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Experience-dependent changes in vibrissae evoked responses in the rodent barrel cortex

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Abstract. A change in vibrissae complement in rodents leads to long-term changes in vibrissae dominance. These changes involve both potentiation of spared vibrissae responses and suppression of deprived vibrissae responses in adolescent animals. In adult animals only potentiation of spared vibrissae responses was detected. Suppression exhibits hetero- and homosynaptic components and appears to be cortical in origin, as is potentiation. The time course for potentiation and suppression in the barrel cortex of adolescent rats is different, with suppression preceeding potentiation by at least one week. There seems to be no critical period for potentiation in superficial layers of barrel cortex, but there is a critical period for suppression. Suppression cannot be evoked if plasticity is induced later than at 6 months of age nor maintained if experimental manipulations begin later than at three months. The molecular mechanisms that underlie plastic changes in the barrel cortex still remain unclear, although α-CamKII and to lesser extend α/β-CREB appear to be involved.

Mini-review

Key words: barrel cortex, plasticity, single unit recording

INTRODUCTION

The barrel cortex is a part of the somatosensory cortex of rodents, forming a somatotopic representation of the contralateral vibrissa pad. Rows of whiskers on the muzzle are represented in layer IV of the barrel cortex in the form of rows of barrels, i.e. aggregates of cell bodies and thalamo-cortical afferents, which can be visualized using simple histochemical staining techniques (Woolsey and Van der Loos 1970). Each barrel corresponds to the single whisker on the contralateral muzzle pad. The barrel is the central element of the barrel column, being the primary recipient area for thalamic input to the barrel cortex. Responses recorded from single cells in the barrel column are usually dominated by the barrels principal whisker, i.e. the one to which is somatotopicaly related. However, a substantial responses evoked by immediately adjacent vibrissae also usually are present (Fig. 1; for details see: Armstrong-James and Fox 1987).

The ventroposterior medial nucleus (VPM) of the dorsal thalamus is the major subcortical source of input to the barrels, while the posterior group (PO) of thalamic nuclei is a major subcortical source of input to the matrix in between barrel columns (Armstrong-James and Fox 1987, Koralek et al. 1988, Chmielowska et al. 1989). An extensive network of intracortical pathways have been described in the barrel cortex. Vertical connections link layer IV with supra- and infragranular layers (Lorente de No 1947). Additionally, layers II/III and V are reciprocally linked (Bernardo et al. 1990). Layers II/III and V have widespread horizontal connections, which extend to, at least adjacent cortical columns (Bernardo et al. 1990, Hoeflinger et al. 1995, Gottlieb and Keller 1997, see also Aroniadou-Anderjaska and Keller 1996).The wave of intracortical excitation caused by deflecting a single vibrissa begins in layer IV and proceeds successively to layer III then II, before it spreads horizontally to adjacent barrels columns (Armstrong-James et al. 1992).

The neurones of the barrel cortex of rodents are plastic, i.e. they have ability to change their receptive field properties due to the manipulation on the periphery. These changes can be visualised (Kossut et al. 1988) and measured (Glazewski and Fox 1996) as changes in vibrissae dominance. Additionally, due to vibrissae denervation,the pattern of the barrels can be changed (Van der Loos and Woolsey 1973). Therefore, two general forms of plastic changes in this system are discernible (Kossut 1992). First, structural plasticity, which can be

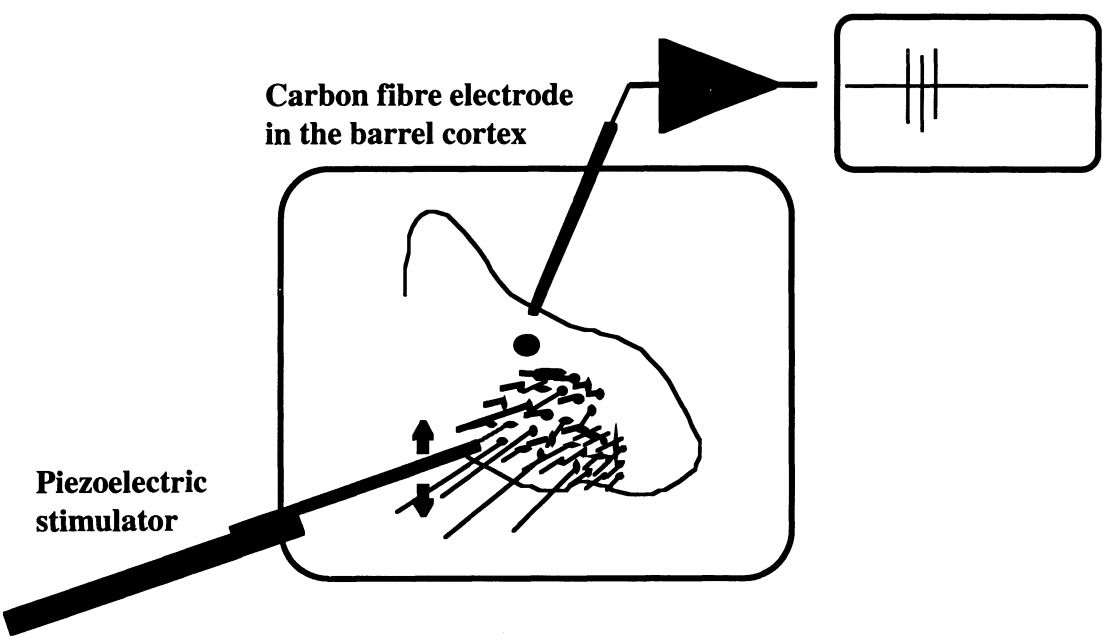

Fig. 1. Schematic of recording configuration. Vibrissae were stimulated using a computer-controlled piezoelectric stimulator (50 stimuli at 1Hz were applied per every cell recorded and whisker tried). Recording was done using glass-insulated carbon fibre microelectrodes. Two parameters of response were measured: the averaged magnitude (number of spikes per stimulus) and the modal latency. The average magnitude of response to stimulation of D1, principal and surround whiskers were calculated for every animal and averaged again for group of animals tested (for details see: Armstrong-James and Fox, 1987).

evoked only very early in development (Woolsey and Van der Loos 1973, Woolsey and Wann 1976) and only by damage to the whiskers follicles, which leads to a deformation in the barrel pattern, followed by changes in vibrissae dominance. Second, functional plasticity, inducible either by damage to whisker follicles, deprivation of activity at all stages of development or sensory conditioning and leading to changes in receptive field properties (Kossut 1992, Siucińska and Kossut 1996).

The feature common to methods which induce plasticity without follicle damage is that they create an imbalance in the degree of activation between vibrissae. Such an imbalance can be created by removing , trimming and overstimulating some of the vibrissae, while leaving others intact for some period of time or sensory conditioning (Simons and Land 1987, Kossut and Hand 1984, Fox 1992, Welker et al. 1992, Armstrong-James et al. 1994, Li et al., 1995, Glazewski and Fox 1996, Siucinska and Kossut 1996, Musial et al. 1998, Melzer and Smith 1998). As a consequence, the representation of intact or overstimulated whiskers expands considerably into the territory of the immediately adjacent de-

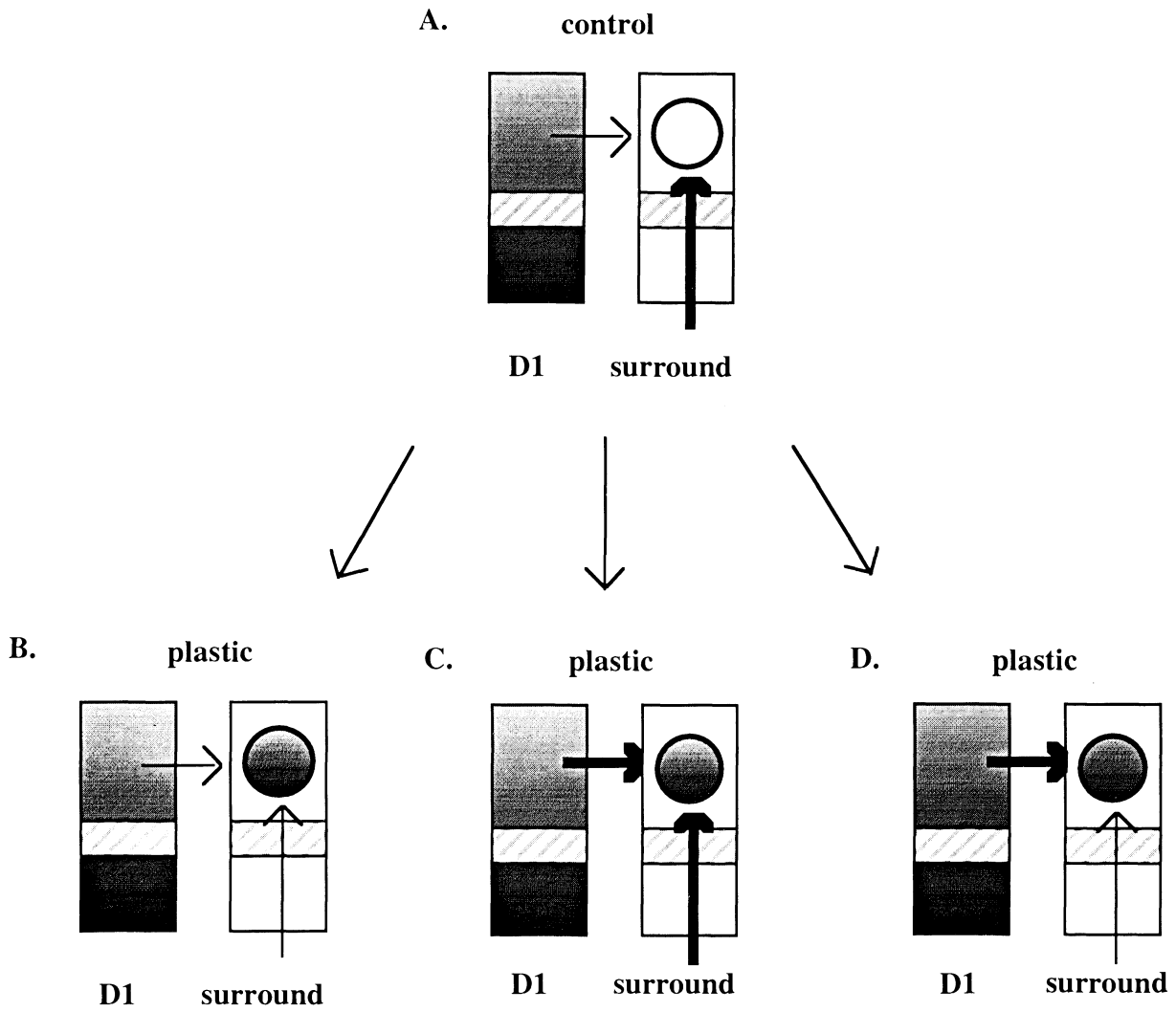

Fig. 2. Three ways to change vibrissae dominance. Vibrissae dominance of neurones in the deprived whisker representations immediately adjacent to the spared D1 representation can change due to suppression of the deprived vibrissa input (B), potentiation of the D1 vibrissa input (C) or both: suppression of the deprived and potentiation of the D1 vibrissae input (D). In the control case neurons have tendency to be dominated by the principal vibrissa input (A). D1, the D1 vibrissa barrel column; surround, the barrel column immediately adjacent to the D1 barrel column; thick arrows indicate strong inputs and thin arrows weak inputs; rings symbolize the areas of supragranular cortex were plastic changes take place; horizontal hatched band indicates the barrel.

prived whiskers representations (or intact whiskers representation in the case of the overstimulation paradigm). This expansion results from a change in vibrissae dominance. Vibrissae dominance, in turn, depends on a change in the balance of activity in two of the inputs to a neurone showing plasticity, i.e. the spared input (or overstimulated input) and the deprived input (or intact input). Thus, plasticity can be split into two components which can be studied in isolation, i.e. potentiation of the spared vibrissa input and, where it occurs (see later) suppression of the deprived vibrissa input (Fig.2, see also Glazewski and Fox 1996).

There seems to be no critical period for activity-dependent plasticity for neurones in layers II/III (Fox 1992, Glazewski et al. 1996). The degree of plasticity is greater early in development than later in life (Fox 1992; where the operational definition of plasticity is presented). Plasticity within layer IV decreases rapidly between postnatal day 0 and postnatal day 4 at least in the D1 spared (compare the detailed description below) vibrissa preparation (Fox 1992, Glazewski et al. 1998a, but see Kossut 1992). The end of the critical period for functional plasticity in this layer coincides with the end of the critical period for structural plasticity (Woolsey and Wann 1976), maturation of layer IV (Schlaggar and OLeary 1994), the end of malleability of thalamo-cortical connections to undergo long-term potentiation (Crair and Malenka 1995). This leads to the conclusion that during early development of barrel cortex and even later, up to the fourth week of age (Kossut and Hand 1984, Glazewski et al. 1992, Skangiel-Kramska et al. 1992, Kossut et al. 1993, Glazewski et al. 1995, Micheva and Beaulieu 1995, Micheva and Beaulieu 1996, De Felipe 1997) processes related to maturation of the barrel cortex interfere with the susceptibility of layer IV neurones to undergo plastic changes. Plastic changes in supragranular portion of the barrel cortex are observable up until, at least 1.5 years of age in mice (Glazewski et al. 1996). Neurones of infragranular barrel cortex have large receptive fields. This makes quantification of plastic changes difficult, what was a reason to exclude infragranular layers from the study.

One of the methods of evoking substantial plasticity in the barrel cortex is by univibrissae rearing, where all whiskers, but D1 are removed out for some time by steady tension applied to the base of the vibrissa (Kossut and Hand 1984, Fox 1992). Here, we review some recent progress made in understanding the origin, development, composition and molecular mechanisms of plasticity evoked by univibrissae rearing in supragranular layers of the barrel cortex of the mature rodents.

METHODOLOGICAL CONSIDERATIONS

Studies on the mechanisms of induction and maintenance of activity-dependent plastic changes in the brain are often considered to be model studies with the general aim of understanding mechanisms of learning and memory. It is commonly assumed, that mechanisms of learning and memory are somehow associated with long-term changes in synaptic strength. These, leading to increase in synaptic efficacy (synaptic potentiation) and these causing suppression (synaptic suppression). Such changes can be induced in several model systems (Wiesel and Hubel 1965, Bliss and Lømo 1973, Artola et al. 1990, Hess et al. 1996) including barrel cortex of rodents (Glazewski and Fox 1996). Learning is by definition experience-dependent, so the type of plasticity studied in relation to learning also has to be experience-dependent. Because whisker plucking is a method employed to evoke plasticity, it was necessary to test that this method indeed introduces only an activity imbalance into the system and does not cause changes to the state of the vibrissae follicles , peripheral receptors or primary afferents. A series of adequate experiments were performed. There was no change found either in the number of myelinated and unmyelinated axons innervating deprived vibrissae follicles, nor morphology of those axons organelles and myelinization (Li et al. 1995). On the other hand such changes were induced by axotomy or cauterization of vibrissal follicles (Li et al. 1995). Moreover, upregulation of neuropeptide Y and galanin, well-known sensors of damage to neurones (White et al. 1994) was not observed in trigeminal ganglion cells deprived of input by plucking, but again, was observed following axotomy and cauterization of vibrissal follicles (Li et al. 1995). Additionally, responsiveness of trigeminal ganglion neurones in animals deprived for 7 days by plucking out all the whiskers was found not to be changed in comparison with control, unplucked animals (Glazewski et al. 1998a). Changes in responsiveness would be expected if plucking really induces some damage to peripheral receptors or axons. Finally, responses recorded in barrel cortex to stimulation of regrown vibrissae of animals in which all but the D1 whisker were plucked for 7 days were indistinguishable from those re-

corded from animals in which all but the D1 whisker were trimmed flush with the skin for a week (Li et al. 1995). Trimming obviously cannot evoke any damage to axons or peripheral receptors. In conclusion, plasticity induced in the barrel cortex by plucking, seems to be purely activity or experience dependent.

Barrel cortex reaches early maturity at the age of one month. This thesis is based on anatomical, histochemical and electrophysiological studies. First, the number of symmetric and asymmetric synapses and the total number of neurones are at adult levels around the age of one month (Micheva and Beaulieu 1995, Micheva and Beaulieu 1996, De Felipe 1997). Second, studies on the development of binding sites for major neurotransmitter receptors in the barrel cortex show a similar tendency. Binding sites for glutamate, (+)-5-methyl-10,11-dihydrodibenzo[a,d]cyclohepten-5,10-imine (MK801), quisqualate, muscimol, iodocyanopindolol, and quinuclidinyl benzilate (QNB) all were found to be at adult levels at the age of one month (Glazewski et al. 1992, Skangiel-Kramska 1992, Kossut et al. 1993, Blue and Johnston 1995, Glazewski et al. 1995). Finally, the magnitude of cortical neuron responses to whisker stimulation at this age is comparable to the magnitude of response obtained by recording from animals a few months older (Glazewski and Fox 1996). For all of aforementioned reasons, effects of whisker deprivation beginning at one month of age are generally not confounded by processes of development of the barrel cortex. However, it is important to note that there may be some developmental changes in animals older than one month (see below).

POTENTIATION OF SPARED VIBRISSA RESPONSES

Until recently, it has not been known precisely either how activity-dependent plasticity develops in the barrel cortex (see however Kossut 1992) nor how its components, potentiation of spared vibrissa responses and suppression of deprived vibrissae responses develop. Indeed, even studies on ocular dominance plasticity have not come up with exhaustive information on development of this phenomenon (but see, Mioche and Singer 1989, Crair et al. 1997). Potentiation of spared vibrissa responses has been studied in the supragranular layers of the D1 spared vibrissa preparation starting with adolescence or adulthood (Glazewski and Fox 1996, Glazewski et al. 1996). Vi-

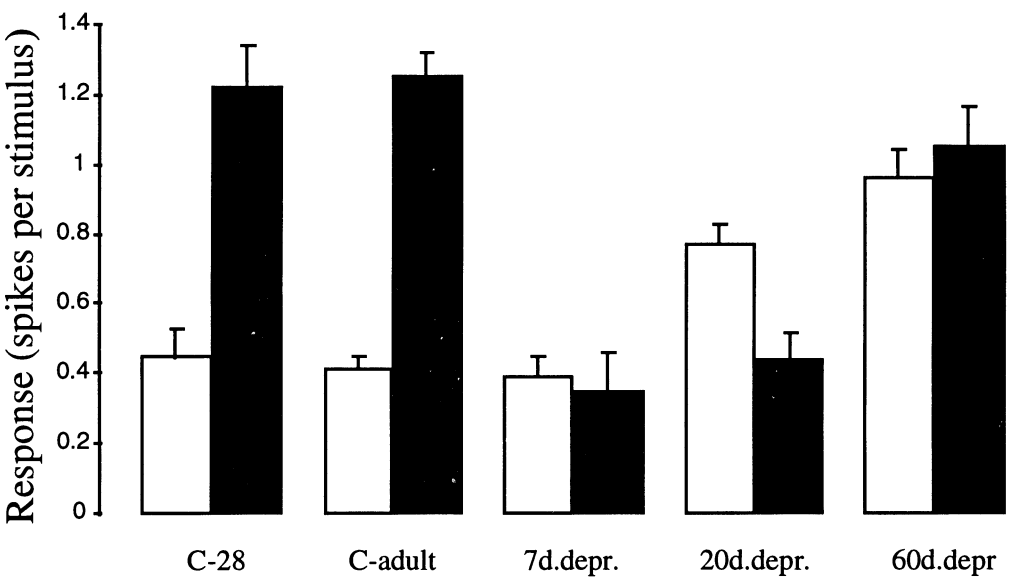

Fig. 3. The effect of deprivation on the responses of supragranular neurons to the D1 and principal vibrissae stimulation. Responsivity of neurones in the barrel cortex to stimulation of the principal vibrissae is age independent for animals older than one month. Suppression of deprived input preceedes potentiation of the spared input in adolescent animals. Maintenance of the suppression is age or deprivation length dependent. C-28, control at the age of 28 days; C-adult, adult control; 7d.depr., animals deprived of all, but D1 vibrissa for 7 days; 20d.depr., animals deprived of all, but D1 vibrissa for 20 days; 60d.depr., animals deprived of all, but D1 vibrissa for 60 days; empty bars indicate the D1 vibrissa evoked responses and the black bars indicate principal vibrissae evoked responses.

brissae were stimulated using a computer-controlled piezoelectric stimulator (50 stimuli at 1Hz were applied per every cell recorded and whisker tried). Recording was done using glass-insulated carbon fibre microelectrodes. Two parameters of response were measured: the averaged magnitude (number of spikes per stimulus) and the modal latency. The average magnitude of response, recorded in barrel column immediately adjacent to D1 barrel column, to stimulation of principal (central receptive field), D1 (D1 surround receptive field) and surround whiskers (surround receptive field) were calculated for every animal and averaged again for group of animals tested (Fig. 1; for details see: Armstrong-James and Fox 1987). It was found that potentiation in supragranular layers, at least if calculated independently of distance from the D1 barrel column (i.e. calculated by averaging responses of neurones in all penetrations made in barrel columns immediately adjacent to D1 barrel column; see also next chapter), does not develop immediately after imbalance of activity was introduced and in adolescence is preceeded by suppression of the deprived input (Fig.3). Potentiation was not observed after one week of deprivation, but was already substantial after three weeks of deprivation (Glazewski and Fox 1996, Glazewski et al. 1996). Moreover, there are probably mechanisms in neurones (see also next chapter) which prevent excessive potentiation, as after 60 days of deprivation potentiation was not much higher that after 20 days of deprivation (Fig.3). On the other hand, because the longest deprivation period used up to this time is 60 days, we cannot be certain of the effects of longer deprivation periods.

Supragranular layers of the barrel cortex differ from layer IV in developmentaly regulated susceptibility to undergo plastic changes evoked by univibrissa rearing. There is no critical period for potentiation in supragranular layers in the D1 spared vibrissa preparation, but in layer IV of the same preparation, potentiation cannot be evoked if deprivation starts on or later than postnatal day 7 (Fox 1992, Glazewski et al. 1996, see however Glazewski et al. 1998a and below).

SUPPRESSION OF DEPRIVED VIBRISSAE RESPONSES

There is a critical period for suppression in the univibrissa reared preparation. Suppression of deprived vibrissae responses can be induced by univibrissa rearing exclusively in relatively young animals (i.e. not older than 6 months of age; see Fig.3) and only in supragranular cortical layers (Fox et al. 1996, Glazewski and Fox 1996, Glazewski et al. 1996, Glazewski et al. 1998a). In adult animals, suppression has not been observed at all (Fig.5; see also Glazewski et al. 1996). Additionally, the time course of suppression is different from that of potentiation. In adolescent animals substantial suppression was observed as early as after one week of deprivation, preceeding potentiation of the spared vibrissae input by at least one week (Fig.3, see also Glazewski and Fox 1996, Glazewski et al. 1996). This suggests that either mechanisms of potentiation and suppression are independent or suppression is, for some reason, a prerequisite for potentiation in adolescence but not in adulthood. If the later is true, it means that neurones in young barrel cortex simply conserve total synaptic weights, but in adult they do not. If a neurone keeps the sum of all synaptic weights constant (conserves it), particular inputs can be potentiated only if other inputs get depressed. Such behaviour has been proposed for many years by theorists (see Miller 1996) as one of the mechanisms for avoiding instability, i.e. in this case, potentiation that grows without limit. The rule of conservation of total synaptic weight might not then operate in adult barrel cortex because potentiation is possible even in the absence of suppression. Thus, it is possible that adult neurones set a limit for potentiation in a different way than do young neurones. It can be done, for instance, by conserving an average pre- or postsynaptic responsivity (Miller 1996). One idea is eliminated from the discussion, it is that there is no limit for potentiation (Fig. 3).

As can be seen in Fig.3, suppression of principal vibrissa responses is much smaller after 60 than following 7 and 20 days of deprivation. This effect may be age dependent or could be related to the length of deprivation, and thus requires a direct experimental test. However, because the ability to induce suppression is regulated by age, the first explanation, i.e. by age dependency is favoured. It seems to be likely that both: induction and maintenance of suppression of the deprived principal vibrissae responses are regulated by age.

COMPONENTS OF SUPPRESSION

The degree of suppression of deprived principal vibrissae input is not equal across supragranular portions of barrel columns deprived of input. It was found that suppression is greater for cells recorded close to the spared vibrissa representation (active barrel column;

Glazewski and Fox 1996). This suggests the involvement of the active barrel in the mechanisms suppressing the deprived input, which means that suppression is, at least in part, heterosynaptic in origin. To study this possibility further, the heterosynaptic influence was increased by rearing animals for 7 days with just one whisker taken out. In parallel, animals were reared for 7 days with all their whiskers removed. In this second experiment the result was, that the principal input was suppressed, but this effect was statistically significant only in supragranular layers (Fig.4, see also Glazewski et al. 1998a). This indicates that homosynaptic suppression mechanisms operate in the barrel cortex. Nevertheless suppression was even greater in animals in which only the D1 vibrissa was removed. In this case suppression was found even in layer IV (Fig. 4). This last discovery means that the critical period for plastic changes is regulated not only by age, but also depends on the paradigm used to induce plasticity. In conclusion, two mechanisms of suppression operate in the barrel cortex of young rodents. The first, homosynaptic in nature can be observed only in supragranular layers. The second, heterosynaptic is detectable even in layer IV.

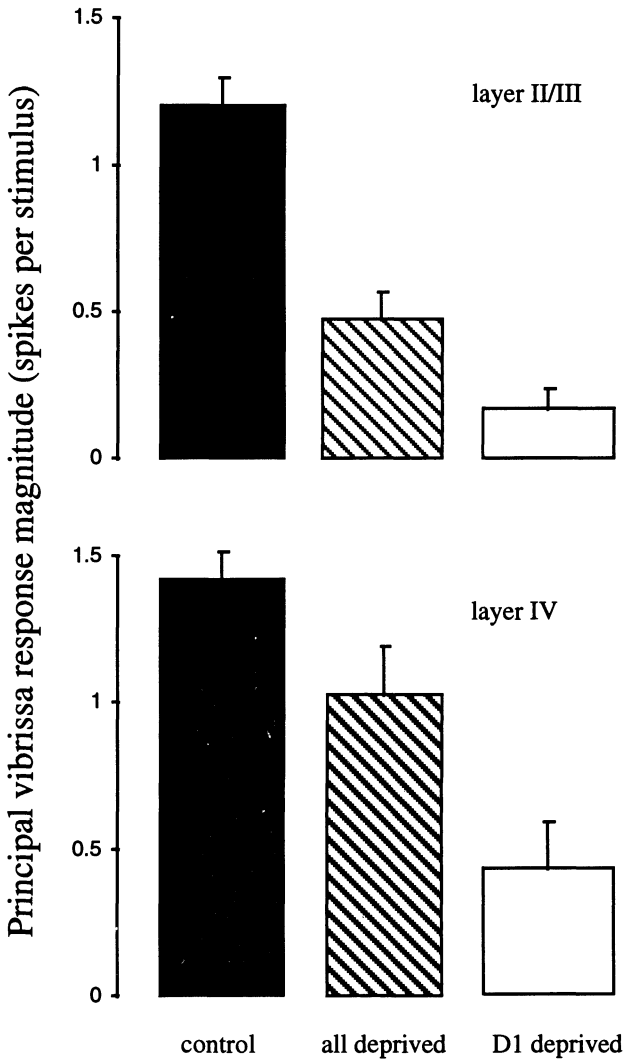

Fig. 4. Effect of deprivation pattern on principal vibrissae responses of adolescent animals. Two mechanisms of suppression of the deprived vibrissae inputs operate in the barrel cortex. First, homosynaptic, i.e. independent of other inputs and second heterosynaptic, dependent on the presence of spared vibrissa input. Black bars indicate principal vibrissa response magnitude recorded from undeprived animals; left hatched bars indicate responses recorded from animals plucked of all their vibrissae for 7 days and empty bars show responses obtained from animals plucked of D1 vibrissa only for 7 days.

ORIGIN OF CORTICAL POTENTIATION AND SUPPRESSION

Origin of potentiation

It is possible to imagine at least two methods of checking whether potentiation originates in the cortex or is passively transmitted from subcortical structures. Both have been already employed with the aim of solving this problem in the barrel cortex. The first method is based on measurements of cortical magnification factor before and after induction of plastic changes. In more simple terms, if the ratio of the cortical to thalamic area driven by the D1 whisker is bigger in the D1 spared vibrissa preparation than the same ratio in control animals, it suggests that potentiation is, at least in part cortical. Such experiment was done using 2-deoxyglucose technology and an answer was positive (Lin et al. 92). The second method is based on the prediction of impairing plasticity in barrel columns surrounding the D1 barrel column (in the D1 sparedvibrissa preparation) in proportion to amount of damage to D1 barrel if plasticity really originates, at least in part in the cortex. A variant of this approach predicts that plasticity will be impaired when a row of lesions is placed between D1 and one of the surrounding barrels in the D1 spared vibrissa preparation. Both variants have been tested and in both cases, the prediction of purely cortical origin of potentiation confirmed (Fox 1994). Additionally, in this latter study specificity of obtained results has been supported by several control experiments. It was shown that, loss of plas-

ticity in the barrel column separated from the D1 barrel by a row of lesions have not been associated with decrease in strength of principal input to this barrel column. At the same time plastic changes in the barrel columns still having connections with the D1 barrel column were not disrupted (Fox 1994).

Origin of suppression

Suppression is much greater in layers II/III than in layer IV in animals deprived of all vibrissae and animals in which only the D1 vibrissa is spared. It is difficult to imagine how suppression can be transmitted passively from subcortical structures to supragranular cortical layers *via* layer IV which is not very suppressed, and constitutes major input to layers II/III. It implies that most if not all suppression originates in the cortex.

As was already mentioned, substantial suppression of deprived vibrissae inputs can be detected in layer IV of animals in which only D1 whisker have been removed. This discovery re-opened the question where suppression arises, cortically or subcortically. Evidence that even the suppression observed in layer IV is of cortical origin comes from the results of recordings made in the ventro--posterior medial (VPM) thalamus, which is the source of lemniscal input to the layer IV (see also Diamond et al. 1992). There was no difference in the averaged magnitude of responses to whisker stimulation found in VPM between representations of spared and plucked whiskers in the D1 only plucked preparation. These averages were also indistinguishable from values obtained from control, undeprived animals (Glazewski et al. 1998a), Additionally, for cells recorded in the deprived and control barrels of animals where only the D1 whisker had been removed, the cumulative latency curves were plotted and revealed new information. On the basis of the critical points of change on the cumulative latency curve for D1 only representations all cells (that is control and tested) were split to three latency bands (for details see Glazewski et al. 1998a) Analysis of the number of neurones and averaged magnitudes of responses in successive latency bands in control and after induction of plasticity revealed that intermediate, 9-14ms latency band was most affected by deprivation. The fraction of cells in this band dropped from 60% in controls to 21% in deprived representations. This suggests that is more likely that the second synapse, i.e. the one after the initial thalamocortical synapse in layer IV is suppressed or even next yet than the first one.

MECHANISMS OF POTENTIATION AND SUPPRESSION

Physiological mechanisms

In the view that both potentiation and suppression seem to originate in the cortex, horizontal or/and oblique axons running in supragranular layers of the barrel cortex seem to be a good candidates for being an anatomical substrate for potentiation and heterosynaptic suppression (Lorente de No. 1947, Bernardo et al. 1992). Plasticity of the synapses made by these axons (i.e., long-term potentiation - LTP and long-term depression - LTD) have been studied successfully *in vitro* and *in vivo* in the barrel cortex (Aroniadou-Anderjaska and Keller 1995, Aroniadou and Keller 1995, Glazewski et al., in preparation) and motor cortex (Hess et al. 1996). Homosynaptic suppression is probably generated in vertical connections, where *in vitro* LTD can be easily evoked by low frequency stimulation (Artola et al. 1990, Kirkwood et al. 1992).

It is not known, but it is possible to test, whether physiological mechanisms of potentiation and LTP have something in common (Glazewski et al. 1998). It is not even known whether potentiation is an active process that is associated with strengthening of excitatory input or simply a passive reflection of change in inhibition. If the latter hypothesis is true, relief of inhibition would need to be input specific and occur only within the deprived barrel (there is no potentiation in supragranular layers of the D1 barrel column, see Glazewski et al. 1996).

There are at least two possible mechanisms for heterosynaptic suppression. Both must be input specific. The first assumes that the spared input generates additional and tonic inhibition upon neurones of the deprived barrel column.The second model is associated with active down regulation of the principal excitatory input to the deprived neurones (see also Glazewski et al. 1998a). Both models are testable.

Molecular mechanisms

Potentiation and suppression are both lasting phenomena, which implies the existence of one or several molecular mechanisms to maintain them.These mechanisms may be based on the activity of regulatory enzymes which are capable of being switched on or off and maintain their activity, or lack of it, for a long period of time.

They may even be associated with-long term changes in expression of some proteins. One such enzyme, which has for a long time been implicated in various processes underlying plastic changes is the calcium and calmodulin dependent protein kinase II (CamKII; Hendry and Kennedy 1986, Silva et al. 1992, Silva et al. 1992a, Lisman 1994, Gordon et al. 1996, Kennedy 1997, Kirkwood et al. 1997, Lisman et al. 1997). This enzyme is abundant in postsynaptic densities of neurones (Kennedy et al. 1993), is calcium dependent, can be switched on quickly by a discrete calcium pulse (De Koninck et al. 1998) and has the capability of maintaining its activity for a long time through autophosphorylation, which relieves its dependence on calcium (Miller and Kennedy 1986).

The possible involvement of CamKII in barrel cortex plasticity has been studied using α-CamKII knockout mice. It was found that potentiation, but not suppression of vibrissae responses in the univibrissae reared animals depends on the presence of α-CamKII (Glazewski et al. 1996). Interestingly, this phenomenon was observed only if an attempt was made to evoke plastic changes in adult animals (i.e. over six months old; Fig. 5). The degree of plasticity seen in adolescent animals deficient for α-CamKII was similar to that found in control wild-type animals (Glazewski et al. 1996). The lack of dependence on α-CamKII in adolescent animals implies that the deficit seen in adult mutants is not associated with a developmental deficit. On the other hand, it is still not known whether the lack of potentiation of spared vibrissa responses is a result of the critical role CamKII plays at this age, or simply an age-dependent decline in the potency of compensation mechanism observed in adolescent animals. If the first hypothesis is true, it means that at least two mechanisms for potentiation operate in the barrel cortex: one in adolescent animals and the second in adults. Similar experiments on univibrissa reared animals have been performed recently using mice deficient for a transcription factor, the α/δ isoforms of cAMP-responsive element binding protein (CREB; Glazewski et al. 1998b). In previous studies, CREB has been found to be critical for long-term memory mechanisms in flies, aplysia and mice (Bourtchuladze et al. 1994, Yin et al. 1994, Bartsch et al. 1995). In supragranular layers of barrel cortex, the absence of α/δ-CREB caused upregulation of the surround responses, i.e. these ones which are evoked by stimulation of .whiskers immediately surrounding the principal whisker. This effect was especially pronounced in adult animals (Glazewski et al., in preparation). However, plasticity was not abolished as was in the case of adult CamKII deficient mice.

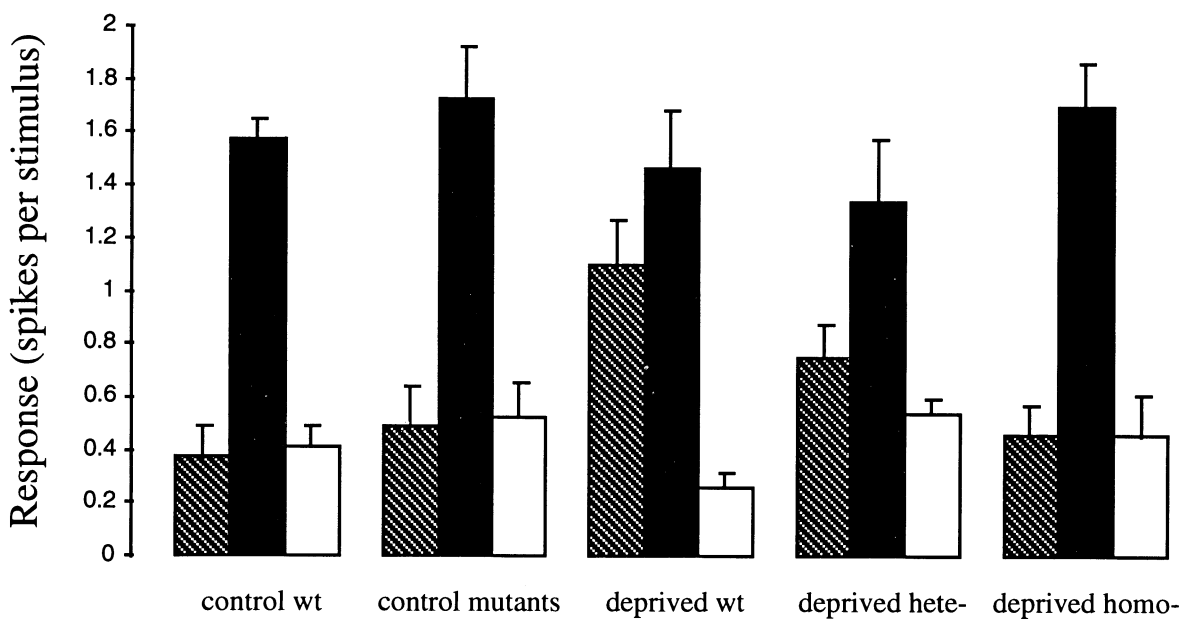

Fig. 5. Plasticity in adult mice deficient for α-CamKII. Notice lack of potentiation of the spared vibrissa input in mutant animals (hatched bars in two most right sets) and lack of the suppression of the deprived vibrissae input in all deprived animals (black bars in three most right sets). Hatched bars - response to D1 vibrissae stimulation; black bars, response to the principal deprived vibrissae stimulation; empty bars, response to the deprived surround vibrissae stimulation; wt, wild type; hete, heterozygote; homo, homozygote.

It was also found that deficiency for α/δ-CREB can also impair long-term potentiation (LTP) in coronal sections cut through barrel cortex. LTP was measured as a change in the peak amplitude and induced in layers II/III by tetanizing layer IV. Over 90 min., LTP was not significantly different in CREB null mutants (132.7 ± 2.8%) compared with control wild type animals levels ($P<0.69$). However, in 3/7 slices from homozygotes, LTP decreased to baseline between 1 and 2 h (Glazewski et al. 1998, in preparation, Staddon and Fox 1998).

These results show that although α and δ isoforms of CREB are not essential for *in vivo* and *in vitro* expression of potentiation in barrel cortex, they produce abnormalities in both forms of plasticity. It remains to be determined whether isoform β is involved and whether CREB plays some part in plasticity of wild-type animals.

SUMMARY AND CONCLUDING REMARKS

Long-term changes in whisker dominance can be induced by the introduction of an imbalance in activity to the whisker-to-barrel system. Plasticity of supragranular cortical layers in adolescent animals is composed of suppression of the deprived vibrissae responses and potentiation of the spared vibrissa responses. There are different time courses for suppression and potentiation, with suppression appearing before potentiation. Moreover, there are two mechanisms of suppression: one, homosynaptic i.e. dependent only upon the deprived input and the second heterosynaptic, regulated by the spared input. Suppression cannot be evoked and possibly cannot be maintained in adult rodents. Both, potentiation and suppression, seem to be cortical in origin. Plasticity depends on the presence of α-CamKII and to lesser extend αδ-CREB, but only in adult animals. Both macromolecules could be involved in plastic mechanisms even in adolescence (if compensation mechanisms exist), but are not critical at this age. In adulthood, involvement of both seems to be important. However, it is not clear whether the observed deficit is a direct effect or is a result of lack of compensation.

Studies into plastic changes in the cortex are directed toward looking for mechanisms of potentiation and suppression which, as we still believe, constitute a basis for the memory trace. Moreover, such studies can help to understand mechanism and a rationale of plastic changes, which could be important from clinical point of view.

Barrel cortex seems to be one of the best model systems for studying mechanisms of potentiation and suppression, due to four reasons: it is mammalian, but still relatively simple, it has an anatomical reference at the level of layer IV (pattern of barrels), which enable precise measurement of physiological changes; plastic changes can be evoked easily by changes in natural stimuli; and finally, it is amenable to study the effects of genetic manipulations.

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