Odorants Stimulate the ERK/Mitogen-activated Protein Kinase Pathway and Activate cAMP-response Element-mediated Transcription in Olfactory Sensory Neurons

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Olfactory sensory neurons (OSNs) respond acutely to volatile molecules and exhibit adaptive responses including desensitization to odorant exposure. Although mechanisms for short term adaptation have been described, there is little evidence that odorants cause long lasting, transcription-dependent changes in OSNs. Here we report that odorants stimulate cAMP-response element (CRE)-mediated transcription in OSNs through Ca2+ activation of the ERK/MAPK/p90<sup>rsk</sup> pathway. Odorant stimulation of ERK phosphorylation was ablated by inhibition of calmodulin-dependent protein kinase II suggesting that odorant activation of ERK is mediated through this kinase. Moreover, a brief exposure in vivo to an odorant in vapor phase stimulated CRE-mediated gene transcription in discrete populations of OSNs. These data suggest that like central nervous system neurons, OSNs may undergo long term adaptive changes mediated through CRE-mediated transcription.

Genes encoding odorant receptors compose an estimated 1% of the genome, reflecting the ancient and primal nature of olfaction. The relative abundance of these genes also explains how animals can discriminate among the innumerable combinations of odorous compounds present in the environment (1, 3). Odorant receptors have distinct but overlapping affinities for odorants and exhibit a semi-organized pattern of expression in the convoluted topography of the olfactory epithelium (4, 5). These features of the sensory apparatus suggest that the initial encoding of odorant features is combinatorial, integrating spatio-temporal differences in receptor activation throughout the epithelium as well as differences in odorant concentration (6). Although each of the perhaps ~1000 individual odorant receptors has unique specificity for ligand binding, most if not all olfactory signaling is mediated through cAMP (7–10). Odorant receptor activation increases intracellular cAMP via an interaction with G<sub>olf</sub> or G<sub>i</sub> and adenyl cyclase activation. This leads to opening of the cyclic nucleotide-gated (CNG)1 ion channel, membrane depolarization, and the generation of action potentials (11). In support of this model, disruption of the genes for G<sub>olf</sub> (12), type III adenylyl cyclase (AC3) (13), or CNG (14) in mice ablates electro-olfactogram responses to odorants in the olfactory epithelium. Furthermore, AC3 mutant mice fail several odorant-based behavioral tests indicating that adenyl cyclase and cAMP signaling are critical for olfactory-dependent behavior.

Activation of the CNG ion channel in OSNs causes a depolarization and a transient increase in intracellular Ca<sup>2+</sup> (15–17). This Ca<sup>2+</sup> signal, to the opposing effect, can lead to activation of Ca2+/CaM-activated phosphodiesterase PDE1C2 (18) and CaM-dependent protein kinase II (CaMKII) which phosphorylates and inhibits AC3 (19–21). Therefore, CaMKII inhibition of AC3 may contribute to termination of olfactory signaling. This idea is supported by data showing that treatment of olfactory sensory neurons with CaMKII inhibitors impairs odor adaptation (22). Other kinases that contribute to modulation and desensitization of olfactory signaling include GRK-3 (23, 24), as well as CaM-dependent protein kinase (PKA) and protein kinase C (PKC) (25). Thus rapid activation and inactivation of the cAMP signal are at the core of a system developed for transient signaling to the olfactory bulb and higher CNS where olfactory memories are thought to be stored.

There are several reports of sensitization of peripheral sensory neurons to odorants at the step of primary detection. By using Pacific Coho salmon, we demonstrated a preference for phenylethyl alcohol in salmon that had been imprinted with the odorant as juveniles, and we found that guanylyl cyclase activity in olfactory cilia isolated from them was enhanced specifically in response to phenylethyl alcohol 2 years after exposure to the odorant (26). Furthermore, mice chronically exposed to specific odorants develop an enhanced EOG signal in response to these odorants (27). Cultured rat OSNs also show an enhanced cAMP signal in response to the second of two odorant exposures (28). These reports suggest the interesting possibility that olfactory sensory neurons may exhibit some form of cellular memory, and they are not simply conduits for transfer of olfactory information to the olfactory bulb.

Because of the well established role of the ERK/MAP kinase regulatory system and CRE-mediated transcription for neuroplasticity in the CNS (for general reviews see Refs. 29–31), we carried out experiments to determine whether exposure to odorants activates these pathways using cultured OSNs and a CRE/LacZ transgenic reporter mouse strain (32, 33). We report the discovery of an unexpected signaling pathway intrinsic to

PKA, cAMP-dependent protein kinase; PKC, protein kinase C; CNS, central nervous system; ERK, extracellular signal-regulated kinase; MAP, mitogen-activated protein; MAPK, MAP kinase; MEK, ERK/MAP kinase; EOG, electro-olfactogram.

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odorant stimulation of mammalian OSNs, providing evidence that this sensory tissue may exhibit neuroplasticity akin to that of CNS neurons. Our data indicate that a brief exposure to odorants activates ERK/MAP kinase signaling and initiates CRE-mediated gene transcription.

**MATERIALS AND METHODS**

**Primary Culture of Neonatal Rat Olfactory Sensory Neurons**—Cultures of primary OSNs were prepared as described by Ronnett et al. (28), with modifications. In brief, olfactory turbinates from 20 to 30 rat pups at 1–2 days of age were removed by dissection, minced, and subjected to mild enzymatic digestion with rocking at 37 °C for 1 h. Subsequently, the tissue was passed through nylon filters of sequentially smaller pore size (250, 50, and 10 μm), and cells were plated at an approximate density of 10 (10) cells/ml on 12-well tissue culture plates that had been coated with 25 ng/ml mouse laminin (Life Technologies, Inc.). Cells were plated and maintained in minimum essential medium containing n-valine (Life Technologies, Inc.), 10% dialyzed fetal bovine serum (Life Technologies, Inc.), 5% NuSerum (Becton Dickinson), and 10 μM Ara-C (Sigma). Experiments were typically performed at day 5 in vitro to allow non-neuronal cells to be selected from the culture.

**Immunocytochemical Detection of Phospho-ERK I/II in Cultured OSNs**—Cells were cultured as described above but were plated on glass coverslips or tissue culture plates as described above. After 1 h in minimum essential medium, cells were stimulated with the indicated odorant at 25 μg/ml for 1 h. One hour prior to stimulation, the culture medium was replaced with pre-warmed serum-free minimum essential medium, n-valine supplemented with 50 mM Hepes buffer, pH 7.4 (MEM-H). Cells were stimulated with either 5 μM forskolin or 15 μM odorant (citralva, isoamyl acetate, or ethyl vanillin) for 4 min, immediately after which all cells were fixed in 5% paraformaldehyde. Immunodetection of phospho-ERK I/II was performed using standard procedures with a rabbit anti-phospho-ERK I/II antibody (New England Biolabs) at 1:500 dilution and a Texas Red mouse anti-rabbit IgG antibody (Jackson Immunochemicals) at 1:500 dilution. Images were captured on a Bio-Rad MRC laser scanning confocal microscope.

**Western Blot Analysis of MEK, ERK I/II, p90_56, and CREB Phosphorylation**—Neurons were cultured and plated on 12-well tissue culture plates as described above. After 1 h in minimum essential medium, n-valine/Hepes, neurons were stimulated with the indicated odorant at 15 or 20 μM A23187. Inhibitors (U0126 and KN-62) were used at 10 μM for 1 h prior to stimulation. After odorant stimulation for the indicated times, cells were harvested in sample buffer (40 mM Tris, pH 6.9, 2 mM EGTA, 10% glycerol, 0.04% bromphenol blue, and 2% SDS) and samples were boiled for 10 min. Samples were subjected to 10% SDS-polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes, which were then blocked in 10% milk in PBST. Membranes were incubated with antibodies to the phosphorylated and activated forms of Raf, MEK, ERK I/II, p90_56, and CREB (New England Biolabs), each at 1:1000 dilution, and an antibody to ERK I/II (Santa Cruz Biotechnology) at 1:1000 to control for protein loading.

**Electro-olfactogram Recordings**—EOG recordings were performed as described previously (14), with minor changes. In brief, mice 14–16 weeks old were sacrificed by decapitation, and heads were bisected through the septum. Septal cartilage was peeled away to expose the apical surface of the olfactory turbinates, from which recordings were taken using an agar- and saline-filled glass microelectrode. The EOG, basal potential minus apical potential, was taken in the open circuit configuration, whereas odorants were applied to the epithelia in 1-s ant puffs produced the same characteristic desensitizing response in vehicle and U0126-treated turbinates, and responses of odorants. Immunocytochemical analysis of cultured OSNs stimulated for 4 min with the odorant citralva revealed robust activation of ERK/MAP kinase in a subpopulation of neurons (Fig. 1a). Whereas forskolin, a direct activator of adenylyl cyclases, stimulated ERK phosphorylation in a majority of neurons (85%) (Fig. 1, a and b), citralva produced this effect in only ~38% of the neurons (Fig. 1, a and b). This observation is consistent with the expression of only a subset of odorant receptors in individual OSNs, yielding a heterogeneously responsive population. The relatively high percentage of cells activated by citralva is not unexpected; the citralva preparation used is a mixture of odorants that stimulates multiple receptors in olfactory cilia. For example, citralva stimulates CaMKII phosphorylation of AC3 in 20–30% of cultured OSNs (21).

Odorant stimulation of cAMP transients and Ca2+ increases in cultured OSNs is quite rapid and occurs within seconds after exposure to odorants (10, 28, 38). If ERK/MAP kinase activation contributes to primary olfactory signaling, it should also occur within this time scale. The kinetics for odorant stimulation of ERK I/II (p44/p42) activation were monitored by Western analysis of cultured OSNs stimulated with several different odorants (Fig. 2). The odorants citralva, isoamyl acetate, and ethyl vanillin stimulated robust phosphorylation of ERK I/II, peaking at 5 min and returning to near control levels by 20 min.

Since the kinetics for activation of ERK/MAP kinase were significantly slower than odorant-stimulated increases in cAMP and Ca2+, ERK activation may not play an important role in primary olfactory signaling. This question was addressed by examining the effects of a MEK inhibitor on electro-olfactogram (EOG) responses stimulated by odorants. The EOG is a measure of odorant-stimulated field potentials generated by changes in ion conductance across the ciliary, dendritic, and somatic membranes of OSNs in an intact olfactory epithelium (39). Incubating isolated turbinates in oxygenated MEM-H containing the MEK inhibitor, U0126 (40), 90 min before recording the EOG response produced no significant perturbation of the amplitude or kinetics of field potentials elicited by a single application of citralva (Fig. 3). The response to a train of odorant puffs produced the same characteristic desensitizing response in vehicle and U0126-treated turbinates, and responses to multiple, spaced applications of odorant were also identical.

Since we were particularly interested in odorant stimulation of downstream transcriptional events, we also monitored odorant activation of p90_56, a CREB kinase that is activated by ERK/MAP kinase. In vivo, CREB phosphorylation at its transactivation site, Ser-133 (41, 42), was also analyzed. Odorants stimulated activation of p90_56 that persisted for at least 20 min (Fig. 4c). CREB phosphorylation was also transiently increased by citralva, in accord with a previous report that also showed formation of elements of a transcriptional complex (Fig. 4d) (43). ERK activation and phosphorylation of CREB were both inhibited by U0126, consistent with the notion that odorants stimulate CREB phosphorylation through the MEK/ERK/
p90\textsuperscript{rb} pathway, one of the major pathways that mediates Ca\textsuperscript{2+} stimulation of CREB phosphorylation in hippocampal neurons and PC12 cells (37). Thus, odorants stimulate a robust induction of ERK/MAP kinase signaling that leads to phosphorylation of the transcription factor CREB.

In attempt to determine mechanisms linking odorant-stimulation to activation of ERK/MAP kinase signaling in OSNs, we measured ERK activation in the presence of several kinase inhibitors after 5 min of odorant stimulation. Interestingly, pretreatment of OSNs with the CaMKII inhibitor KN-62 markedly attenuated the induction of phospho-ERK in response to citralva, ethyl vanillin, or the calcium ionophore A23187 (Fig. 5). Inhibitors of other protein kinases including PKA ((R\textsuperscript{P})-8-bromo-cAMPs, (R\textsuperscript{P})-CPT-cAMPs), PKC (Go\textsuperscript{¢} 6983, chelerythrin), or PKG (KT5823) produced no discernible effect on odorant-stimulated ERK I/II phosphorylation (data not shown). These data suggest that Ca\textsuperscript{2+} increases caused by odorants stimulate CaMKII, which in turn leads to activation of the ERK/MAP kinase pathway. Odorant stimulation of ERK/MAP kinase in OSNs may be due to CaMKII phosphorylation and inhibition of p135 SynGAP by CaMKII (44). Thus, we may have identified another mechanism, in addition to CaMKII inhibition of AC3, by which CaMKII contributes to adaptive responses to odorants.
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The kinetics of ERK I/II activation, phosphorylation of CREB, and lack of acute effect of MEK inhibition on the EOG response suggested that the target for odorant-stimulated ERK I/II activity may be enhanced transcription. Given that odorants stimulated CREB phosphorylation and Ca\(^{2+}\) stimulation of CRE-mediated transcription in CNS neurons is mediated by the MEK/ERK/p90\(^{rsk}\) pathway, we tested the hypothesis that simple odorant exposure may stimulate this pathway in OSNs. This was accomplished using a CRE/LacZ reporter mouse strain we developed to monitor activation of CRE-mediated transcription by various physiological stimuli (32, 33). CRE/LacZ mice were exposed to a gentle stream of air carrying the vapor phase of a 1 mM solution of the odorant citralva for 2 min. Isolated olfactory epithelia were then analyzed for CRE-mediated transcription by Western analysis and immunocytochemistry for β-galactosidase expression. Compared with animals that received no exogenous odorant exposure, the citralva-exposed mice exhibited a substantial induction of transgene expression by Western analysis (Fig. 6a), and ICC analysis revealed that neurons immunopositive for β-galactosidase were restricted predominantly to a layer of the epithelium located in zone four (Fig. 6b). Thus, a simple odorant stimulus is sufficient to lead to a transcription event in OSN that has been implicated in the enactment of long term changes and memory formation in CNS tissue but, until now, was not known to occur in sensory tissue.

**DISCUSSION**

The concept that sensory tissue might have the ability to adapt to specific, frequently encountered stimuli such that it is optimized for subsequent detection makes intuitive sense. Chemosensation, evolutionarily ancient and essential to the survival of countless organisms, would seem particularly likely to possess such a capacity. Although OSNs exhibit rapid adaptive responses to odorants including desensitization (18, 24, 25, 45, 46), sensory structures such as OSNs have generally thought of as conductors of information, not participating actively in its subsequent use. As such, reports of longer lasting olfactory sensory neuron sensitizations are provocative (26–28). However, there is currently little insight concerning signaling mechanisms that might mediate long lasting changes in OSNs, other than the initial cAMP and Ca\(^{2+}\) increases caused by odorant stimulation.

We describe here the induction of the ERK/MAP kinase pathway in mammalian OSNs in response to a variety of odorants, exposing a novel component of their signaling properties that may have an important role in olfaction. Pharmacological inhibition of CaMKII resulted in a diminished ability of odorants to stimulate ERK I/II phosphorylation. Furthermore, odorants stimulated ERK/MAP kinase-dependent phosphorylation of CREB, suggesting the possibility that individual OSNs link odorant detection to gene transcription from CRE-containing promoters. However, CREB phosphorylation is necessary but not sufficient for stimulation of CRE-mediated transcription (32, 47–49). Consequently, it was critical to determine whether CRE-mediated transcription is activated in OSNs when an animal is exposed to an odorant. We discovered that brief exposure *in vivo* to an odorant leads to region-specific

![Fig. 3. Inhibition of MEK does not acutely affect EOG. Isolated olfactory turbinates were examined for their electrophysiological response to the odorant citralva with or without inhibition of MEK by U0126. Upper traces (Single) are the EOG responses when turbinates were treated with two single puffs of citralva separated by 1 min in the absence (vehicle) or presence of 50 μM U0126. Lower traces (Train) are the EOG responses when turbinates were treated with a single citralva puff following a train of 10 puffs delivered at 1 Hz in the absence (vehicle) or presence of 50 μM U0126.](http://www.jbc.org/)

![Fig. 4. Citralva stimulates the activation of Raf, ERK, p90\(^{rsk}\), and CREB. a, the ability of citralva to activate other members of the ERK/MAP kinase cascade in cultured OSNs was examined by Western analysis. Stimulation with citralva led to phosphorylation of Raf, MEK, ERK I/II, and p90\(^{rsk}\). Levels of phospho-Raf and MEK were sustained for 20 min, whereas downstream targets ERK I/II and p90\(^{rsk}\) displayed more transient kinetics of phosphorylation. b, the ability of citralva to stimulate CREB phosphorylation and its dependence on ERK I/II activity were examined in cultured OSNs by Western analysis. Stimulation with citralva led to phosphorylation of CREB that reached a maximum at 5–10 min. Pretreatment of cells with a MEK inhibitor, 10 μM U0126, for 90 min significantly attenuated citralva-stimulated CREB phosphorylation.](http://www.jbc.org/)
CRE-mediated gene transcription in the olfactory epithelium. Interestingly, genetic mutation of the Ras homologue LET-60 Ras disrupts chemotaxis in Caenorhabditis elegans, suggesting that ERK/MAP kinase may contribute to olfactory detection in simpler organisms (50). In contrast to our study with mice that demonstrated odorant stimulation of ERK/MAP kinase maximally at 5 min, odorant stimulation of ERK/MAP kinase in C. elegans occurs within seconds. This suggests that the ERK/MAP kinase pathway may play different roles in vertebrate and invertebrate olfaction.

Activation of the MAPK pathway in neurons occurs via differing mechanisms and has a number of physiological consequences (for a review see Ref. 31). Ca²⁺-stimulated CREB-dependent gene transcription in the hippocampus requires ERK/I/II activation and supports learning and memory (37, 51, 52). Moreover, the same signal transduction pathway that is important for synaptic plasticity also contributes to neuronal survival. For example, brain-derived neurotrophic factor blocks apoptosis in cortical neurons by stimulation of the MAPK pathway (53, 54). Possible mechanisms linking odorant receptor stimulation to ERK/MAP kinase activity include those proceeding through Ras-GRF (44) and cAMP-GEFs (55). Indirect mechanisms for stimulation of Ras activity via PKA and CaMKII have also been demonstrated (56–59). KN-62 has been reported to have nonkinase-directed effects including blockade of calcium and/or potassium channels. To discount these possibilities from our observations, we also treated cultured OSNs with the calcium ionophore A23187 with and without KN-62 preincubation. A23187 stimulated a robust ERK I/II phosphorylation that was significantly inhibited by KN-62, indicating that KN-62 most likely exerts its inhibition of odorant-stimulated ERK I/II phosphorylation downstream of membrane ion channels, on CaMKII. Our finding that inhibition of CaMKII activity attenuates the odorant and Ca²⁺ ionophore stimulation of ERK I/II phosphorylation is, to our knowledge, the first such observation in olfactory neurons. A novel implication is that CaMKII, which phosphorylates and inhibits AC3, links the termination of the cAMP signal to activation of ERK/MAP kinase. This raises the interesting concept that CaMKII functions as a “gatekeeper” in regulating downstream signaling in OSNs.

Transcription of gene families activated through the CRE/CRE pathway is thought to play a major role in several forms...
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of neuroplasticity in the CNS including long lasting long term potentiation and memory for contextual and passive avoidance-associative learning (32, 33). Furthermore, a brief exposure to light during the subjective night activates the ERK/MAP kinase signaling cascade in suprachiasmatic nuclei, and there are striking circadian variations in MAPK activity and CRE-mediated transcription within the suprachiasmatic nuclei, suggesting that the MAPK cascade is involved in clock rhythmicity (60, 61). Activation of CRE-mediated transcription may also play an important role for developmental neuronal plasticity in the CNS (62, 63). In this study, we have discovered a new odorant-stimulated signal transduction pathway in OSNs that activates the CREB/CRE transcriptional pathway and provides a mechanistic framework with which to understand long term adaptive changes in OSNs. Our data are the first to show an activity-dependent stimulation of ERK/MAP kinase signaling and CRE-mediated transcription in sensory neurons. This discovery may broaden the regulatory role of the ERK/CREB/CRE transcriptional pathway to include adaptive changes in sensory tissue.

REFERENCES

1. Buck, L. & Axel, R. (1991) Cell 65, 175–187
2. Levy, N. S., Bakalyar, H. A. & Reed, R. R. (1991) J. Steroid Biochem. Mol. Biol. 39, 633–637
3. Parmentier, M., Libert, F., Schurmans, S., Schiffmann, S., Lefort, A., Eggerickx, D., Ledent, C., Mollereau, C., Gerard, C., Perret, J., Grootegoed, A., and Vassart, G. (1992) Nature 353, 435–455
4. Mombaerts, P., Wang, D., Dalcq, C., Zhao, S. K., Nemes, A., Mendelson, M., Edmondson, J., and Axel, R. (1995) Cell 87, 675–686
5. Malnic, B., Hirota, J., Sato, T., and Bock, L. B. (1999) Cell 96, 713–723
6. Duchamp-Viret, P., Chapat, M. A., and Dautry, A. (1999) Science 284, 2171–2174
7. Pace, U., Hanski, E., Salomon, Y. and Lancet, D. (1985) Nature 316, 255–258
8. Sklar, P. B., Anhalt, R. R. and Snyder, S. H. (1986) J. Biol. Chem. 261, 15538–15543
9. Lowe, G., Nakamura, T. and Gold, G. H. (1989) Proc. Natl. Acad. Sci. U.S.A. 86, 5641–5645
10. Breer, H., Bockhorst, I. and Tarelius, E. (1990) Nature 345, 65–68
11. Nakamura, T. and Gold, G. H. (1987) Nature 325, 442–444
12. Belluscio, L., Gold, G. H., Nemes, A. and Axel, R. (1998) Neuron 20, 69–81
13. Weng, S. T., Trinh, K., Hacker, B., Chan, G. C., Lowe, G., Gaggar, A., Xia, Z., Gold, G. H. and Storm, D. R. (2000) Nature 404, 487–497
14. Brunet, L. J., Gold, G. H. and Ngi, J. (1996) Neuron 17, 681–693
15. Zufall, F., Shepherd, G. M. and Firestein, S. (1991) Proc. R. Soc. Lond. 246, 225–230
16. Frings, S., Benz, S. and Lindemman, B. (1991) J. Gen. Physiol. 97, 725–747
17. Leinders-Zufall, T., Rand, M. N., Shepherd, G. M., Greer, C. A. and Zufall, F. (1997) J. Neurosci. 17, 4136–4144
18. Belasco, J. G., Zufall, F., Ronnett, G. V., Cunningham, A. M., Julifs, D., Beavo, J. and Snyder, S. H. (1992) J. Neurosci. 12, 915–923
19. Wayman, G. A., Impey, S. and Storm, D. R. (1995) J. Biol. Chem. 270, 21480–21486
20. Wei, J., Wayman, G. and Storm, D. R. (1996) J. Biol. Chem. 271, 24231–24235
21. Wei, J., Zhao, A., Chan, G. C., Baker, L. P., Impey, S., Beavo, J. A. and Storm, D. R. (1998) Neuron 21, 495–504
22. Leinders-Zufall, T., Ma, M. and Zufall, F. (1999) J. Neurosci. 19, 1–6
23. Dawson, T. M., Arriza, J. L., Jaworsky, D. E., Borsay, F. F., Attramadal, H., Leftkowitz, R. J. and Ronnett, G. V. (1993) Science 259, 825–828
24. Peppel, K., Bockhoff, I., McDonald, P., Breer, H., Caron, M. G. and Leftkowitz, R. J. (1997) J. Biol. Chem. 272, 25425–25428
25. Bockhoff, I. and Breer, H. (1992) Proc. Natl Acad. Sci. U.S.A. 89, 471–474
26. Dittman, A. H., Quinn, T. P., Nevitt, G. A., Hacker, B. and Storm, D. R. (1997) Neuron 19, 381–388
27. Wang, H. W., Wisocki, C. J. and Gold, G. H. (1993) Science 260, 998–1000
28. Ronnett, G. V., Furr, D. J., Hester, L. D. and Snyder, S. H. (1991) Proc. Natl Acad. Sci. U.S.A. 88, 2366–2369
29. Tully, T. (1998) Nat. Neurosci. 1, 543–545
30. Silva, A. J., Kogan, J. H., Frankland, P. W. and Kida, S. (1998) Annu. Rev. Neurosci. 21, 127–148
31. Impey, S., Obrietan, K. and Storm, D. R. (1999) Neuron 23, 11–14
32. Impey, S., Marks, M., Villacres, E. C., Poser, S., Chavkin, C. and Storm, D. R. (1998) Neuron 16, 973–982
33. Impey, S., Smith, D. M., Obrietan, K., Donahue, R., Wade, C. and Storm, D. R. (1998) Nat. Neurosci. 1, 595–601
34. Rosen, L. B., Ginty, D. D., Weber, M. J. and Greenberg, M. E. (1994) Neuron 12, 1207–1221
35. Vossler, M. R., Yao, H., York, R. D., Pan, M. G., Rim, C. S. and Vassart, G. (1997) J. Biol. Chem. 272, 18623–18632
36. Yamamoto, K. O., Gonzalez, G. A., Biggs, W. H. and Montminy, M. R. (1988) Science 241, 484–498
37. Gonzalez, G. A. and Montminy, M. R. (1989) Cell 59, 675–680
38. Moon, C., Sung, Y. K., Reddy, R. L. and Ronnett, G. V. (1999) Proc. Natl. Acad. Sci. U.S.A. 96, 14610–14614
39. Chen, H. R., Diener, M., Ugas, A. and Kandel, E. R. (1997) Neuron 18, 899–912
40. Impey, S., Obrietan, K., Wang, S. T., Poser, S., Yano, S., Wayman, G., Deloulme, J., Chan, G. and Storm, D. R. (1998) Neuron 21, 869–883
41. Ziefert, F., Firestein, S. and Shepherd, G. M. (1991) J. Neurosci. 11, 3573–3580
42. Lowe, G. and Gold, G. H. (1991) J. Physiol. (Lond.) 442, 147–168
43. Favata, M. F., Horiuchi, R. Y., Manos, E. J., Daulerio, A. J., Stradley, D. A., Feser, W. S., Van Dyk, D. E., Fitz, W. J., Earl, R. A., Hobbs, F., Copeland, R. A., Magolda, R. L., Scherle, P. A. and Trzaskos, J. M. (1998) J. Biol. Chem. 273, 18623–18632
44. References Downloaded from http://www.jbc.org/ by guest on July 25, 2018
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