Reduction of GABAA receptor binding of [3H]muscimol in the barrel field of mice after peripheral denervation: Transient and long-lasting effects

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ORIGINAL PAPER

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Reduction of $GABA_A$ receptor binding of [^{3}H]muscimol in the barrel field of mice after peripheral denervation: transient and long-lasting effects

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Abstract The effect of peripheral sensory deprivation upon $GABA_A$ receptor binding of [^{3}H]muscimol was investigated in the barrel cortex – cortical representation of mystacial vibrissae of mice – by means of in vitro quantitative autoradiography. Unilateral lesions of all vibrissae or selected rows of whiskers were performed neonatally or in adulthood. [^{3}H]muscimol binding was examined after various survival times up to 60 days. Both types of lesions performed in adult mice resulted in a transient decrease (10–25%) of binding values in the deafferented areas of the barrel field as compared with the unoperated control side. Sixty days after denervation [^{3}H]muscimol binding returned to control values. Similar results were found after neonatal removal of all vibrissae. Neonatal lesion of selected rows of vibrissae, however, resulted in a decrease of [^{3}H]muscimol binding (by about 26%) lasting up to 60 days in corresponding rows of barrels. This last result was accompanied by severe cytoarchitectonic malformation of the barrel field. The results support the hypothesis that a decrease of inhibition plays a facilitatory role in the plastic reorganization of cortical circuitry.

Key words $GABA_A$ receptor · Barrel cortex
Plasticity · Autoradiography · Mouse

Introduction

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the cerebral cortex, and is believed to play an essential role in shaping neuronal responsiveness (Sillito 1975; Dykes et al. 1984; Alloway et al. 1989). An immunocytochemical study has demonstrated that up to 25% of all neurons in primary somatosensory cortex are GABA-immunopositive (Ren et al. 1992). Many forms of neuronal inhibition are thought to be mediated by the $GABA_A$ receptor complex that comprises a chloride channel (for a review see Stephenson, 1988). The composition of subunits and presumably the properties of $GABA_A$ receptors in early postnatal rats differ markedly from those expressed in the adult brain (Laurie et al. 1992). Furthermore, regional differences in expression of various $GABA_A$ receptor subtypes have been observed (Wisden et al. 1992).

Activity-dependent changes of the $GABA_A$ receptors have been reported in the visual cortex. In adult monkeys, monocular deprivation reduces immunoreactivity of $GABA_A$ receptors and [^{3}H]muscimol binding in the deprived eye columns (Hendry et al. 1990). In kittens, Skangiel-Kramska and Kossut (1984) and Shaw and Cynader (1988) have reported an increase of the binding values of $GABA_A$ receptors after monocular deprivation, while Mower et al. (1986) have demonstrated no changes in [^{3}H]muscimol binding values. Other indices of the GABAergic system, such as immunoreactivity of glutamate decarboxylase (GAD) and GABA, decrease after denervation of sensory areas of the cortex (Hendry and Jones 1986; Warren et al. 1989; Welker et al. 1989a; Kossut et al. 1991a), and increase upon sensory stimulation (Welker et al. 1989b). The response of the $GABA_A$ receptor to deafferentation of the somatosensory cortex has not previously been described; we attempted to assess it using the vibrissae to barrels system, which allows an easy identification of the central projection site of peripheral receptors.

The aim of the present study was to examine whether the peripheral deafferentation that produces plastic changes in neonatal and adult animals (Van der Loos and Woolsey 1973; Kossut et al. 1988; Kossut 1992) affects the pattern of distribution and the level of labelling of $GABA_A$ receptor sites in the barrel field of mice. $GABA_A$ receptors have a pattern of distribution that mimics the pattern of the histologically defined barrel field (Chmielowska et al. 1987). This property al-

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lowed us to follow the possible alterations of $GABA_A$ receptor sites after induction of plastic changes. For this purpose we performed unilateral removal of the hair follicles of selected rows of whiskers or lesions of all vibrissal follicles in newborn or in adult mice, and used quantitative receptor autoradiography to register possible alterations in $GABA_A$ receptor levels and in the pattern of their distribution in the barrel field.

In the present paper we report a transient decrease in binding values after mechanoreceptor lesions in adult animals and a lasting decrease when neonatal vibrissal lesions distort cortical cytoarchitecture. Preliminary data have been reported in abstract form (Kossut et al. 1991b).

Materials and methods

Animals and surgery

Fifty Swiss-Webster mice were used. In the first group, at postnatal day 2, the mice were cooled on ice and either all vibrissae or rows B and C were removed unilaterally. In the second group, adult mice (2 months old) were injected subcutaneously with 10 µl of atropine sulphate and then 30 min later intramuscularly with ketamine (1 µg/kg mouse) and either all whiskers or row B and/or C were removed on one side. Removal of vibrissal follicles was performed as previously described (Kossut et al. 1988). Before perfusion, the effects of surgery were checked, and only the mice with successful lesions and no regrowing whiskers were taken for experiments. In all mice the skin of the lesioned side of the snout was sectioned and checked for the presence of regrowing follicles; in no case were they found.

$GABA_A$ receptor-binding autoradiography

The mice were anaesthetized with Nembutal (50 mg/kg) and rapidly perfused with cold phosphate-buffered saline (PBS) followed by 0.1% formaldehyde in PBS. The brains were removed, frozen in isopentane cooled with dry ice, and stored at −70° C until use. Serial sections (20 µm) were cut on a cryostat coronally or tangentially to the barrel field. Glass-mounted sections were stored at −70° C until processed for binding of [^{3}H]muscimol as previously described (Skangiel-Kramska et al. 1986).

Sections were preincubated in 50 mM TRIS-citrate buffer (pH 7.1) for 20 min at 4° C, then incubated in the presence of 50 nM [^{3}H]muscimol (18.6 Ci/mmol, Amersham) in the same buffer for 40 min at 4° C. To evaluate non-specific binding, several adjacent sections were incubated in the same incubation medium containing 100 µM GABA. After incubation the slides were rinsed twice in cold buffer and distilled H_2O, dried under a stream of cold air and stored over desiccant at room temperature till the next day. Slide-mounted sections and tritium standards (Amersham), calibrated against sections of cortical paste with different concentrations of [^{3}H]isoleucine, were apposed to ^{3}H Hyperfilm (Amersham). When the autoradiograms had been made, the sections were stained with cresyl violet. In some cases, selected sections were processed for succinyl dehydrogenase (SDH) histochemistry

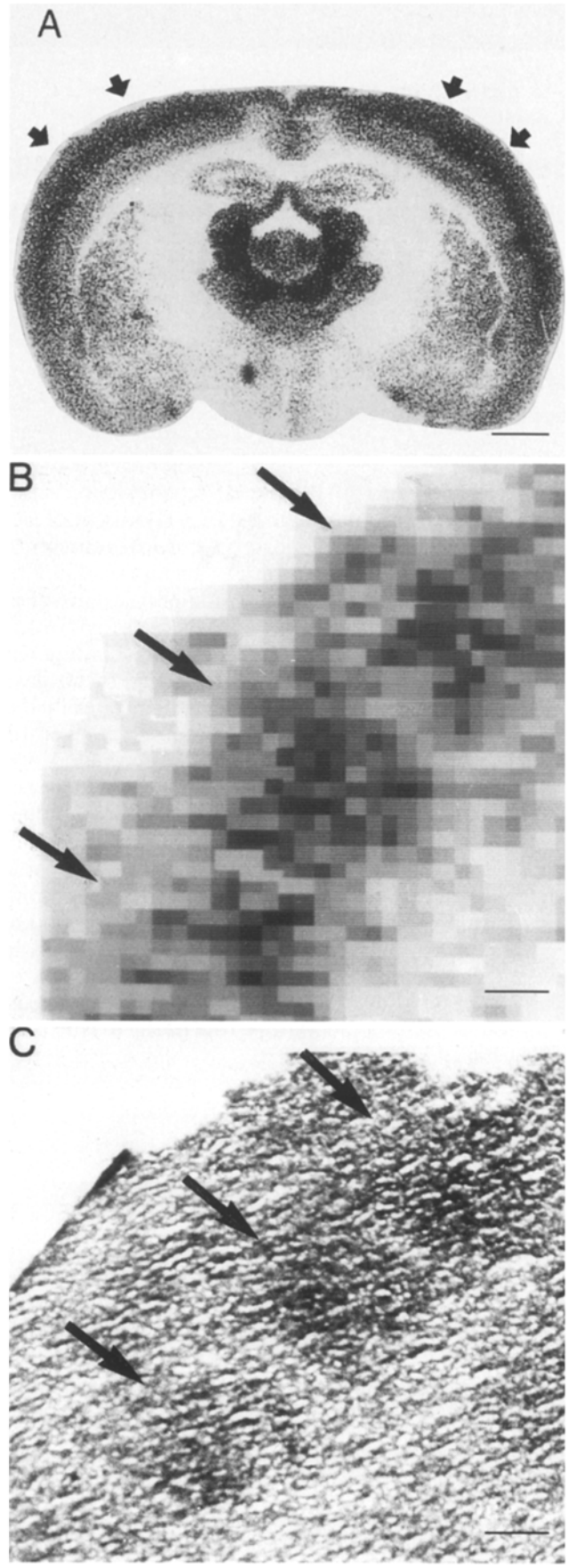

Fig. 1A–C Autoradiogram of [^{3}H]muscimol binding sites in a coronal section at the level of the barrel cortex. **A** Entire section, *arrows* point to barrel fields. *Scale bar* 1 mm. **B** Autoradiogram of a segment of barrel cortex at higher magnification, quantified by the image analyser; *arrows* point to the barrels. *Scale bar* 125 µm. **C** Succinyl dehydrogenase (SDH) staining of an adjacent section; *arrows* point to the barrels. *Scale bar* 125 µm

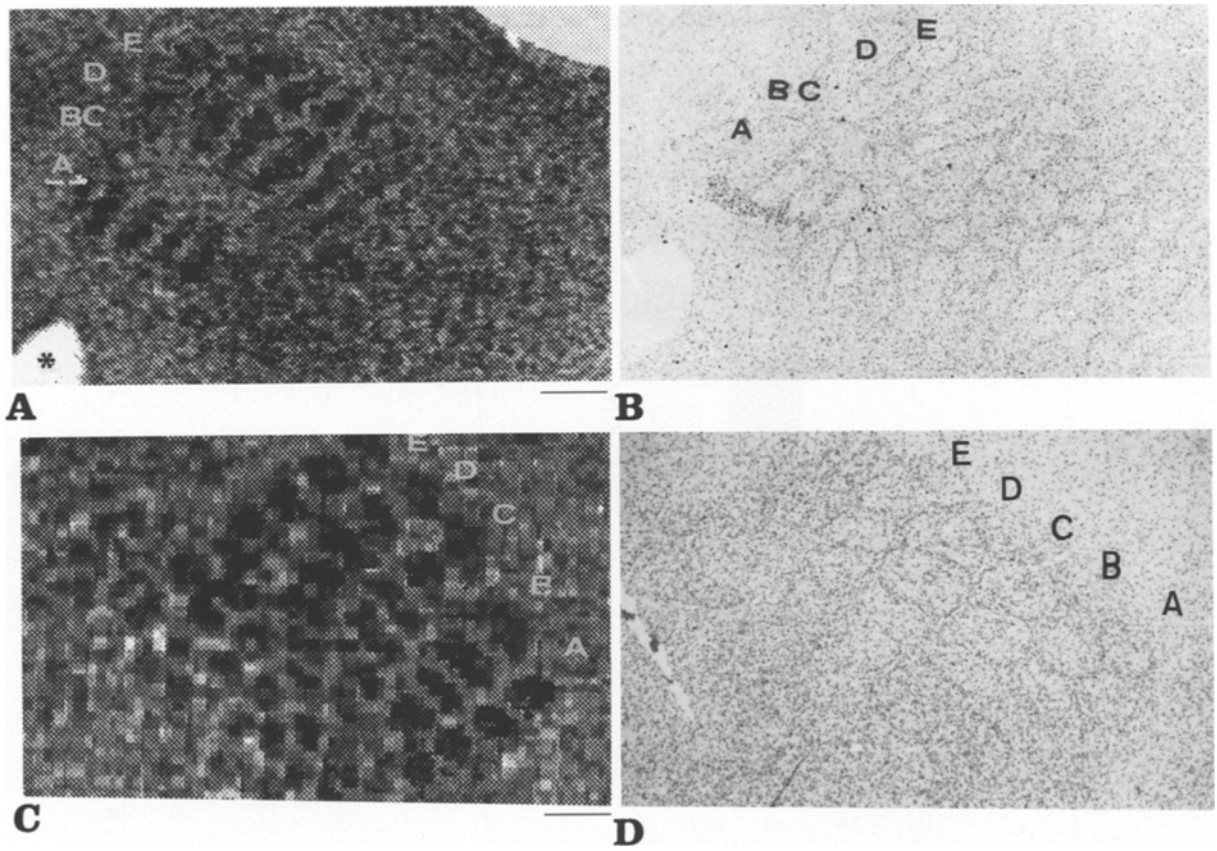

Fig. 2A–D $GABA_A$ binding in the barrel field 2 months after neonatal lesions of rows B and C. **A** Autoradiogram of [^{3}H]muscimol-binding sites from the section cut tangentially to the barrel field, quantified by the image analyser (*darker shades* indicate higher binding). Note that the area corresponding to rows B and C shows lower binding than remaining rows of barrels. **B** Nissl stained fragment of the same section. *Asterisks* show fiducial marks made in the frozen brain. **C** Autoradiogram of [^{3}H]muscimol-binding sites in the control barrel field (ipsilateral to the lesioned side). Note lack of differences in binding intensity between rows of barrels. **D** Nissl stained control section. (**A–E**, rows of barrels) *Scale bars* 250 μm

immediately after sectioning and served for quick identification of the position of the barrel field.

Quantification of the autoradiograms

Autoradiograms of brain sections and of the tritium standards were analysed with a computer-assisted image-analysing system (256 gray levels). The counterstained (cresyl-violet) sections from which autoradiograms were obtained were filmed by CCD camera, and then the section outline and the position of the barrel field were marked on the video screen. Then the appropriate autoradiograms were located in the section outlines and the labelling of the barrel field was analysed with respect to the contours of the barrels. No correction was made for non-specific binding because it did not exceed 1% of total binding. Readings of binding density were taken for each row of barrels (A, B, C, D, E) on autoradiograms from sections at the level of layer IV. On autoradiograms from other layers, where the barrels are not present, the presumed location of the representations of each row of whiskers was extrapolated with the aid of fiducial marks made in the brain before sectioning. Three readings were taken from each row on each autoradiogram.

To check the possibility of differential absorption of beta radioactivity, we evaluated quenching by apposition of cryostat sections on slides covered with [^{3}H]leucine dissolved in 0.5% gelatine, as described by us elsewhere (Głażewski et al. 1992). Results of quenching evaluation confirm the previous observation of Chmielowska et al. (1987), showing no differences in beta absorption within the barrel field tissue. Paired-sample *t*-test and analysis of variance (ANOVA) were used for data analysis.

Results

Pattern of $GABA_A$ receptor sites in the barrel-cortex

In coronal sections obtained from adult mice, in the region of the primary somatosensory cortex that corresponds to the histologically defined barrel cortex, an easily visible pattern of [^{3}H]muscimol binding can be observed (Fig. 1), matching the pattern of cortical barrels revealed by SDH histochemistry or Nissl staining. The heaviest labelling was found in cortical layer IV, amounting to 1.7 ± 0.04 pmol/mg protein.

In sections cut tangentially to the cortical surface in layer IV, a well-defined barrel-like pattern of [^{3}H]muscimol binding was observed (Fig. 2B). In the upper part of layer IV, the highest labelling was found in the centres of barrels (1.8 ± 0.05 pmol/mg protein), whereas in the surrounding septa the labelling was low-

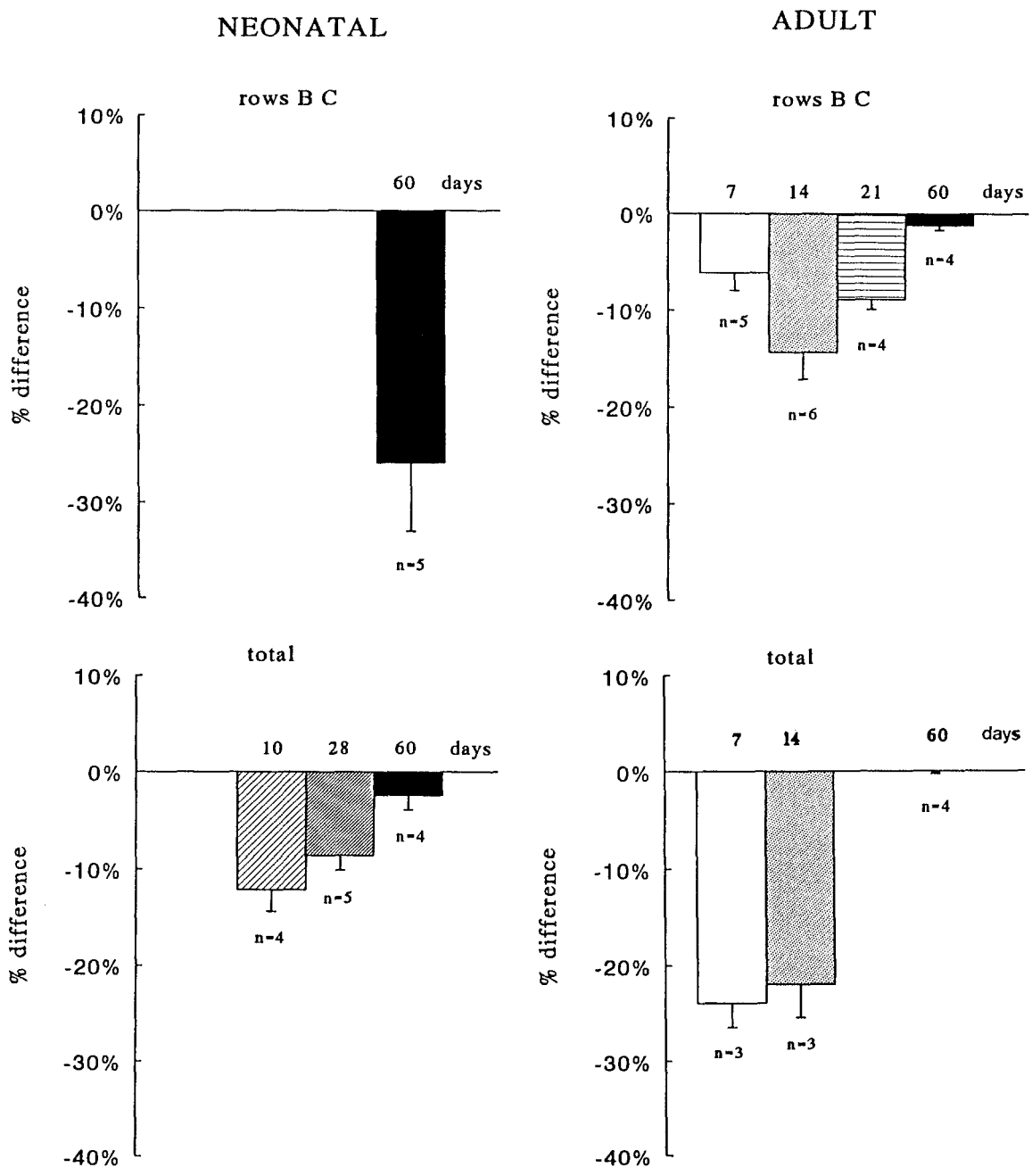

Fig. 3 Changes of [^{3}H]muscimol binding to the barrel field after unilateral denervation of selected rows of whiskers (*rows BC*) or denervation of all whiskers (*total*) performed in neonatal or adult mice. The results represent the differences between binding values in the deafferented barrel cortex and those found in the barrel field on the intact side of the same animal, which are considered as 100%. The results represent mean ± SEM (*n*, the number of animals; number of days [7–60], the survival time after denervation of whiskers)

er by about 20%.(Fig. 1B). No differences were found in the levels of [^{3}H]muscimol labelling between rows of barrels (ANOVA).

The effect of neonatal lesions

Neonatal denervation of all whiskers on one side of the muzzle produced a transient decrease in [^{3}H]muscimol-binding density in the corresponding barrel field, as compared to the control contralateral barrel field of the same animal. The level of [^{3}H]muscimol labelling dropped slightly 10 days after denervation (by about $12.0 \pm 2.3\%$, $P < 0.05$), and this tendency still appeared to be present after 28 days, but it was not then statistically significant. Two months after surgery no differences could be detected between [^{3}H]muscimol-binding intensity in denervated and control barrel field (Fig. 3).

Denervation of selected rows of whiskers in neonatal mice had a much more distinct and long-lasting effect upon [^{3}H]muscimol binding. Two months after lesions

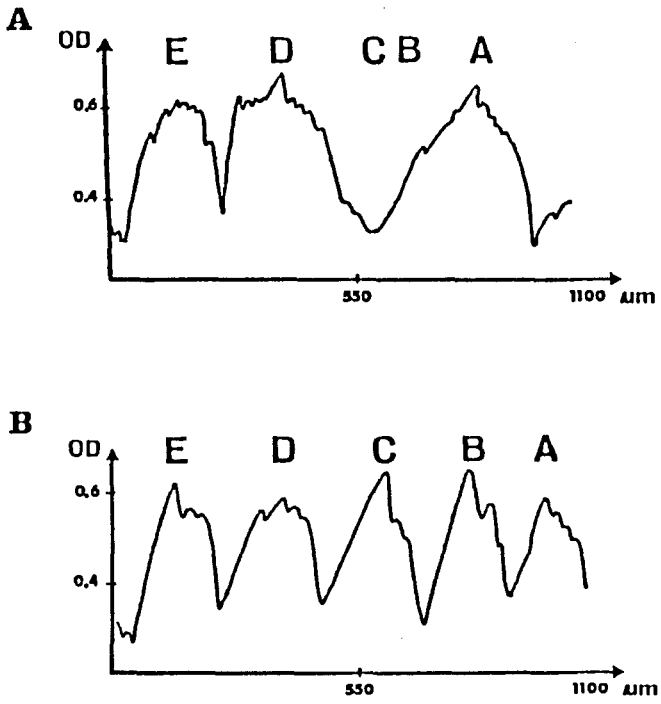

Fig. 4A,B Densitometric scans across the rows of barrels showing the effect of neonatal lesion of rows B and C. **A** Recording from the deafferented barrel field 2 months after neonatal lesion of rows B and C. **B** Recording from the control barrel field from the same animal. (*Ordinate* optical density in arbitrary units, *abscissa* cortical distance in micrometres, **A–E**, individual rows of barrels)

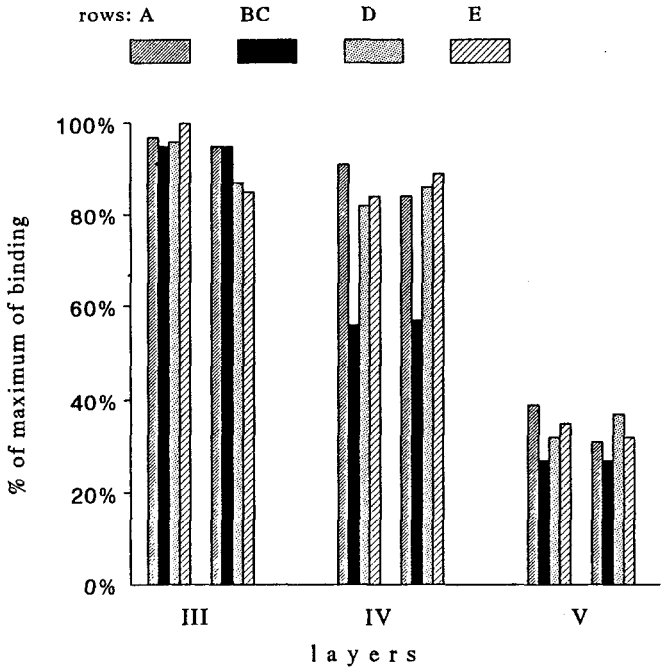

Fig. 5 Typical example of [^{3}H]muscimol binding values in rows of barrels and in corresponding regions of supragranular and infragranular layers in an animal with neonatal lesion of rows B and C, examined 2 months later. *Bars* represent means for three readings per row of barrels per tangential section. Each group of bars gives results for each section. All sections come from the hemisphere contralateral to the lesioned vibrissae. Results are expressed as percentage of maximal binding on this side of the brain

of rows B and C of whiskers, the labelling in the corresponding rows of barrels was less on average by $26.0 \pm 7.1\%$ ($P < 0.05$) than in the neighbouring rows (Figs. 2–4). This effect was limited to cortical layer IV; no differences in labelling could be detected in cortical layers III and V (Fig. 5). The level of labelling in rows A, D, and E was similar to that registered in the control hemisphere ipsilateral to the lesioned side (ANOVA), indicating that the observed effects indeed represent a decrease of binding in the denervated row and not an increase in the neighbouring rows.

Denervation performed in adulthood

Denervation of all whiskers performed unilaterally in adult mice produced a decrease of labelling in the corresponding barrel field as compared to the control hemisphere. Seven days after the lesion, [^{3}H]muscimol labelling dropped by $24.0 \pm 2.5\%$ ($P < 0.01$). Two weeks after lesion the decrease still seemed to be present, but was not statistically significant. One month after surgery [^{3}H]muscimol labelling was at the control level (Fig. 3).

Denervation of rows B and/or C also produced a decrease of [^{3}H]muscimol labelling in corresponding rows of barrels as compared with normally innervated neighbouring rows (Fig. 6). There seemed to be a decrease 7 days after surgery, but this was not statistically significant. Two weeks after surgery the binding values dropped by $14.0 \pm 2.7\%$ ($P < 0.01$). Again this effect disappeared after a longer survival time. Two months after surgery the labelling in denervated rows was the same as in neighbouring rows (Fig. 3).

Discussion

The main finding in the present study is the activity-dependent down regulation of the $GABA_A$ receptor. The difference was observed in the response of $GABA_A$ receptor sites after neonatal and adult denervation of selected rows of whiskers. Such deafferentation of vibrissal follicles performed neonatally led to a permanent decrease of [^{3}H]muscimol labelling in corresponding rows of barrels, whereas lesions performed in adult mice produced only a transient reduction of labelling restricted to the denervated rows of barrels.

This difference in $GABA_A$ receptor responses in neonatal versus adult brain probably indicates different mechanisms of plastic change occurring after neonatal versus adult denervation of selected rows of whiskers. Neonatal denervation of vibrissae causes permanent, pronounced alterations in the cytoarchitecture of the barrel field (Van der Loos and Woolsey 1973). Persistent changes in $GABA_A$ receptor binding may reflect the altered morphology of the barrels after partial neonatal denervation. These changes are more drastic if only selected rows of vibrissae are removed than when all follicles are damaged (Killackey et al. 1976). The less severe

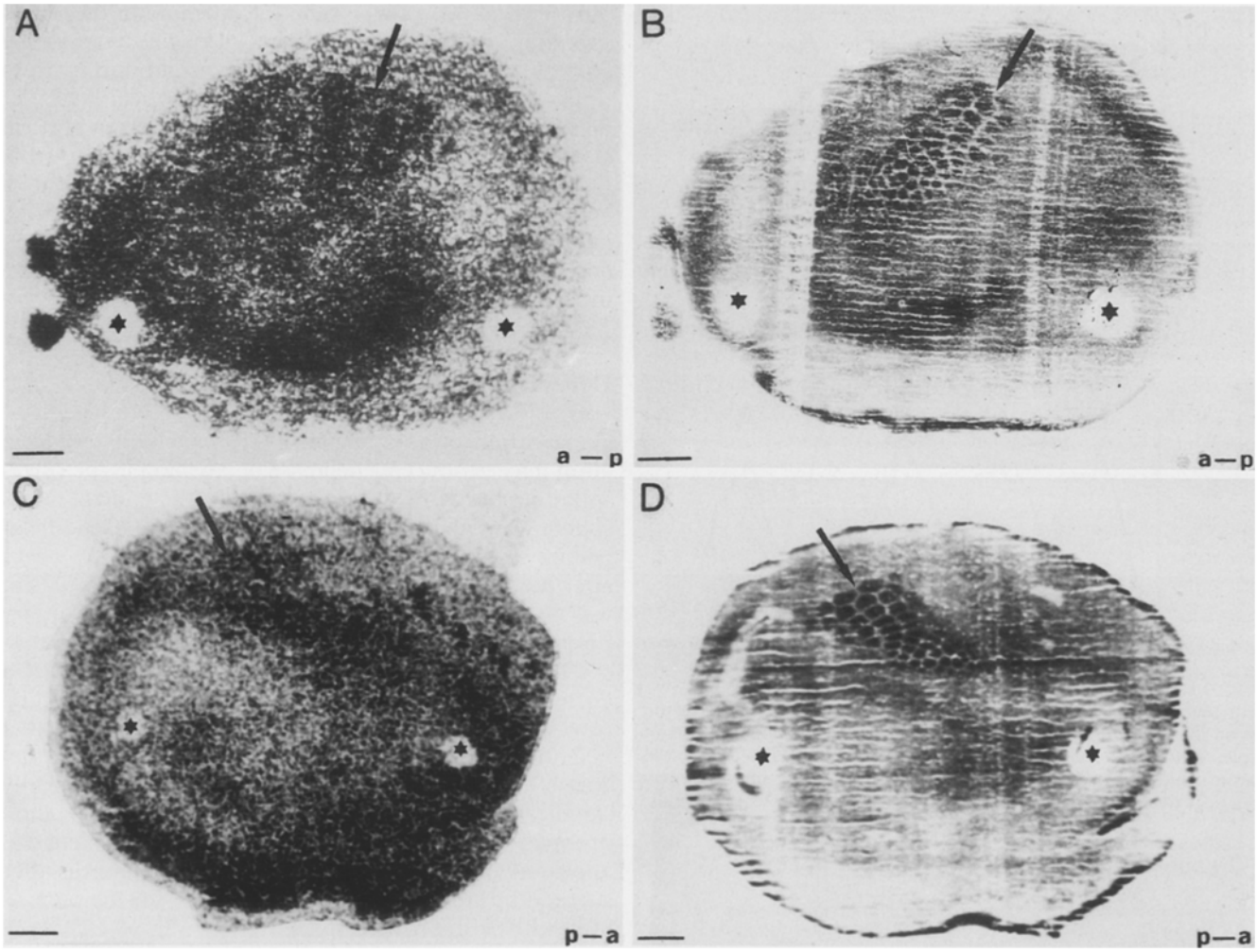

Fig. 6A–D $GABA_A$ binding 7 days after row C lesion in an adult mouse. **A** Autoradiogram of [^{3}H]-muscimol-binding sites from the section cut tangentially to the barrel field quantified by the image analyser. Note lower binding intensity in row C as compared with remaining rows of barrels. **B** SDH staining of adjacent section. **C** Autoradiogram of control barrel field of the same animal. **D** SDH staining of control barrel field. *Arrows* point to row C. *Asterisks* show fiducial marks made in the frozen brain. Orientation markers: anterior (*a*) and posterior (*p*). *Scale bars* 1 mm

cytoarchitectonic changes following total denervation may be one of the reasons for the transitory nature of the observed receptor-binding changes. Denervation performed in adulthood altered functionally the cortical representation of vibrissae without changing the cytoarchitectonics of the barrel field (Weller and Johnson 1975; Kossut et al. 1988).

It is known that neurotransmitter receptors could be up and down regulated by the action of specific ligands and also by increases or decreases in the electric activity of neurons (see Hollenberg 1985; Jarett and Smith 1985). One possible cause of observed down regulation of $GABA_A$ receptors could be the increase of GABA release. However, our previous results, showing the loss of GABA-immunopositive neurons and puncta found in the barrel cortex after neonatal denervation (Kossut et al. 1991a), are not consistent with this explanation. It has recently been demonstrated that lesion of the nucleus basalis magnocellularis reduces the level of acetylcholine in the cortex and at the same time decreases the binding to M_1 and M_2 cholinergic muscarinic receptors (Bogdanovic et al. 1993). Therefore, one can speculate that the decrease in [^{3}H]muscimol labelling in rows of barrels corresponding to denervated whiskers could be the manifestation of down regulation of $GABA_A$ receptor sites after the reduction of peripheral input. Thus the restoration of activation of the barrel field neurons by intact, neighbouring sensory inputs (Kossut 1992) should counteract observed down regulation of $GABA_A$ receptor sites, and restore the normal level of [^{3}H]muscimol labelling. A similar result was reported by Hendry and Jones (1988), who found a restoration of GABA levels to normal after subsequent eyelid opening in monocularly deprived monkeys. These results clearly indicate that the peripheral input activity regulates the GABAergic system within the neocortex. The decrease in $GABA_A$ receptor labelling, found by us after denervation of selected rows of whiskers, was limited to cortical layer IV. These observations agree with the results of Welker et al.(1989a), Warren et al. (1989) and Kossut et al.(1991), who found that peripheral deprivation led to a

decrease in GAD or GABA immunoreactivity in layer IV, whereas the supragranular and infragranular layers did not reveal changes in immunostaining that could be related to the deprivation. The possible reasons for the reappearance of normal [^{3}H]muscimol are: (1) the reactivation of the deprived cortical region by regenerating sensory nerves or by other inputs, or (2) a novel GABAergic innervation arising from neurons of neighbouring barrels. Removal of all whiskers produced a transient effect both when performed neonatally and in adulthood. It is well documented that body maps in the somatosensory cortex can change after peripheral denervation (for review see Kaas et al. 1984; Wall 1988). Waite and Taylor (1978) and Pidoux et al. (1980) have demonstrated that if the vibrissae are removed neonatally the barrel field can be activated by the common fur of the mystacial pad and other neighbouring somatosensory inputs. We have found recently that the invasion of the common fur representation into the barrel field can be seen 1 month (but not earlier) after removal of all vibrissae in adult rats (Kossut and Siucińska 1990). A complete takeover of the barrel field by adjacent inputs is plausible after a month of peripheral denervation, and if the cortex is fully activated, the neurotransmitter receptor levels may return to normal values. In the case of neonatal removal of rows of vibrissae, the deformed rows of deafferented barrels would also be functionally taken over by inputs from the intact whiskers (Kossut et al. 1988), but a profound change in cytoarchitectonic structure of these rows may result in a permanent deficit of cortical circuitry and receptor binding.

The observed decrease of $GABA_A$ receptor binding values followed by a return to normal values may be associated with the restoration of functional activity. The local loss of inhibitory activity may be beneficial for promoting the dominance of the new input in poorly activated denervated cortex. A partial blocking of $GABA_A$ receptors is a necessary condition for inducing long-term potentiation in slices of rat visual cortex (Artola and Singer 1990) and in slices of rat barrel cortex (Lee et al. 1991). Loss of primary afferent input may locally reduce the intracortical inhibition, facilitating strengthening of new functional connections. Once the new connections are established, the reduction in inhibitory activity may subside.

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