridge, 1993; Malenka and Nicoll, 1999). In addition to being long-lasting – triggered rapidly (within seconds), it can last for hours in *in vitro* preparations and days *in vivo* – long-term potentiation is input-specific, which means that when generated at one set of synapses by repetitive activation, the increase in synaptic strength does not normally occur in other synapses on the same cell. Long-term potentiation is also associative, that is, strong activation of one set of synapses can facilitate long-term potentiation at an independent set of adjacent active synapses on the same cell if both sets of synapses are activated within a finite temporal window. Associativity has often been viewed as a cellular analog of associative or classical conditioning.

The involvement of the *N*-methyl-D-aspartic class of glutamate receptors in the induction of long-term potentiation (Collingridge et al., 1983) relies on the special properties of their channel complex, in particular the voltage-dependent block of their channel by Mg^{2+} (Nowak et al., 1984). The temporal association of presynaptic glutamate release with postsynaptic depolarization, necessary to eject Mg^{2+} from the channel, allows Ca^{2+} to enter the dendritic spine. The consequent rise in intracellular Ca^{2+} ($[Ca^{2+}]_i$) is the critical trigger for long-term potentiation (Lynch et al., 1983; Malenka et al., 1988).

Since its discovery in the hippocampus, long-term potentiation has been observed at glutamatergic excitatory synapses throughout the mammalian brain, including the cerebral cortex both *in vivo* and *in vitro* (e.g., Racine et al., 1983; Artola and Singer, 1987; Iriki et al., 1989; Artola et al., 1990; Kirkwood et al., 1993). That long-term potentiation can be most reliably generated in brain regions involved in learning and memory is often used as evidence for its functional relevance.

In theory, long-term potentiation alone cannot provide a robust synaptic model for learning (Sejnowski, 1977). Use-dependent decreases in synaptic efficacy, as well as the increases seen during long-term potentiation, are also needed and are accounted for by homosynaptic long-term depression, which has also been demonstrated in a large number of adult cortical regions, both *in vivo* and *in vitro* (e.g., Stanton and Sejnowski, 1989; Artola et al., 1990; Fujii et al., 1991; Dudek and Bear, 1992; Mulkey and Malenka, 1992; for review see Malenka and Bear, 2004). Interestingly, the induction of homosynaptic long-term depression also requires adequate postsynaptic depolarization (Artola et al., 1990; Kerr and Abraham, 1995) and appears to be triggered by a rise in $[Ca^{2+}]_i$ (Bröcher et al., 1992; Mulkey and Malenka, 1992). Here too, Ca^{2+} influx through *N*-methyl-D-aspartic receptor-gated channels might be critical for the induction of some forms of LTD (Fujii et al., 1991; Dudek and Bear, 1992; Mulkey and Malenka, 1992; for review see Malenka and Bear, 2004). Therefore, the conditions for the induction of homosynaptic long-term depression and long-term potentiation happen to be very similar. This raises the question as to which factors control the magnitude and sign of synaptic changes.

Initial results in the neocortex (Artola et al., 1990) have led to the hypothesis that the direction and the degree of the synaptic change are a function of postsynaptic depolarization. In its standard form, the hypothesis is as follows: the postsynaptic depolarization and the resulting elevation in $[Ca^{2+}]_i$ determine the magnitude and sign of the synaptic modification: long-term depression is obtained following low levels of postsynaptic depolarization and $[Ca^{2+}]_i$ whereas long-term potentiation is produced by stronger ones (Lisman, 1989; Artola and Singer, 1993) (Fig. 1). Validation of this induction rule is provided by experiments using a pairing protocol — directly depolarizing the postsynaptic cell while continuing low-frequency, low

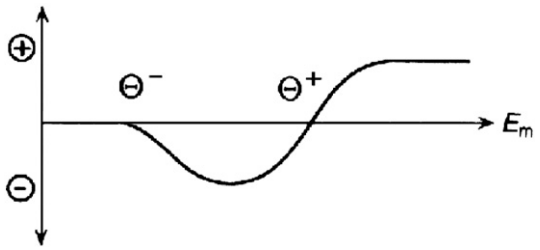

Fig. 1. The direction of the synaptic change depends on the membrane potential (E_m) of the postsynaptic cell or in more mechanistic terms, on the amplitude of the increase in $[Ca^{2+}]_i$. If the first threshold Θ^- is reached, a mechanism is activated that leads to long-term depression; if the second threshold Θ^+ is reached, another process is triggered that leads to long-term potentiation (from Artola and Singer, 1993).

intensity synaptic activation: long-term potentiation is obtained at higher, more depolarized membrane potentials (V_{ms}) than long-term depression (Ngezahayo et al., 2000; Artola et al., 2005). Similarly, the phase of synaptic input relative to ongoing theta (Huerta and Lisman, 1995; Holscher et al., 1997; Hyman et al., 2003) or gamma frequency oscillations (Wespatat et al., 2004) controls bidirectional plasticity. Synapses undergo long-term potentiation when excitatory postsynaptic potentials (EPSPs) coincide with the peaks of V_m oscillations but exhibit long-term depression when EPSPs coincide with the troughs (Hyman et al., 2003; Wespatat et al., 2004). Another factor that has demonstrated ability to control the sign of plasticity is stimulation frequency, the total number of pulses being held constant. Long-term depression is induced at low frequencies (typically: 1–5 Hz) whereas long-term potentiation needs higher frequencies (typically: 50–100 Hz) (Dudek and Bear, 1992; Kirkwood et al., 1993; Mayford et al., 1995; see also Dunwiddie and Lynch, 1978). The frequency–response curve for the induction of long-term depression-long-term potentiation is equivalent to the voltage–response curve if it is assumed that the measure of postsynaptic response relevant to synaptic plasticity (postsynaptic depolarization and, possibly, elevation in $[Ca^{2+}]_i$) is proportional to the stimulation frequency. This rule of synaptic plasticity might also be consistent with spike timing-dependent plasticity in which the timing of the back propagating action potential relative to the EPSP determines the sign and magnitude of synaptic modification: long-term potentiation is induced when the back propagating action potential occurs near the beginning of the EPSP (provided that this protocol is repeated many times), and long-term depression when it occurs in a small window (<40 ms) just before the EPSP (Markram et al., 1997; Debanne et al., 1998; Bi and Poo, 1998; Feldman, 2000, Sjöström et al., 2001). Indeed, the transient increase in $[Ca^{2+}]_i$ happens to also depend on the relative order of back propagating action potentials and EPSPs: it is larger if back propagating action potentials follow EPSPs — leading to long-term potentiation — than if they precede them — leading to long-term depression (Koester and Sakmann, 1998). However, there are many unresolved questions. Has $[Ca^{2+}]_i$ only a permissive role — some baseline $[Ca^{2+}]_i$ needs to be reached to enable biochemical processes for synaptic plasticity — or an actual instructive role — a specific $[Ca^{2+}]_i$ is necessary: low $[Ca^{2+}]_i$ induces long-term depression whereas high $[Ca^{2+}]_i$ leads to long-term potentiation — is still unclear (Perkel et al., 1993; Cummings et al., 1996; Neveu and Zucker, 1996). Does the sign of the synaptic change also depend on the duration of $[Ca^{2+}]_i$ elevation (Yang et al., 1999)? Assuming that Ca^{2+} influx through *N*-methyl-D-aspartic receptor-gated channels is the primary intracellular source of Ca^{2+}, what is the role of other sources of Ca^{2+}: influx through voltage-dependent Ca^{2+} channels, release from intracellular Ca^{2+} stores, …? Is a rise of Ca^{2+} alone sufficient to trigger long-term potentiation or are additional factors presumably provided by synapse activity required to trigger a synaptic change? These questions are beyond the scope of this review.

Anyhow, two different biochemical pathways appear to be involved in the induction of long-term potentiation and long-term depression. Activation of kinases, in particular the α-Ca^{2+}-calmodulin-dependent protein kinase II, leads to long-term potentiation whereas that of phosphatases produces long-term depression (for review see Bliss and Collingridge, 1993; Malenka and Nicoll, 1999; Malenka and Bear, 2004).

3. Diabetes mellitus and synaptic plasticity

Diabetes mellitus is characterized by hyperglycaemia due to defect in the secretion of, or resistance to insulin or both (American Diabetes Association, 2002).

Morbidity associated with diabetes results from complications that affect many organs such as eyes, kidneys, heart, blood vessels and nerves. There is now increasing evidence that both type 1 and type 2 diabetes also lead to clinically relevant end-organ damages to the brain. In addition to acute insults (e.g. stroke, hypoglycaemia; reviewed in Bell, 1994; Cryer et al., 1994), diabetes-induced metabolic and vascular disturbances produce gradually developing alterations to the brain that may present themselves by electrophysiological and structural changes and impairment of cognitive functioning (Ryan, 1988; Strachan et al., 1997; reviewed in Gispen and Biessels, 2000; Brands et al., 2004; Allen et al., 2004). Thus, mirroring the recognized benefit of near-normal glycaemic control to the retina, kidney, peripheral nerves, and cardiovascular system, close glycaemic control appears to have also subtle beneficial effects on cognitive ability. For example, patients with type 1 diabetes who have been carefully followed for an average of 18 years, do not show any evidence of substantial long-term declines in cognitive function (despite relatively high rates of recurrent severe hypoglycaemia; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, 2007). On the other hand, poor metabolic control, with subsequent development of micro- and macrovascular complications, is associated with the development of mild cognitive impairments (Ferguson et al., 2003; Ryan et al., 2003) and subtle abnormalities in brain structure (Wessels et al., 2006b) and activation (Wessels et al., 2006a).

Another important issue is the interaction between diabetes and age-related cognitive impairments. Suggested by cross-sectional studies (Strachan et al., 1997; Stewart and Liolitsa, 1999), an association between type 2 diabetes, cognitive decline (particularly in aspects of verbal memory) and dementia has been confirmed by longitudinal studies (Ott et al., 1999; Allen et al., 2004).

The effect of diabetes mellitus on learning and memory is now well documented in diverse array of animal species (Flood et al., 1990; Biessels et al., 1996; Kamal et al., 2000). Consequently, animal models of diabetes, such as streptozotocin-induced diabetic mice and rats, can be useful in understanding the underlying neural changes that mediate diabetes effects.

In the hippocampus of streptozotocin-induced diabetic rats, high-frequency stimulation produces either no or a very small potentiation, whereas low-frequency stimulation induces a larger long-term depression compared with control animals (Biessels et al., 1996; Chabot et al., 1997; Kamal et al., 1999,

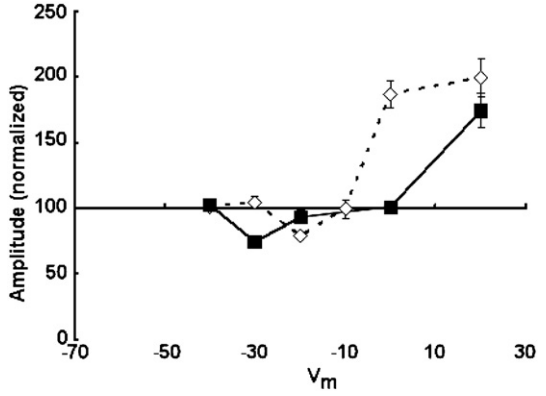

Fig. 2. Voltage–response functions for synaptic plasticity in naive synapses on CA1 neurons in diabetic (filled symbols) and control rats (open symbols). Diabetes produces a 10 mV leftward shift in the threshold for inducing long-term depression and 10 mV rightward shift in the long-term depression–long-term potentiation crossover point of the voltage–response curve for synaptic plasticity (from Artola et al., 2005).

2000). There are several possible explanations to account for the failure to induce long-term potentiation in diabetic rats. These rats may experience an alteration in the metabolic processes, subsequent to the elevation of $[Ca^{2+}]_i$, that lead to the potentiation of synaptic transmission. An alternative explanation is that the threshold for inducing long-term potentiation has changed, being shifted to the right, that is, in diabetic rats, induction of long-term potentiation requires a larger effective depolarization than in control animals. To distinguish between these two possibilities, it is necessary to depolarize the postsynaptic cell as much as needed by, for instance, using a pairing protocol (see above).

Using such a protocol, it was shown (Artola et al., 2005) that hippocampal synapses can undergo similarly robust homosynaptic long-term potentiation and long-term depression in diabetic as in control rats. But, in diabetic rats, long-term depression is obtained at more polarized and long-term potentiation at more depolarized V_{ms} compared with control rats: the long-term depression threshold is shifted 10 mV to the left and the long-term depression–long-term potentiation crossover point, concomitantly, 10 mV to the right (Fig. 2). These results thus support the hypothesis that the metabolic processes leading to long-term depression and long-term potentiation are not altered during diabetes. Rather, induction of long-term depression requires a smaller postsynaptic depolarization and that of long-term potentiation, a larger one which means that long-term depression is facilitated and long-term potentiation inhibited in diabetic rats.

4. Behavioural stress and synaptic plasticity

Stress is defined as any condition that seriously perturbs physiological and psychological homeostasis ranging from anxiety to posttraumatic stress disorder; and it has been shown to have profound effects on cognitive functions. Whereas brief periods of stress can potentiate memory formation, severe or prolonged behavioural stresses have detrimental effects on subsequent cognitive performances in many species including humans (for review see McEwen, 1999; de Kloet et al., 1999; Kim and Diamond, 2002).

The effects of behavioural stress on synaptic plasticity in hippocampus are also well documented. Acute (Foy et al., 1987; Shors et al., 1990; Xu et al., 1997; but see Mesches et al., 1999) and chronic stressors (Gerges et al., 2001, 2004; Pavlides et al., 2002; Alfarez et al., 2003; Artola et al., 2006) virtually abolish long-term potentiation in hippocampus. Concomitantly, long-term depression is facilitated (Kim et al., 1996; Xu et al., 1997; Artola et al., 2006). It is interesting to note that the effect of behavioural stress on synaptic plasticity appears to exhibit some kind of 'dose-dependency'. Whereas long-term potentiation is only reduced – i.e. the degree of potentiation is smaller in stressed- than in control animals – in rats that are exposed to either social defeat or individual housing, it is completely suppressed in rats that are exposed to both stressors (Artola et al., 2006).

There is evidence to support the view that, as diabetes mellitus, stress does not affect the metabolic processes for synapse strengthening or weakening but rather changes the thresholds — the levels of effective postsynaptic depolarization that are required for inducing long-term depression and long-term potentiation. First, exposure to a predator blocks primed burst potentiation, a low threshold form of plasticity, but not high-frequency stimulation-induced long-term potentiation (Mesches et al., 1999). Second, long-term potentiation can be demonstrated in stressed animals if synapses have been previously depressed (Kim et al., 1996); prior induction of long-term depression is known to lower the threshold for induction of long-term potentiation (see below). Finally, in stressed rats, CA1 synapses that do not undergo long-term potentiation following high-frequency stimulation at test intensity, can nevertheless be potentiated provided that stimulus intensity – and thus effective postsynaptic depolarization – during high-frequency stimulation is increased (Artola et al., 2006). Thus, during stress, long-term potentiation can still be elicited but it requires a higher effective postsynaptic depolarization. Together with the evidence that stress concurrently facilitates the induction of long-term depression (Kim et al., 1996; Xu et al., 1997; Artola et al., 2006), these results support the hypothesis that, during stress, the levels of postsynaptic depolarization for inducing long-term depression and long-term potentiation are concomitantly shifted in opposite directions, to the left and to the right, respectively (Coussens et al., 1997; Artola et al., 2006). It is noteworthy that Kim and Yoon (1998) proposed a model where only the long-term depression–long-term potentiation crossover point is shifted to the right.

5. Normal ageing and synaptic plasticity

Normal ageing is another example of a decline in cognitive functions associated with changes in neural plasticity or cellular alterations that directly affect mechanisms of plasticity. Age-associated changes in synaptic plasticity in the hippocampus and neocortex have recently been summarized (e.g. Foster 1999, 2002; Burke and Barnes, 2006).

Age-dependent changes in synaptic plasticity in the hippocampus and neocortex are consistent with the hypothesis that there is a shift towards higher, more depolarized V_{ms} of the

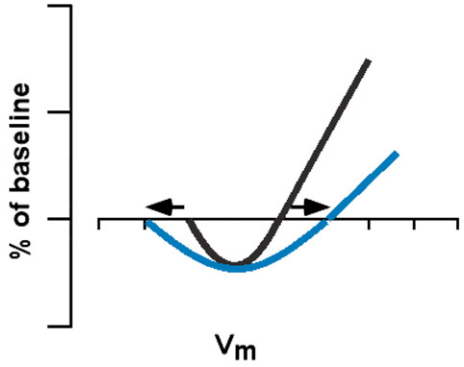

Fig. 3. Schematic representation of diabetes-, stress- and ageing-dependent changes in the voltage–response function for synaptic plasticity.

level of postsynaptic depolarization to elicit long-term potentiation. Aged animals show intact long-term potentiation induction (Barnes, 1979; Landfield and Lynch, 1977; Landfield et al., 1978; Diana et al., 1994a,b; Dieguez and Barea-Rodriguez, 2004) when robust high-frequency, high current amplitude stimulation protocols are used. On the other hand, deficits in the induction of long-term potentiation are observed when using weak stimulation parameters. That induction of long-term potentiation requires a larger level of postsynaptic depolarization in aged compared with young rats can show itself directly in an increase in the threshold for potentiation (Barnes et al., 2000; but see Barnes et al., 1996) or, indirectly, in a reduced magnitude of potentiation following a given (weak) stimulation protocol (Rosenzweig et al., 1997; Tombaugh et al., 2002; Deupree et al., 1991; Moore et al., 1993). Conversely, aged rats are more susceptible than are young rats to long-term depression and to the reversal of long-term potentiation (Norris et al., 1996; Foster and Norris, 1997).

Overall, results obtained in rats indicate that diabetes-, stress- and ageing-related changes in synaptic plasticity are similar. The mechanisms of up- and downregulation of synaptic strength are not impaired — diabetic, stressed and aged rats can show intact long-term depression and long-term potentiation induction. But, in the three groups, induction of long-term potentiation requires larger levels of postsynaptic depolarization and that of long-term depression lower ones compared with young control rats (Fig. 3).

6. Activity-dependent modulation of synaptic plasticity or metaplasticity

There is growing evidence that the induction of synaptic plasticity also depends on prior synaptic activity. Activity-dependent modulation of subsequent synaptic plasticity is usually referred to as priming or metaplasticity (Abraham and Bear, 1996; Abraham and Tate, 1997).

The phenomenology of metaplasticity is now characterized: it involves concomitant shifts in opposite directions in the levels of postsynaptic depolarization required for inducing subsequent long-term depression and long-term potentiation (Ngezahayo et al., 2000). Strong synaptic activation, whether it induces long-term potentiation or no overt long-term change in synaptic efficacy, can decrease the threshold for the induction of subsequent long-term depression and, simultaneously, elevate that for long-term potentiation (Barrionuevo et al., 1980; Coan et al., 1989; Stäubli and Lynch, 1987; Fujii et al., 1991, 1996; Christie and Abraham, 1992; Huang et al., 1992; Wexler and Stanton, 1993; Larson et al., 1993; Bortolotto et al., 1994; O'Dell and Kandel, 1994; Christie et al., 1995; Wagner and Alger, 1995; Wang et al., 1998; Holland and Wagner, 1998; Ngezahayo et al., 2000; Mockett et al., 2002). Conversely, prior synaptic stimulation sufficient to induce long-term depression lowers the threshold for the induction of subsequent long-term potentiation and, concomitantly, raises that for long-term depression (Ngezahayo et al., 2000). There is thus a continuum of voltage–response functions for the induction of long-term depression and long-term potentiation determined by prior synaptic activity. The threshold for long-term depression induction, Θ^-, is progressively shifted toward more polarized V_{ms} whereas, the long-term depression–long-term potentiation crossover point, Θ^+, is shifted toward more depolarized V_{ms} opening the voltage window for long-term depression induction, as initial synaptic strength increases and, *vice versa*, as it decreases (Fig. 4).

Bienenstock et al. (1982) designed a model of experience-dependent synaptic plasticity to account for the development of visual cortex. This model predicts that the value of the long-term depression–long-term potentiation crossover point (θ_m, equivalent to Θ^+), increases after a period of increased activity — promoting synaptic depression and inhibiting synaptic potentiation — and decreases after a period of decreased activity — facilitating synaptic potentiation and inhibiting synaptic depression. Experimental evidence thus confirms this very feature of this theory. However, concomitant opposite shifts in a second threshold, Θ^-, need to be considered to fully account for the phenomenology of metaplasticity.

Diabetes-, stress and ageing-related changes, on the one hand, and activity-induced modulation, on the other hand, of synaptic plasticity thus exhibit the very same phenomenology.

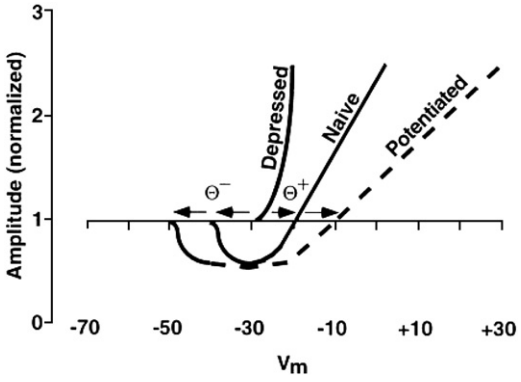

Fig. 4. The voltage–response function for the induction of long-term depression and long-term potentiation varies with prior synaptic activity. Superimposed voltage–response functions for the induction of long-term depression and long-term potentiation in depressed, naive, and potentiated synapses on CA1 neurons in adult mice. The part of the curve in potentiated synapses with stripped lines is putative. From depressed to potentiated synapses, Θ^- and Θ^+ slide away from each other (arrows), progressively opening the voltage window for inducing long-term depression (from Ngezahayo et al., 2000).

Moreover, both stress- (Kim et al., 1996) and activity-induced (Huang et al., 1992; Fujii et al., 1996; Abraham and Huggett, 1997; Mockett et al., 2002; but see Wexler and Stanton, 1993) facilitation of long-term depression and inhibition of long-term potentiation require the activation of *N*-methyl-D-aspartic receptors. Finally, prior induction of long-term potentiation produces a 10 mV leftward shift in V_{ms} for inducing long-term depression in control but not in diabetic rats, suggesting that the facilitation of long-term depression during diabetes occludes that produced by synaptic activity (Artola et al., 2005). These results are consistent with the hypothesis that diabetes-, stress- and ageing-related changes in synaptic plasticity and metaplasticity share similar expression mechanisms.

Overall, the above reviewed results suggest that during diabetes mellitus, behavioural stress and normal ageing, there is a bias of metaplasticity toward a facilitation of long-term depression and, concomitantly, an inhibition of long-term potentiation. It is important to note, however, that whereas both activity-dependent facilitation of long-term depression (Fujii et al., 1991; Christie and Abraham, 1992; Holland and Wagner, 1998; Wang et al., 1998) and inhibition of long-term potentiation (Huang et al., 1992; Frey et al., 1995; Abraham and Huggett, 1997) are reversible within a few hours, diabetes-, some stress- (see Artola et al., 2006) and ageing-related changes in the induction of long-term depression and long-term potentiation appear to be irreversible.

7. Which mechanisms can underlie the concomitant facilitation of long-term depression and inhibition of long-term potentiation?

The mechanisms underlying metaplasticity remain to be fully characterized. However, the phenomenology of metaplasticity put some major constraints on the possible mechanisms. First, they must account for the phenomenology: the level of postsynaptic depolarization to elicit long-term potentiation and long-term depression are sifted in opposite directions. For instance, transient activation of protein kinase C (PKC) with phorbol-ester enhances long-term depression and suppresses long-term potentiation (Stanton, 1995; Wang et al., 1998). But, PKC activation has also been shown to facilitate the persistence of long-term potentiation of population spike (Blank et al., 2002).

A second constraint for possible mechanisms arises from the evidence that the same opposite shifts in the levels of postsynaptic depolarization for eliciting long-term potentiation and long-term depression are observed following very different experiences. Indeed, diabetic, stressed and aged rats exhibit various patterns of both degenerative changes and functional sparings. But the three patterns must include the putative mechanism(s) for opposite shifts. It is possible that diabetes- and age-related changes in Ca^{2+} regulation cause some of the observed diabetes- and age-related changes in synaptic plasticity. The post-burst afterhyperpolarization is enhanced in hippocampal neurons from diabetic (Kamal et al., 2003) and aged animals (Landfield and Pitler, 1984; Moyer et al., 1992; Power et al., 2002), likely through enhanced sI_{AHP} (Power et al., 2002; Kamal et al., 2003), a Ca^{2+}-dependent K^+ current. The amplitude of this K^+ current depends on the amount of Ca^{2+} available to cause channel activation. It has been hypothesized that the age-related enhancement of the afterhyperpolarization is secondary to an enhanced Ca^{2+} influx (Pitler and Landfield, 1990), particularly that through L-type voltage-dependent Ca^{2+} channels (Campbell et al., 1996; Thibault and Landfield, 1996; Chen et al., 2000). There is an age-related increase in the number of L-type voltage-dependent Ca^{2+} channels (Thibault and Landfield, 1996). And blockade of L-type voltage-dependent Ca^{2+} channels (Power et al., 2002) as well as inhibition Ca^{2+} release from intracellular stores (Kumar and Foster, 2004) cause quantitatively greater reductions in the sI_{AHP} in aging than in young neuron. Reducing the amplitude of the afterhyperpolarization through blockade of K^+ channels facilitates the induction of long-term potentiation (Sah and Bekkers, 1996; Behnisch and Reymann, 1998; Norris et al., 1998; Cohen et al., 1999). Interestingly, reducing the afterhyperpolarization by blocking either ryanodine receptors (Kumar and Foster, 2004) or L-type voltage-dependent Ca^{2+} channels (Norris et al., 1998), that is, paradoxically by reducing $[Ca^{2+}]_i$, also facilitates the induction of long-term potentiation in aged animals. It is assumed that, in aged rats, the increase in $[Ca^{2+}]_i$ due to Ca^{2+} influx through L-type channels and Ca^{2+} release from intracellular stores is overcome by the larger afterhyperpolarization which decreases *N*-methyl-D-aspartic receptor-gated currents (see Foster, 2007). However, enhanced afterhyperpolarization alone cannot account for age-related changes in synaptic plasticity since reduced afterhyperpolarization also facilitates low-frequency stimulation-induced long-term depression (Stackman et al., 2002).

Altered *N*-methyl-D-aspartic receptor function is another obvious possible mechanism for regulating Ca^{2+} influx and synaptic plasticity thresholds. *N*-methyl-D-aspartic receptor-dependent EPSPs are decreased after 3–4 months diabetes due to a reduction in *N*-methyl-D-aspartic receptors that contain the NR-2B subunit (Di Luca et al., 1999; Gardoni et al., 2002; but see Chabot et al., 1997). And, though this is still an actively debated topic, it is possible that *N*-methyl-D-aspartic receptors also decrease in the hippocampus with age (for review see Foster, 2007). Overexpression of the NR-2B subunit is associated with a facilitation of the induction of long-term potentiation (Tang et al., 1999). However, selectively blocking these receptors abolishes the induction of long-term depression but not that of long-term potentiation (Liu et al., 2004).

Another possibility is related to corticosteroïds. Corticosterone (in rodents) and cortisol (in humans) bind to mineralocorticoid and glucocorticoid receptors with a ten fold difference in affinity. During "normal" physiological conditions, when lower corticosterone concentrations occur within the hippocampus, high affinity mineralocorticoid receptors are preferably activated. On the other hand, with higher concentrations of corticosterone during stress (for review see Kim and Yoon, 1998; de Kloet et al., 1999) or ageing (for review see Patel and Finch, 2002), both mineralocorticoid and glucocorticoid receptors will be activated. Long-term potentiation is hard to obtain while long-term depression is robust in the presence of high corticosteroid concentration or of a selective glucocorticoid receptor agonist (Diamond et al., 1992; Pavlides et al., 1995,

1996; Coussens et al., 1997). And a glucocorticoid receptor antagonist prevents the occurrence of long-term depression (Xu et al., 1998). Three weeks after social defeat, binding to mineralocorticoid receptors is strongly reduced while that to glucocorticoid receptors remains unaffected (Buwalda et al., 1999, 2001). Such a bias toward glucocorticoid receptors might underlie the inhibition of long-term potentiation and facilitation of long-term depression.

8. Concluding remarks

Diabetic, stressed and aged rats experience cognitive impairments. Much attention has been focused on the mechanisms that underlie up- and downregulation of synaptic strength. It is now clear, however, that in diabetic, stressed and aged rats, the very mechanisms of up- or downregulation of synaptic strength are not impaired. Rather, long-term depression is facilitated and, concomitantly, long-term potentiation inhibited. It is possible that a persistent bias in activity-dependent modulation of synaptic plasticity, or metaplasticity, accounts for these changes in the susceptibility to synaptic plasticity and thus, through activity-dependent synapse weakening, contributes to cognitive impairments.

These results suggest that the mechanisms of metaplasticity might be potential targets to treat cognitive impairments. Unfortunately, these mechanisms are still poorly understood. Likely possibilities must account for the very characteristic phenomenology – shifts in the level of postsynaptic depolarization for eliciting long-term depression and long-term potentiation in opposite directions – and the various experiences leading to such shifts.

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