Acta Neurobiol. Exp. 2000, 60: 411-418

Inducing gene expression in barrel cortex - focus on immediate early genes

Robert K. Filipkowski

Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA; Department of Molecular and Cellular Neurobiology, Nencki Institute of Experimental Biology, 3 Pasteur St., 02-093 Warsaw, Poland, Email:filip@cshl.org

Abstract. Using only their vibrissae, rats and mice are able to recognize and differentiate surfaces not distinguishable by primates using their fingertips. It has been shown that sensory stimulation elicits the expression of immediate-early genes (IEG), e.g., *c-fos* and *zif268*, in the sensory cortex of rats and mice. Though most of these findings come from visual system, mice and rats rely more on their vibrissal system which also offers many advantages for designing precise and precisely controlled experiments. In this review, new models for the selective and simple stimulation of vibrissae are presented and discussed. The data demonstrating IEG expression in the vibrissal system is also reviewed.

Key words: c-Fos, Zif268, sensory stimulation, learning and memory, plasticity, parvalbumin

OF WHISKERS AND GENES

In rats and mice, the vibrissae are critical sensory organs, playing a key role in balance, orientation, spatial learning, movement, distinguishing objects, depth perception, roughness discrimination, swimming, acquiring food, as well as aggressive, predatory and copulatory behaviors (Vincent 1912, Schiffman et al. 1970, Bugbee and Eichelman 1972, Gustafson and Felbain-Keramidas 1977, Ahl 1986, Guic-Robles et al. 1989, Carvell and Simons 1990, Biały and Beck 1993). In spite of the observations that the tactile cues are prepotent over visual ones (Schiffman et al. 1970), the vast majority of data concerning the effects of sensory deprivation and stimulation on immediate-early genes (IEG) expression in cortex was obtained from investigating mammalian visual cortex (Kaczmarek and Chaudhuri 1997). There is only a few observations concerning barrel cortex, the cortical representation of vibrissae. In this review I would like to tie together our recent findings concerning c-Fos expression in rat barrel cortex following tactile experience, presented at the Satellite to ISN/ESN Berlin'99 Meeting in Rydzyna (Filipkowski et al. 2000), with those of other investigators of the field.

The barrel cortex is a part of rodent primary somatosensory cortex representing mechanoreceptors connected to vibrissae. It is a remarkable model system to study the relation between anatomy and function and the effects of sensory stimulation on cortical activity. The sensory signal caused by the movement of vibrissae is sent from whisker follicles through the brainstem and the thalamus, mainly to the fourth layer of somatosensory cortex. This layer contains cylinder-shaped anatomical structures called barrels made of densely packed neurons (Fig. 1). The barrels, present only in layer IV, are a part of functional cortical columns extending throughout the thickness of the cortex and spanning all its layers. There is a one-to-one correspondence between each vibrissa and each barrel structure. The representation is contralateral, i.e. the barrel cortex on one side of the brain represents the vibrissae on the other side of the snout (Kossut 1992b).

Even "subtle" treatment of animals, such as sensory stimulation, evokes changes in gene expression. Since these genes encode transcription factors, and possibly influence the expression of many genes, they might lead to permanent alternations in structure and function of cells. It is also likely that these changes play a key role in plasticity of the nervous system.

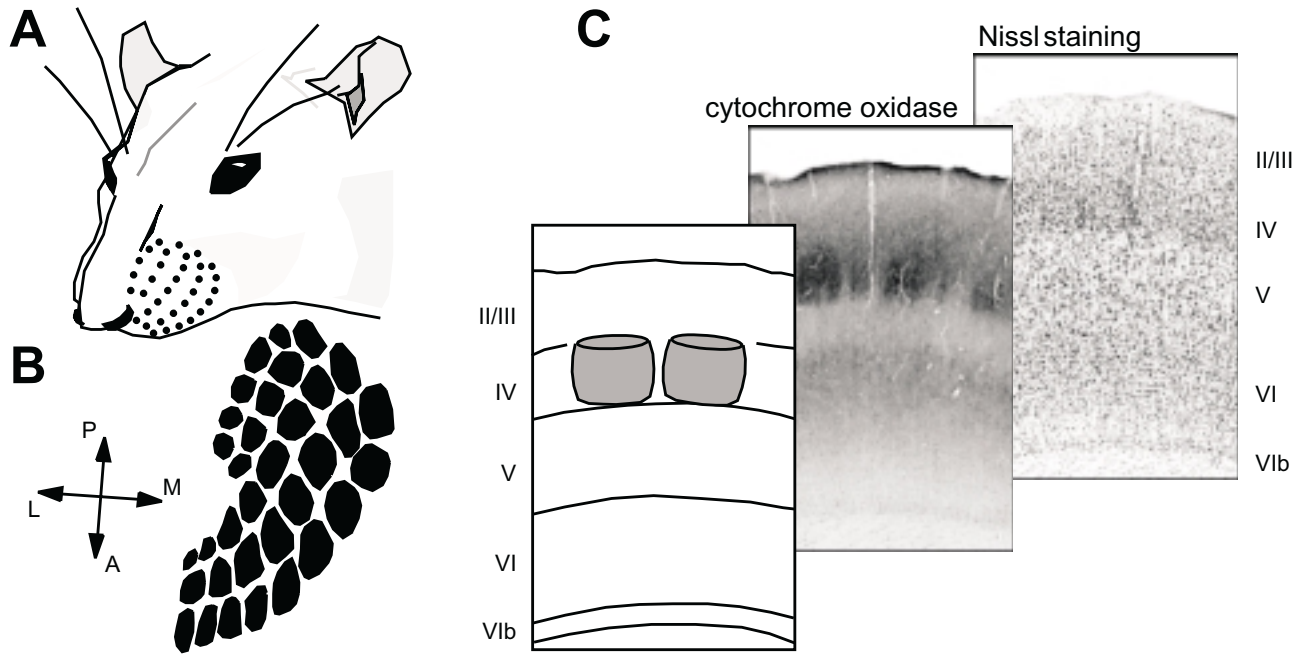

Fig. 1. Barrels of rat somatosensory cortex. Distribution of vibrissae on the snout (A) corresponds with the distribution of barrels in layer IV of the cortex, in horizontal plane (B) with the relation: 1 vibrissa – 1 barrel; (C) histological staining showing layers of the cortex and position of two barrels.

Zif268 and c-Fos proteins are widely used to map functional activity of the brain (Sagar et al. 1988, Dragunow and Faull 1989, Smeyne et al. 1992, Chaudhuri and Cynader 1993, Sharp et al. 1993, Smeyne et al. 1993, Hughes and Dragunow 1995, Chaudhuri et al. 1997, Savonenko et al. 1999). Genes encoding these proteins belong to the group of immediate-early genes (IEG). Activation of transcription of these genes in the brain takes place rapidly, minutes after stimulation, and does not require protein synthesis (Morgan and Curran 1991). Though the increase of the level of expression of some IEG was observed after many stimuli, such as addition of hormones, neurotrophins, and neurotransmitters, it has to be stressed that IEG expression does not merely reflect neuronal metabolic activity. Such an activity, measured by 2-deoxyglucose, is not always accompanied by changes in IEG content (Dragunow and Faull 1989, Sharp et al. 1993) whose expression is rather limited to certain regions and types of cells (Kimpo and Doupe 1997). Also, the patterns of expression of different IEG can vary (Hope et al. 1994a,b, Kaminska et al. 1994, Kasof et al. 1995).

DEPRIVING AND STIMULATING BARRELS (LOOKING FOR MODELS)

Deprivation of sensory signals coming to the barrel cortex can be accomplished by clipping or removing the vibrissae (Schiffman et al. 1970, Fox 1992, Kossut 1992a, Biały and Beck 1993, Steiner and Gerfen 1994, Melzer and Steiner 1997, Fuchs and Salazar 1998, Polley et al. 1999). It can also be done by removing the whole or a part of skin pad from the snout (whiskerpad) together with vibrissae and vibrissal follicles or by cutting the infraorbital nerve (Jacquin et al. 1993). It is possible to achieve partial deprivation by removing only some vibrissae, and sparing one side of (Steiner and Gerfen 1994), one row of (Dunn-Meynell et al. 1992, Levin and Dunn-Meynell 1993, Siucińska and Kossut 1994) or just one vibrissa (Kossut et al. 1988, Levin and Dunn-Meynell 1991, Melzer and Steiner 1997).

There are three main ways of stimulating barrels which lead to IEG activation: (1) using pharmacological agents; (2) using direct, mechanical stimulation; and (3) allowing the animal to explore around novel environment.

Apomorphine, a dopamine receptor agonist, when injected subcutaneously, increases the locomotor activity of animals, especially causing whisking and sniffing behavior which ultimately results in increased vibrissae stimulation (Szechtman et al. 1982, Beck et al. 1986). Since many cells in the brain are under direct influence of apomorphine, therefore in this model both sensory-related and non-sensory stimulation is observed (Steiner and Gerfen 1994).

Direct, mechanical stimulation with various objects is often used. This is usually done with a brush (Kossut 1992a, Mack and Mack 1992, Siucińska and Kossut 1996, Filipkowski et al. 2000), hair clipper (Schwarting et al. 1994) as well as with cable, stick or other kind of probe (Barneoud et al. 1991, Hurwitz et al. 1991, Jacobs and Juliano 1995). Usually all vibrissae on one side of the snout are stimulated or some of them, e.g., one row only (Jabłońska et al. 1996, Siucińska and Kossut 1996). The problem with direct brushing is the high activity and mobility of mice and rats. This can be eliminated by anesthetizing (Mack and Mack 1992) or restraining the animals (Siucińska and Kossut 1996). It needs to be stressed, however that both the use of anesthesia and stress might influence investigated gene expression and are far different from physiological conditions. A particular example of direct vibrissae stimulation is the Lausanne stimulator, an electromagnetic coil with strong magnetic field bursts moving metal pieces glued to whiskers (Welker 1964, Melzer et al. 1985, Welker et al. 1989, 1992, Rocamora et al. 1996, Melzer and Steiner 1997). One might argue, however, that passive movement of vibrissae, not associated with touching objects or investigating the surroundings might not reflect the physiological movement of whiskers.

Placing animals in a new environment as a means of stimulating whiskers is rarely used (Welker et al. 1992, Montero 1997, Filipkowski et al. 2000). This relies on a natural tendency of rats to explore (Eilam and Golani 1989) in combination with a novelty element, known to elicit IEG expression (Anokhin et al. 1991). Montero (1997) placed rats in a complex environment with multiple levels formed by boxes and platforms of different sizes and textures (wood, cardboard, fabric, metal, glass, brushes) scattered in all surface levels.

The aforementioned experimental models of vibrissae stimulation, that may be used to investigate IEG expression, involve either immobilization and pain (see also: Lukasiuk et al. 1999), anesthesia, or other artificial situations like the Lausanne stimulator or introduction of animals into a very elaborate environment. We have developed simpler experimental systems to investigate effects of tactile stimulation of vibrissae on the gene

expression (Filipkowski et al. 2000). In the case of direct brushing, we solved the "mobility problem" by placing the rats on the top of a copper cylinder. The idea was based on the observation that laboratory mice and rats tend to refrain from jumping and sliding from an elevated surface. Once the animals habituated to sitting on the cylinder their vibrissae on one side of the snout were brushed by hand. The expression of c-Fos in barrel cortex corresponding to stimulated and to non-stimulated vibrissae was compared.

As a new environment we used a metal, wired cage in which rats brought up in a plexiglass cage were placed. The expression of c-Fos in the barrel cortex of these animals was compared with its expression in naive rats. Our previous experience shows that not just the presence of new objects but also their nature (especially the presence of holes between bars) elicit whisker-dependent c-Fos expression (not published). This is in accordance with the findings of Lipp and Van der Loos (1991) who observed that mice appear to use their whiskers for detecting openings rather then texture.

Several models have been described that use vibrissae stimulation in learning. Some of them employ T- and Y-shaped mazes in which an animal has to choose the correct arm in order to receive a reward (e.g. food) using as a cue the surface of the walls of the maze's corridors (Lipp and Van der Loos 1991) or direct stimulation by the experimentator (Hurwitz et al. 1990, 1991, Jacobs and Juliano 1995). Sometimes the choice between two routes involves jumping to one of two or more platforms that are positioned and marked in such a way that an animal can investigate them using the vibrissae only (Guic--Robles et al. 1989, Carvell and Simons 1990, Barneoud et al. 1991, Guic-Robles et al. 1992). These models can not be used for investigating IEG expression since the time required to learn the basic task can be as long as 2 weeks whereas IEG expression is often sudden and temporary, detected 1-2 h after sensory stimulation (Mack and Mack 1992, Steiner and Gerfen 1994, Chaudhuri et al. 1997). However, such paradigms can be redesigned with added transfer training session (compare: Nikolaev et al. 1992). For example, rats could be trained to discriminate between platforms (learning the basic task), then on the final day the platforms can have their surfaces (textures) modified to the extend that allows the animal to learn the new vibrissae-dependent task in a few hours. A different model was described by Siucińska and Kossut (1996) which combined electric shock (as US) with brushing the vibrissae of an immobilized mouse. This model is ideal for investigating IEG expression but it involves restraining of animals.

EXPRESSION OF *C-FOS* AND *ZIF268* IN BARREL CORTEX (LOOKING FOR GENES)

In unstimulated barrel cortex, there is a very low level of expression of *c-fos* in contrast to the high level of *zif268* expression (Mack and Mack 1992, Steiner and Gerfen 1994, Melzer and Steiner 1997). After depriva-

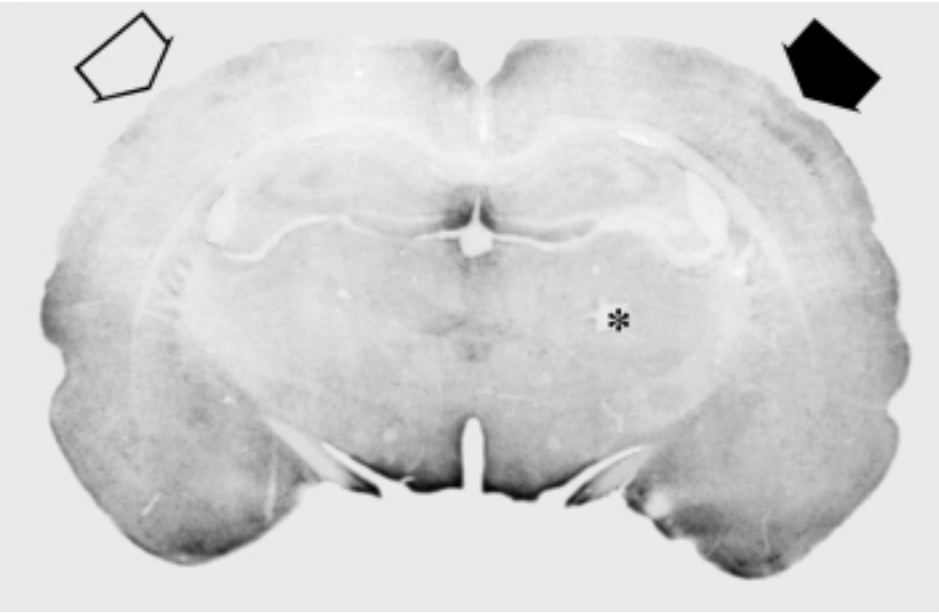

Fig. 2. c-Fos protein expression is induced in the barrel cortex following apomorphine injection, especially when the vibrissae are present. Empty arrow shows the barrel cortex corresponding to the deprived vibrissae. Full arrow indicates to the barrel cortex corresponding to the stimulated (spared) vibrissae. Asterisk, fiducial mark.

tion, i.e., clipping the vibrissae, no changes in *c-fos* expression are observed while the levels of *zif268* expression drop (Steiner and Gerfen 1994, Melzer and Steiner 1997, Filipkowski et al., unpublished results). Treatment of rats with apomorphine results in the accumulation of *c-fos* and *zif268* mRNA in various brain regions including somatosensory cortex (Steiner and Gerfen 1994). This effect is input specific, since clipping of the whiskers prevented the apomorphine-evoked increase of IEG expression in the corresponding barrel cortex. These observations were also confirmed on the protein level (Fig. 2; Filipkowski et al., unpublished results). Furthermore, Melzer and Steiner (1997) showed that the expression of both genes was largely restricted to the radial columns across the barrels representing the stimulated whiskers, with the magnitude of expression being proportional to the intensity of stimulation. Previously, Mack and Mack (1992) achieved unilateral cortical elevation of c-Fos and Zif268 protein expression by selective mechanical stimulation of the whiskers on one side of the snout under anesthesia. All these studies imply that sensory input is critical for *c-fos* and *zif268* activation in the barrel cortex, similar to the visual cortex (see: Kaczmarek and Chaudhuri 1997). In the two new paradigms (Filipkowski et al. 2000) there was an increase in c-Fos expression in barrel cortex corresponding to the brushed vibrissae and in barrel cortex of animals introduced to a new cage. In both models, this effect was most pronounced in layer IV and observed in layers II/III and V/VI. No effect of the stimulation on c-Fos expression was observed in layer VIb. Layers II-VI process sensory information (Waite and Tracey 1995) in contrast to layer VIb. This layer was also shown to exhibit specific pattern of gene expression (Valverde et al. 1989, Alcantara and Greenough 1993, Gaspar et al. 1995). Finally, it is worth mentioning that sensory stimulation also up-regulated the expression of brain-derived neurotrophic factor (BDNF, Rocamora et al. 1996) and zinc finger motif protein (NGFI-C, Mack et al. 1995) in barrel cortex.

CELLS AND PLASTICITY

Many observations, analogous to those described above regarding c-Fos and Zif268 expression patterns as well as the fact that these proteins are transcription factors prompted many investigators to come up with the hypothesis that the neurons with elevated expression of these IEG undergo plastic changes (Kaczmarek and Nikolajew 1990, Sheng and Greenberg 1990, Robertson 1992, Kaczmarek 1993a, b, Herdegen and Zimmermann 1995, Hughes and Dragunow 1995, Kaczmarek 1995). According to this view the role of these IEG would be information integration as the gene regulatory regions may act as coincidence detectors. However, the link between IEG and plasticity is still not firm and IEG' role may be also that of maintenance and replenishment only (discussed in: Kaczmarek 1995, Kaczmarek and Chaudhuri 1997).

It was shown that the longer exposure (4-90 days) to a novel environment causes a cascade of anatomical changes in the cortex (Wallace et al. 1992, Rosenzweig 1996, Rosenzweig and Bennett 1996, Kolb and Whishaw 1998). It is plausible that changes in *c-fos* and *zif268* gene expression are required for and trigger these long-term anatomical changes.

We observed only some cells in the barrel cortex that show elevated c-Fos expression after stimulation. Similar findings have been presented by Melzer and Steiner (1997). We have extended this observation to show that the majority of c-Fos-expressing cells are probably not inhibitory neurons, since they do not show parvalbumin staining. However, cells containing both c-Fos and parvalbumin were observed occasionally in all layers investigated. Parvalbumin, a calcium-binding protein, is a marker of inhibitory interneurons (Celio 1986, Ren et al. 1992, Kubota and Jones 1993, Hiscock et al. 1996). Our findings are in good agreement with the results obtained by Chaudhuri et al. (1995) who showed that the information-dependent expression of Zif268 in the cortex of monkeys was restricted to excitatory neurons, lacking parvalbumin. It remains to be clarified in further studies why excitatory neocortical neurons display increased c-Fos expression whereas the large, fast-spiking, non spiny interneurons on layer IV do not.

The whisker-to-barrel system offers exquisite possibilities for designing experiments investigating gene expression in the cortex evoked by sensory stimulation. The anatomy of the barrel cortex offers advantages for designing the experiments and use of imaging techniques. The new methods of stimulating whiskers should be helpful in these experiments.

ACKNOWLEDGEMENTS

The author is grateful to Yalin Wang, Junjiro Horiuchi, Avi Chaudhuri, and Leszek Kaczmarek for helpful comments on the manuscript and to IBRO and

NSF for supportive fellowships. The experimental work was supported by State Committee for Scientific Research (KBN, Poland) grants no. 6 P04A 064 10 and 6 P04A 008 08.

REFERENCES

Ahl A.S. (1986) The role of vibrissae in behavior: a status review. Vet. Res. Commun. 10: 245-268.

Alcantara A.A., Greenough W.T. (1993) Developmental regulation of Fos and Fos-related antigens in cerebral cortex, striatum, hippocampus, and cerebellum of the rat. J. Comp. Neurol. 334: 75-85.

Anokhin K.V., Mileusnic R., Shamakina I.Y., Rose S.P. (1991) Effects of early experience on c-fos gene expression in the chick forebrain. Brain Res. 544: 101-107.

Barneoud P., Gyger M., Andres F., van der Loos H. (1991) Vibrissa-related behavior in mice: transient effect of ablation of the barrel cortex. Behav. Brain Res. 44: 87-99.

Beck C.H., Chow H.L., Cooper S.J. (1986) Dose-related response of male rats to apomorphine: snout contact in the open-field. Physiol. Behav. 37: 819-825.

Biały M., Beck J. (1993) The influence of vibrissae removal on copulatory behaviour in male rats. Acta Neurobiol. Exp. 53: 415-419.

Bugbee N.M., Eichelman B.S., Jr. (1972) Sensory alterations and aggressive behavior in the rat. Physiol. Behav. 8: 981-985.

Carvell G.E., Simons D.J. (1990) Biometric analyses of vibrissal tactile discrimination in the rat. J. Neurosci. 10: 2638-2648.

Celio M.R. (1986) Parvalbumin in most gamma-aminobutyric acid-containing neurons of the rat cerebral cortex. Science 231: 995-997.

Chaudhuri A., Cynader M.S. (1993) Activity-dependent expression of the transcription factor Zif268 reveals ocular dominance columns in monkey visual cortex. Brain Res. 605: 349-353.

Chaudhuri A., Matsubara J.A., Cynader M.S. (1995) Neuronal activity in primate visual cortex assessed by immunostaining for the transcription factor Zif268. Vis. Neurosci. 12: 35-50.

Chaudhuri A., Nissanov J., Larocque S., Rioux L. (1997) Dual activity maps in primate visual cortex produced by different temporal patterns of zif268 mRNA and protein expression. Proc. Natl Acad. Sci. USA. 94: 2671-2675.

Dragunow M., Faull R. (1989) The use of c-fos as a metabolic marker in neuronal pathway tracing. J. Neurosci. Methods 29: 261-265.

Dunn-Meynell A.A., Benowitz L.I., Levin B.E. (1992) Vibrissectomy induced changes in GAP-43 immuno-reactivity in the adult rat barrel cortex. J. Comp. Neurol. 315: 160-170.

Eilam D., Golani I. (1989) Home base behavior of rats (Rattus norvegicus) exploring a novel environment. Behav. Brain Res. 34: 199-211.

Filipkowski R.K., Rydz M., Berdel B., Morys J., Kaczmarek L. (2000) Tactile experience induces c-fos expression in rat barrel cortex. Learn. Mem. 7: 116-122.

Fox K. (1992) A critical period for experience-dependent synaptic plasticity in rat barrel cortex. J. Neurosci. 12: 1826-1838.

Fuchs J.L., Salazar E. (1998) Effects of whisker trimming on GABA(A) receptor binding in the barrel cortex of developing and adult rats. J. Comp. Neurol. 395: 209-216.

Gaspar P., Bloch B., Le Moine C. (1995) D1 and D2 receptor gene expression in the rat frontal cortex: cellular localization in different classes of efferent neurons. Eur. J. Neurosci. 7: 1050-1063.

Guic-Robles E., Jenkins W.M., Bravo H. (1992) Vibrissal roughness discrimination is barrelcortex-dependent. Behav. Brain Res. 48: 145-152.

Guic-Robles E., Valdivieso C., Guajardo G. (1989) Rats can learn a roughness discrimination using only their vibrissal system. Behav. Brain Res. 31: 285-289.

Gustafson J.W., Felbain-Keramidas S.L. (1977) Behavioral and neural approaches to the function of the mystacial vibrissae. Psychol. Bull. 84: 477-488.

Herdegen T., Zimmermann M. (1995) Immediate early genes (IEGs) encoding for inducible transcription factors (ITFs) and neuropeptides in the nervous system: functional network for long-term plasticity and pain. Prog. Brain Res. 104: 299-321.

Hiscock J.J., MacKenzie L., Willoughby J.O. (1996) Fos induction in subtypes of cerebrocortical neurons following single picrotoxin-induced seizures. Brain Res. 738: 301-312.

Hope B.T., Kelz M.B., Duman R.S., Nestler E.J. (1994a) Chronic electroconvulsive seizure (ECS) treatment results in expression of a long-lasting AP-1 complex in brain with altered composition and characteristics. J. Neurosci. 14: 4318-4328.

Hope B.T., Nye H.E., Kelz M.B., Self D.W., Iadarola M.J., Nakabeppu Y., Duman R.S., Nestler E.J. (1994b) Induction of a long-lasting AP-1 complex composed of altered Fos-like proteins in brain by chronic cocaine and other chronic treatments. Neuron 13: 1235-1244.

Hughes P., Dragunow M. (1995) Induction of immediate-early genes and the control of neurotransmitter-regulated gene expression within the nervous system. Pharmacol. Rev. 47: 133-178.

Hurwitz B.E., Dietrich W.D., McCabe P.M., Alonso O., Watson B.D., Ginsberg M.D., Schneiderman N. (1991) Amphetamine promotes recovery from sensory-motor integration deficit after thrombotic infarction of the primary somatosensory rat cortex. Stroke 22: 648-654.

Hurwitz B.E., Dietrich W.D., McCabe P.M., Watson B.D., Ginsberg M.D., Schneiderman N. (1990) Sensory-motor

deficit and recovery from thrombotic infarction of the vibrissal barrel-field cortex. Brain Res. 512: 210-220.

Jabłonska B., Kossut M., Skangiel-Kramska J. (1996) Transient increase of AMPA and NMDA receptor binding in the barrel cortex of mice after tactile stimulation. Neurobiol. Learn. Mem. 66: 36-43.

Jacobs S.E., Juliano S.L. (1995) The impact of basal forebrain lesions on the ability of rats to perform a sensory discrimination task involving barrel cortex. J. Neurosci. 15: 1099-1109.

Jacquin M.F., Zahm D.S., Henderson T.A., Golden J.P., Johnson E.M., Renehan W.E., Klein B.G. (1993) Structure-function relationships in rat brainstem subnucleus interpolaris. X. Mechanisms underlying enlarged spared whisker projections after infraorbital nerve injury at birth. J. Neurosci. 13: 2946-2964.

Kaczmarek L. (1993a) Glutamate receptor-driven gene expression in learning. Acta Neurobiol. Exp. (Warsaw) 53: 187-196.

Kaczmarek L. (1993b) Molecular biology of vertebrate learning: is c-fos a new beginning? J. Neurosci. Res. 34: 377-381.

Kaczmarek L. (1995) Towards understanding of the role of transcription factors in learning processes. Acta Biochim. Pol. 42: 221-226.

Kaczmarek L., Chaudhuri A. (1997) Sensory regulation of immediate-early gene expression in mammalian visual cortex: implications for functional mapping and neural plasticity. Brain Res. Brain Res. Rev. 23: 237-256.

Kaczmarek L., Nikołajew E. (1990) C-fos protooncogene expression and neuronal plasticity. Acta Neurobiol. Exp. 50: 173-179.

Kaminska B., Filipkowski R.K., Zurkowska G., Lason W., Przewłocki R., Kaczmarek L. (1994) Dynamic changes in the composition of the AP-1 transcription factor DNA-binding activity in rat brain following kainate-induced seizures and cell death. Eur. J. Neurosci. 6: 1558-1566.

Kasof G.M., Mandelzys A., Maika S.D., Hammer R.E., Curran T., Morgan J.I. (1995) Kainic acid-induced neuronal death is associated with DNA damage and a unique immediate-early gene response in c-fos-lacZ transgenic rats. J. Neurosci. 15: 4238-4249.

Kimpo R.R., Doupe A.J. (1997) FOS is induced by singing in distinct neuronal populations in a motor network. Neuron 18: 315-325.

Kolb B., Whishaw I.Q. (1998) Brain plasticity and behavior. Annu. Rev. Psychol. 49: 43-64.

Kossut M. (1992a) Effects of sensory deprivation upon a single cortical vibrissal column: a 2DG study. Exp. Brain Res. 90: 639-642.

Kossut M. (1992b) Plasticity of the barrel cortex neurons. Prog. Neurobiol. 39: 389-422.

Kossut M., Hand P.J., Greenberg J., Hand C.L. (1988) Single vibrissal cortical column in SI cortex of rat and its alterations in neonatal and adult vibrissa-deafferented animals: a quantitative 2DG study. J. Neurophysiol. 60: 829-852.

Kubota Y., Jones E.G. (1993) Co-localization of two calcium binding proteins in GABA cells of rat piriform cortex. Brain Res. 600: 339-344.

Levin B.E., Dunn-Meynell A. (1991) Adult rat barrel cortex plasticity occurs at 1 week but not at 1 day after vibrissectomy as demonstrated by the 2-deoxyglucose method. Exp. Neurol. 113: 237-248.

Levin B.E., Dunn-Meynell A. (1993) Regulation of growth--associated protein 43 (GAP-43) messenger RNA associated with plastic change in the adult rat barrel receptor complex. Brain Res. Mol. Brain Res. 18: 59-70.

Lipp H.P., Van der Loos H. (1991) A computer-controlled Y-maze for the analysis of vibrissotactile discrimination learning in mice. Behav. Brain Res. 45: 135-145.

Lukasiuk K., Savonenko A., Nikolaev E., Rydz M., Kaczmarek L. (1999) Defensive conditioning-related increase in AP-1 transcription factor in the rat cortex. Brain Res. Mol. Brain Res. 67: 64-73.

Mack K.J., Mack P.A. (1992) Induction of transcription factors in somatosensory cortex after tactile stimulation. Brain Res. Mol. Brain Res. 12: 141-147.

Mack K.J., Yi S.D., Chang S., Millan N., Mack P. (1995) NGFI-C expression is affected by physiological stimulation and seizures in the somatosensory cortex. Brain Res. Mol. Brain Res. 29: 140-146.

Melzer P., Steiner H. (1997) Stimulus-dependent expression of immediate-early genes in rat somatosensory cortex. J. Comp. Neurol. 380: 145-153.

Melzer P., Van der Loos H., Dorfl J., Welker E., Robert P., Emery D., Berrini J.C. (1985) A magnetic device to stimulate selected whiskers of freely moving or restrained small rodents: its application in a deoxyglucose study. Brain Res. 348: 229-240.

Montero V.M. (1997) c-fos induction in sensory pathways of rats exploring a novel complex environment: shifts of active thalamic reticular sectors by predominant sensory cues. Neuroscience 76: 1069-1081.

Morgan J.I., Curran T. (1991) Stimulus-transcription coupling in the nervous system: involvement of the inducible proto-oncogenes fos and jun. Annu. Rev. Neurosci. 14: 421-451.

Nikolaev E., Werka T., Kaczmarek L. (1992) C-fos protooncogene expression in rat brain after long-term training of two-way active avoidance reaction. Behav. Brain Res. 48: 91-94.

Polley D.B., Chen-Bee C.H., Frostig R.D. (1999) Two directions of plasticity in the sensory-deprived adult cortex [see comments]. Neuron 24: 623-637.

Ren J.Q., Aika Y., Heizmann C.W., Kosaka T. (1992) Quantitative analysis of neurons and glial cells in the rat somatosensory cortex, with special reference to GABAergic

neurons and parvalbumin-containing neurons. Exp. Brain Res. 92: 1-14.

Robertson H.A. (1992) Immediate-early genes, neuronal plasticity, and memory. Biochem. Cell Biol. 70: 729-737.

Rocamora N., Welker E., Pascual M., Soriano E. (1996) Upregulation of BDNF mRNA expression in the barrel cortex of adult mice after sensory stimulation. J. Neurosci. 16: 4411-4419.

Rosenzweig M.R. (1996) Aspects of the search for neural mechanisms of memory. Annu. Rev. Psychol. 47: 1-32.

Rosenzweig M.R., Bennett E.L. (1996) Psychobiology of plasticity: effects of training and experience on brain and behavior. Behav. Brain Res. 78: 57-65.

Sagar S.M., Sharp F.R., Curran T. (1988) Expression of c-fos protein in brain: metabolic mapping at the cellular level. Science 240: 1328-1331.

Savonenko A., Filipkowski R.K., Werka T., Zielinski K., Kaczmarek L. (1999) Defensive conditioning-related functional heterogeneity among nuclei of the rat amygdala revealed by c-Fos mapping. Neuroscience 94: 723-733.

Schiffman H.R., Lore R., Passafiume J., Neeb R. (1970) Role of vibrissae for depth perception in the rat (Rattus norvegicus). Anim. Behav. 18: 290-292.

Schwarting R.K., Pei G., Soderstrom S., Ebendal T., Huston J.P. (1994) Unilateral stimulation or removal of rat vibrissae: analysis of nerve growth factor and tyrosine hydroxylase mRNA in the brain. Behav. Brain Res. 60: 63-71.

Sharp F.R., Sagar S.M., Swanson R.A. (1993) Metabolic mapping with cellular resolution: c-fos vs. 2-deoxyglucose. Crit. Rev. Neurobiol. 7: 205-228.

Sheng M., Greenberg M.E. (1990) The regulation and function of c-fos and other immediate early genes in the nervous system. Neuron 4: 477-485.

Siucińska E., Kossut M. (1994) Short term changes of cortical body maps following partial vibrissectomy in adult mice. Acta Neurobiol. Exp. 54: 345-354.

Siucińska E., Kossut M. (1996) Short-lasting classical conditioning induces reversible changes of representational maps of vibrissae in mouse SI cortex—a 2DG study. Cereb. Cortex 6: 506-513.

Smeyne R.J., Schilling K., Oberdick J., Robertson L., Luk D., Curran T., Morgan J.I. (1993) A fos-lac Z transgenic mouse that can be used for neuroanatomic mapping. Adv. Neurol. 59: 285-291.

Smeyne R.J., Schilling K., Robertson L., Luk D., Oberdick J., Curran T., Morgan J.I. (1992) fos-lacZ transgenic mice: mapping sites of gene induction in the central nervous system. Neuron 8: 13-23.

Steiner H., Gerfen C.R. (1994) Tactile sensory input regulates basal and apomorphine-induced immediate- early gene expression in rat barrel cortex. J. Comp. Neurol. 344: 297-304.

Szechtman H., Ornstein K., Teitelbaum P., Golani I. (1982) Snout contact fixation, climbing and gnawing during apomorphine stereotypy in rats from two substrains. Eur. J. Pharmacol. 80: 385-392.

Valverde F., Facal-Valverde M.V., Santacana M., Heredia M. (1989) Development and differentiation of early generated cells of sublayer VIb in the somatosensory cortex of the rat: a correlated Golgi and autoradiographic study. J. Comp. Neurol. 290: 118-140.

Vincent S.B. (1912) The function of the vibrissae in the behaviour of the white rat. Behav. Monogr. 1: 1-81.

Waite P.M.E., Tracey D.J. (1995) Trigeminal sensory system. In: The rat nervous system, 2nd ed. (Ed. G. Paxinos). Academic Press, San Diego, p. 705-724.

Wallace C.S., Kilman V.L., Withers G.S., Greenough W.T. (1992) Increases in dendritic length in occipital cortex after 4 days of differential housing in weanling rats. Behav. Neural Biol. 58: 64-68.

Welker E., Rao S.B., Dorfl J., Melzer P., van der Loos H. (1992) Plasticity in the barrel cortex of the adult mouse: effects of chronic stimulation upon deoxyglucose uptake in the behaving animal. J. Neurosci. 12: 153-170.

Welker E., Soriano E., Dorfl J., Van der Loos H. (1989) Plasticity in the barrel cortex of the adult mouse: transient increase of GAD-immunoreactivity following sensory stimulation. Exp. Brain Res. 78: 659-664.

Welker W.I. (1964) Analysis of sniffing of the albino rat. Behaviour 22: 223-244.