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Induction of Immediate-early Genes and the Control of Neurotransmitter-regulated Gene Expression within the Nervous System*

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I. Immediate-early Genes and the Control of Gene Expression

A. Classes of Transcription Factors

The neuron is the basic unit of the nervous system. Neurons are often described as being "plastic," because they can show short- or long-lasting changes in their phenotype in response to different stimuli. Neurons are able to respond to changes in their environment because of the existence of universal, stimulus-response information processing mechanisms that can be found within all living cells.

The responses of the neuron to environmental cues can be divided into early and late responses. Early responses occur rapidly after stimulation of the neuron and last from milliseconds to minutes. These early responses, brought about by interactions of environmental first-messengers (i.e., neurotransmitters or growth factors) with cell-surface located receptors, occur because of activation of second-messenger systems. All of the known second-messenger systems characterised to date activate specific protein kinases that in turn actively phosphorylate specific neuronal proteins (Nishizuka, 1988; Berridge, 1993; Pelech and Sanghera, 1992; Garthwaite, 1991; Axelrod et al., 1988; Bronstein et al., 1993; Nairn et al., 1985). The biological response activated in this manner lasts within the limits of the persistence of protein phosphorylation, which is often short-lived because of the fine-control of phosphorylation patterns within the neuron by phosphatases (Cohen, 1992).

The late responses occur within a time frame of hours to days and in certain circumstances may be rendered permanent within the neuron, and these types of changes may underlie processes such as learning and memory, drug tolerance/sensitisation, etc. Changes in gene expression seem necessary for these late responses (Comb et al., 1987; Goelet et al., 1986; Bliss and Collingridge, 1993; Armstrong and Montminy, 1993). The changes in gene expression that underlie the late responses of the neuron to environmental cues occur because, either directly (for example, steroid-hormone receptor complex) or indirectly (second-messenger-mediated), the information carried by the first-messenger interacts with the cellular DNA to regulate and change its expression. These changes in gene expression bring about the production of specific mRNAs‡ and the associated proteins that, by performing their phys-

‡ Abbreviations: mRNA, messenger ribonucleic acid; DNA, deoxyribonucleic acid; PKC, protein-kinase C; MAP, mitogen-activated protein; TCF, ternary complex factor; cAMP, cyclic adenosine monophosphate; CREB, cyclic AMP response element binding protein; IEG, immediate-early gene; IEGP, immediate-early gene protein; ZENK, *zif* 268, *egr*-1, NGFIA, *krox*-24; CNS, central nervous system; MSV, murine sarcoma virus; NGF, nerve growth factor; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; TF, transcription factor; RNA, ribonucleic acid; cDNA, complementary deoxyribonucleic-acid; G, glycine; A, adenine; T, thymine; U, uracil; VSCC, voltage-sensitive calcium channel; AP-1, activating protein-1; TRE, TPA response element; cAMP, cyclic adenosine monophosphate; CHA, cyclohexyladenosine; CRE, cAMP response element; CREM, CRE binding site modulator protein; CaRE/CRE, calcium/cAMP response element; ATF, activating transcription factor; LTP, long-term potentiation; HI, hypoxia-ischemia; PVN, paraventricular nucleus; AD, afterdischarge; SCN, suprachiasmatic nucleus; NE, norepinephrine; i.v., intravenous; i.p., intraperitoneal; i.c.v., intracerebroventricular; 6-OHDA, 6-hydroxydopamine; 5-HT, 5-hydroxytryptamine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; 8-OH-DPAT, 8-hydroxy-2-(di-N-propylamino)tetralin; MDMA, 3,4-methylenedioxymethamphetamine; DARPP-22, dopamine- and cAMP-regulated phosphoprotein; s.c., subcutaneous injection; CCK, cholecystokinin; SE, status epilepticus; LTD, long-term depression; LC, locus coeruleus; PCD, programmed cell death; DND, delayed neuronal death; EPS, extrapyramidal side-effects; BDNF, brain-derived neurotrophic factor; PENK, proenkephalin; NMDA, N-methyl-D-aspartate; SRE, serum-response element; SRF, serum response factor.

iological role within the cell, modify the phenotype of the cell. The genes that code for these proteins can be termed "late-response" genes. The challenge in molecular neurobiology has been to identify the pathways and DNA binding effector molecules (*TFs*) that are involved in controlling the expression of "late-response genes" that produce phenotypical changes in neurons after activation of second-messenger pathways and indeed to identify the "late-response genes" themselves.

Work over the last decade has shown that within cells, at least three families of signal-regulated TFs exist (Mitchell and Tjian, 1989; Manniatis et al., 1987) (fig. 1). The first type of TF protein is constitutively expressed within the cell. Its transcriptional activity is regulated by post-translation modification, i.e., by phosphorylation of serine or threonine amino-acid residues. For this reason, they are known as *post-translationally activated TFs*.

Second-messenger systems activate protein kinases (PKC, calmodulin-dependent kinases I and II, MAP kinase) that in turn phosphorylate the TF. The simultaneous activation of phosphatases by second-messenger systems is also important in many cases, because removal of phosphate groups from TFs can also modulate their transcriptional activity. Once activated, the TF can, alone or in combination with other TFs, bind to the (usually upstream) regulatory regions of target genes and regulate their expression. An example of this type of TF is CREB (Montminy et al., 1990; Sheng et al., 1991).

The second type of TF is the *ligand-activated TF*. These molecules are intracellular receptors for steroid

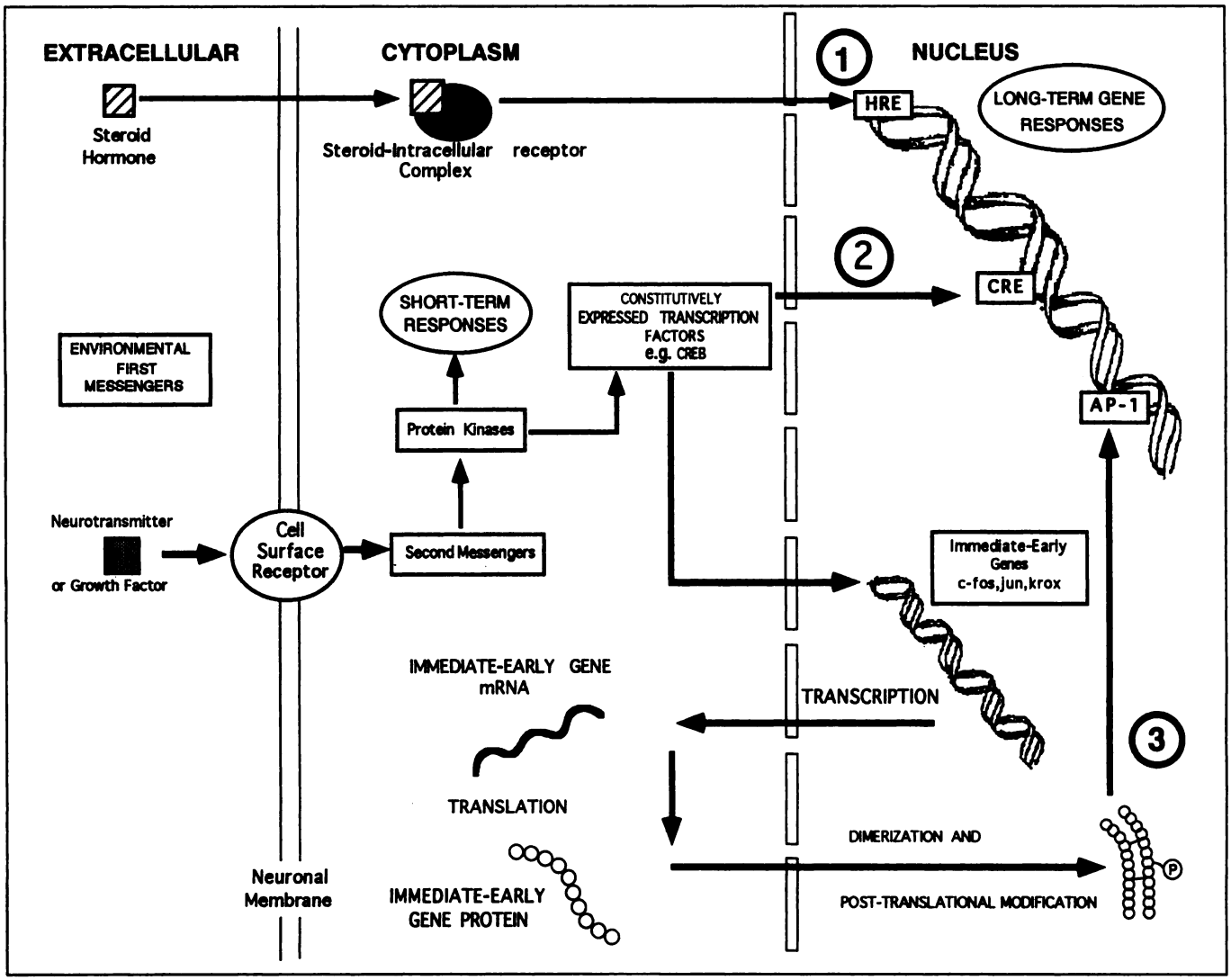

FIG. 1. Signal-regulated transcription factors mediate long-term changes in gene expression within the neuron. The responses of the neuron to its environment may be divided into short and long-term responses. Short-term responses within the neuron last within the limits of the persistence of protein phosphorylation and are produced by activated protein kinases. Long-term responses within the neuron involve changes in neuronal gene expression. These changes in gene expression are controlled by signal-regulated TFs. Three families of signal-regulated TFs exist. (*1*) Ligand-activated TFs of the steroid hormone family; (*2*) Post-translationally activated TFs, e.g., CREB family; (*3*) transcriptionally activated TFs, e.g., immediate-early gene family.

hormones (Evans, 1988). Because the steroid hormones are small, lipid-soluble molecules, they can readily pass through the outer plasma membrane of the cell by simple diffusion. Once they pass into the cytoplasm, they interact and bind with their corresponding cytoplasmic receptor. The receptor protein undergoes a conformational change and becomes activated. This receptor-ligand complex is then able to directly interact with DNA to regulate gene expression. One such receptor is the glucocorticoid receptor.

The third type of TF protein regulates gene expression in an "indirect" way. These TFs are not usually expressed constitutively within the cell and only regulate gene expression once they themselves are transcribed and translated. For this reason, they are called *transcriptionally activated TFs*. The genes coding for these TF proteins are called IEGs (note that not all IEGs are transcription factors). This family of genes includes c-*fos*, *fra*-1, *fra*-2, *fos*-B(Long), *fos*-B(Short), c-*jun*, *jun*-B, *jun*-D, *krox*-20, and *krox*-24 (also known as *zif*268, *NGFI*-A, *egr*-1, or ZENK) (Sheng and Greenberg, 1990; Morgan and Curran, 1991b). When a cell is stimulated, the first wave of gene transcription involves IEG activation. Once translated, the products of these genes (IEGPs) re-enter the nucleus and activate other "late-response" genes, resulting in a delayed secondary wave of gene activity.

This review will document (*a*) the evidence that suggests that IEGs are important components of the signal-transduction pathway from receptor to genome in neurons and (*b*) the evidence of a role for IEGs in CNS plasticity and pathology.

B. Origin as Proto-oncogenes: Oncogenes as Components of Signal Transduction Pathways

In 1911, Peyton Rous isolated a factor from a tumour filtrate that could produce sarcomas when injected into chickens—the Rous sarcoma virus (Takeya and Hanafusa, 1983; Wyke, 1983). In 1966, three researchers, Finkel, Biskis and Jinkin, using essentially similar methodology as Rous, isolated a factor from an osteosarcoma found on the ribs and thoracic spine of a 260-day-old CF1/An 1 mouse. The isolated factor had the ability to induce bony tumour growths when it was administered to young mice. Investigation of the tumours led to the identification of viral particles that were designated FBJ-MSV (Finkel et al., 1966). Another osteosarcoma virus that was subsequently discovered in a X/GF mouse after treatment with ^{90}Sr was designated FBR-MSV. Genetic analysis of the Rous sarcoma virus in the late 1960s identified a gene, v-*src*, that was present in addition to those genes that were required for viral replication (Martin, 1970). It was reasoned that this gene enabled the virus to induce sarcomas in vivo. The term "oncogene" (cancer-causing gene) was coined.

Five years later, it was discovered that this gene could be found within the DNA of all vertebrates (Stehelin et al., 1976). This finding showed that normal cellular DNA contains counterparts to viral oncogenes (v-*oncs*). The viral oncogene was found to encode a tyrosine kinase termed pp60^{src} (Collett and Erikson, 1978). As they were initially identified, the cellular counterparts of the viral oncogenes were termed proto-oncogenes or cellular oncogenes (c-*oncs*). Genetic analysis of FBJ-MSV and FBR-MSV virus strains identified that both harboured oncogenes. The product of the FBJ-MSV oncogene (designated v-*fos*) was identified as a 55-kD protein (Curran and Teich, 1982). The product of the FBR-MSV oncogene was a 75-kD protein. Genetic and protein analysis showed that both v-*fos* and the FBR-MSV oncogene had homologous regions (Curran and Verma, 1984).

It became clear that viral oncogenes were derived from the DNA of vertebrate cells (Bishop, 1983; Bishop, 1985; Stehelin et al., 1976). The invading virus "captures" the gene from the DNA of infected cells. However, the gene is not always captured as a whole. In normal cells, these cellular proto-oncogenes do not cause cancer, because they are in a restrictive environment quite distinct from their viral counterparts. However, over-expression of viral oncogenes occurs within the unrestricted environment of virally infected cells, because v-*onc* gene fragments inserted within the viral DNA are often lacking expression-limiting regulatory regions that exist within the normal proto-oncogene. The over-expression of the gene in virally infected cells causes unrestricted cell growth and division—the basis of the tumour.

To date, some 50 oncogenes have been identified and have had their proto-oncogene counterparts cloned. High conservation of nucleotide sequence of cellular and viral oncogenes between species suggests that these genes may have some important role to play in the functioning of the cell (Bishop, 1983). Indeed, it is now recognised that many of the viral oncogenes are neoplastic, because they encode proteins that have fundamental roles in intercellular communication and intracellular signal transduction mechanisms from the cell membrane to the nucleus (Macara, 1989; Storms and Bose, 1989). For example, the oncogene v-*sis* codes for a subunit of the growth factor PDGF, whereas the v-*erbB* oncogene encodes for an analog of the receptor for EGF. The v-*ras* oncogene protein shares homology with G-proteins, binds guanine nucleotides, and has intrinsic guanosine triphosphatase activity. Oncogenes that encode cytoplasmic proteins involved in cellular signal transduction include v-*raf* (serine/threonine kinase) and v-*src* (tyrosine kinase). The v-*erbA* oncogene codes for the intracellular thyroid hormone receptor.

Over-expression of these proteins in virally infected cells leads to tumour formation, because signal pathways specifying growth and division become overstimulated (Carbone and Levine, 1990). Some of the oncogenes identified were found to have a *nuclear localisation*. One of these oncogenes was v-*fos* (Sambucetti and Curran,

1986). Other nuclear oncogenes included v-*jun* and v-*myc*; v-*jun* is the oncogene of avian sarcoma virus 17 (Vogt and Bos, 1990), whereas v-*myc* is the oncogene of the avian myelocytomatosis virus (MC29).

C. Induction of Immediate-early Genes in Cultured Cells

Induction of c-*fos* in cultured cells was first identified in experiments that aimed to identify growth-factor-responsive genes that might control the re-entry of G_0 resting cells into the cell cycle. Growth factors have been characterised according to their effects on BALB/c 3T3 fibroblasts. For example, PDGF renders cells competent to begin the cell cycle. Thus, PDGF is characterised as a "competence factor." The competence factor does not have to be continuously present (Pledger et al., 1978). Competent cells then require a second mitogen such as EGF to fully initiate a cycle of cell division. EGF is thus characterised as a "progression factor." Progression factors must be present throughout the G_1 phase (Stiles et al., 1979). It was postulated that changes in gene expression might underlie the long-lasting ability of cells to respond to progression factors such as EGF and insulin-like growth factor-1 after brief application of competence factors such as PDGF.

Experiments were initiated to find and characterise these "competence genes." In the very first studies, the c-*fos* and c-*myc* proto-oncogenes were identified as genes whose rapid but transient transcription was activated in response to brief exposure of cells to mitogens (Rollins and Stiles, 1988), specifically PDGF (Kelly et al., 1983; Kruijer et al., 1984; Cochran et al., 1984), serum (Greenberg and Ziff, 1984), and EGF (Bravo et al., 1985). Subsequently, c-*jun* was also found to be induced by mitogens (Lamph et al., 1988). This finding was followed closely by the identification of several more putative "competence genes" by screening serum-inducible cDNA libraries for clones related in sequence to c-*fos* and c-*jun*. In this way, *fra*-1 (Cohen and Curran, 1988), *jun*-B (clone 465; Lau and Nathans, 1987; later identified as a c-*jun*-related gene; Ryder et al., 1988), *fos*-B (Zerial et al., 1989), and *fra*-2 (Nishina et al., 1990) were identified. Although *jun*-D expression was not markedly stimulated by serum, its high constitutive expression in 3T3 cells allowed its identification as the third member of the c-*jun*-related gene family (Hirai et al., 1989; Ryder et al., 1989).

The zinc finger-containing genes *krox*-20 and *krox*-24 (Lemaire et al., 1988), also termed *zif* 268 (Christy et al. 1988), *NGFI*-A (Milbrandt, 1987), or *egr*-1 (Sukhatme et al., 1988) were also activated rapidly after serum stimulation of 3T3 cells, suggesting that these genes may also be involved in the generation of cell competence. More recently, an alternatively spliced variant of *fos*-B has been shown to be induced in 3T3 cells by mitogens—termed *fos*-B(*S*) in contrast to the longer gene transcript *fos*-B(*L*) (Nakabeppu and Nathans, 1991; Mumberg et al., 1991).

Because these genes were activated by competence factors and had a nuclear localisation and could bind to DNA, it was postulated that they could act as TFs to control DNA replication by regulating the activation of target-genes expressed later in the growth response (Kingston et al., 1985; Sambucetti and Curran, 1986). Although experiments designed to test these ideas demonstrated that expression of c-*fos* or c-*myc* alone was not sufficient to initiate the cellular growth response, antisense experiments demonstrated that expression of c-*fos* and c-*myc* was essential for the optimum mitogenic response of cells to growth factors and lymphocyte mitogens (Heikkila et al., 1987; Holt et al., 1986; Nishikura and Murray, 1987), suggesting that in some way, these genes were involved in the processes controlling cell growth (Rollins and Stiles, 1988).

In addition, these early studies also identified several features of the induction of the cellular proto-oncogenes. The first characteristic identified was that induction occurred rapidly within the cell. Secondly, it was identified that induction was transient, and thirdly that induction was protein-synthesis-independent. Indeed, in the presence of protein-synthesis inhibitors (cycloheximide/anisomycin), induction of c-*fos* mRNA by mitogens was super-induced, maximal levels of c-*fos* mRNA were increased, and the persistence of c-*fos* mRNA within the cell was prolonged (Cochran et al., 1984; Greenberg et al., 1986). The effect of protein-synthesis inhibition suggested that factors responsible for initiating transcription preexisted within the cell (i.e., were constitutively present) and were activated by posttranslational modification. Induction of c-*fos* transcription by proteins that only require posttranslational modification for activation (i.e., phosphorylation), would explain how induction of c-*fos* mRNA can be produced within minutes, after mitogen stimulation of the cell. In addition, the transient nature of c-*fos* mRNA induction by mitogens and the super-induction of c-*fos* mRNA produced by protein-synthesis inhibition suggested that a *de-novo* synthesised, mitogen-induced protein, was required for shut-off of c-*fos* transcription (Sassone-Corsi et al., 1988b; Auwerx and Sassone-Corsi, 1991; Lucibello et al., 1989; Wilson and Treisman, 1988).

The newly synthesised protein responsible for transcriptional shut-off of the c-*fos* gene was identified as its protein product, Fos (Sassone-Corsi et al., 1988b; Gius et al., 1990; Lucibello et al., 1989). Such a negative-feedback mechanism (*trans*-repression) occurred only when c-*fos* transcription was induced by mitogens and, consequently, only c-*fos* serum-inducible promoter elements (i.e., the SRE) are molecular targets of repression (see next section.) In vitro binding studies suggest that the Fos protein directly interacts with the transcriptional complex that dictates the mitogen response. Two regions of the c-*fos* promotor seem necessary for auto-repression,

a region that encompasses the SRE and the AP-1/TRE-like site, and a sequence located between base-pairs -283 and -213 that has regions of homology with the human HSP70 promotor (Sassone-Corsi et al., 1988b).

Replacement of Fos peptide sequences C-terminal to amino acid 337 blocks down-regulation of c-*fos* transcription by Fos protein, suggesting that these regions are involved in *trans*-repression (Wilson and Treisman, 1988). In addition, mutant Fos proteins lacking the basic amino-acid DNA binding domains used to bind to the AP-1 site do not lose the ability to *trans*-repress (Gius et al., 1990; Lucibello et al., 1989), suggesting that different mechanisms are involved in *trans*-repression and *cis*-activation of genes by Fos. Fos is also able to down-regulate Krox-24 protein by interaction with the SRE in the regulatory region of this gene (Gius et al., 1990). (See next section.) Other mechanisms, in addition to prevention of transcriptional shut-off, may also contribute to the superinduction effect, such as enhancement of mRNA stability (Lemaire et al., 1988), the prevention of new synthesis of labile degradation enzymes, or other effects of protein-synthesis inhibitors (Mahadevan and Edwards, 1991; Edwards and Mahadevan, 1992).

In addition to *trans*-repression by its own product, the induction of c-*fos* mRNA is rendered transient because of untranslated AT-rich sequences found within the 3′ region of the transcript. This 67-nucleotide region, located some 500 nucleotides down-stream from the end of the coding domain and about 120 nucleotides upstream of the poly(A) addition signal sequence, influences the stability of c-*fos* mRNA (Blanchard et al., 1988). Removal of this noncoding region results in a ten-fold increase in the amount of Fos protein translated and confers transforming potential on the mutant gene (Verma and Graham, 1987).

The occurrence of such AU/AT-rich sequences in most transiently expressed mRNAs suggests the presence of a common system of degradation (Caput et al., 1986). The induction of c-*jun* mRNA expression also rises rapidly in cells stimulated by mitogen (Almendral et al., 1988; Lamph et al., 1988; Rauscher et al., 1988). However, in contrast to the *trans*-repression of c-*fos* gene by Fos protein, the c-*jun* proto-oncogene is positively autoregulated by its product c-Jun (Angel et al., 1988). The c-Jun protein binds to a high-affinity AP-1-like site (*GTGACATCAT*) within its promoter and further stimulates c-*jun* transcription. Because the c-Jun protein positively autoregulates the expression of its own gene, powerful negative mechanisms of regulation must also exist to control c-*jun* mRNA levels, inasmuch as induction of c-*jun* mRNA, such as that of c-*fos*, occurs transiently. As for c-*fos*, 3′ AT-rich untranslated regions of the c-*jun* mRNA have been suggested to result in its rapid breakdown by RNAases. Transcripts encoding *fos*-B, *jun*-B, *krox*-20, and *krox*-24 are also induced rapidly and transiently in a protein-synthesis independent manner in fibroblasts with time-courses similar to c-*fos* and c-*jun* induction (Ryder et al., 1988; Zerial et al., 1989; Lemaire et al., 1988; Chavrier et al., 1988). The rapid, protein synthesis-independent induction of these genes in cells is characteristic of the IEGs carried by many viruses and has led to the classification of this family of proto-oncogenes (c-*fos*, c-*myc*, *fos*-B, c-*jun*, *jun*-B, *jun*-D, *krox*-20, and *krox*-24) as cellular IEGs.

After the generation of specific antibodies to the c-*fos*, *fos*-B, c-*jun*, *jun*-B and *jun*-D gene products, (Kovary and Bravo, 1991), studies at the protein level revealed that Fos protein presented the most rapid and transient increase in synthesis after stimulation of quiescent 3T3 cells with serum. Fos levels were maximal at 30 min and had decreased to low levels at 2 h. Fos-B induction was delayed in relation to Fos being maximal at 1 h and near basal at 3 h. The three Jun proteins were induced rapidly (absolute level of induction was greater for Jun-B > c-Jun > Jun-D) and were found to have a prolonged life-span in relation to the two Fos proteins. Both c-Jun and Jun-B proteins remained at high levels at 8 h post-stimulation, albeit at levels much decreased from those seen at the time of maximal induction. Although the maximal induction of Jun-D was less pronounced than that of c-Jun and Jun-B, it was the most persistent of the Jun proteins, with maximal levels still seen at 8 h (Kovary and Bravo, 1991).

Fra proteins, i.e., Fra-1, and Fra-2 also have a delayed and protracted induction time-course, similar to that of the Jun proteins (Kovary and Bravo, 1992; Cohen and Curran, 1988; Nishina et al., 1990; Franza et al., 1987; Suzuki et al., 1991). Thus, it seems that the induction time-courses of IEGPs are similar but not identical to some species (Fra-1, Fra-2, Jun proteins), persisting longer than others (Fos, Fos-B proteins).

D. Induction of Immediate-early Genes in PC12 Cells

The rat PC12 pheochromocytoma cell line has been used to study the mechanisms of action of NGF. PC12 cells are the tumour counterparts of adrenal chromaffin cells. When PC12 cells are treated with NGF, they acquire over a period of days a sympathetic neuron-like phenotype characterised by the cessation of proliferation and the promotion of neurite outgrowth and electrical excitability. Early reports using the PC12 cell line reported that growth factors such as NGF and EGF induced transcription of the c-*fos* proto-oncogene (Greenberg et al., 1985), and peripherally active benzodiazepines were found to super-induce the induction of c-*fos* by NGF (Curran and Morgan, 1985).

These results were in agreement with the growth factor-mediated induction of *c-fos* in other cultured cell types as described above. It was suggested that *c-fos* gene expression (Greenberg et al., 1985) and, subsequently, that of other IEGs (Milbrandt, 1987), might be involved in producing the program of rapid transcription-dependent (Burstein and Greene, 1978) cellular changes in PC12 cells after NGF application that led to

differentiation (Greenberg et al., 1985; Curran and Morgan, 1985).

Additional work in PC12 cells appeared in 1986; it suggested that IEG induction might serve a more general role in the transduction of a wide variety of signals from cell-surface receptors to gene expression. The first study reported that application of nicotine to nondividing, neuronally differentiated PC12 cells induced rapid c-*fos* gene expression by activating VSCCs (Greenberg et al., 1986). The other two reports demonstrated induction of c-*fos* in PC12 cells after direct activation of VSCCs and showed that c-*fos* induction involved calmodulin-dependent mechanisms, inasmuch as inhibitors of calmodulin (W7, chlorpromazine, and trifluoperazine) antagonised the induction of c-*fos* (Curran and Morgan, 1986; Morgan and Curran, 1986).

Specific patterns of proto-oncogene expression also occurred after either growth factor stimulation or membrane depolarisation of PC12 cells. For example, although growth factor application stimulated strong induction of c-*fos*, *jun*-B, c-*jun* and *zif*268 (*krox*-24) genes, membrane depolarisation resulted in strong induction of c-*fos* and *jun*-B, with a reduced induction of *zif*268 and no induction of c-*jun* (Bartel et al., 1989). It also became obvious in several studies that extensive post-translational modification of the Fos protein can occur after induction. The extent of post-translational modification is determined by the nature of the stimulus (Curran and Morgan, 1986). For example, when Fos protein was induced by mitogens or phorbol esters (agents that activate PKC), it was extensively modified. In contrast, much less post-translational modification of Fos protein occurred when Fos was induced by depolarising agents or barium ions (agents that increase intracellular Ca^{2+}).

The different forms of Fos protein could be distinguished on gels by their different molecular weights (Curran and Morgan, 1986). In addition, more extensive studies using 3T3 fibroblast cells demonstrated that different members of the IEGP family undergo different levels of post-translational modification when induced by the same signal (Kovary and Bravo, 1991). After stimulation with serum, Fos, Fos-B, c-Jun, Jun-B and Jun-D proteins are induced in 3T3 cells. Within several hours of induction, Fos, Fos-B and Jun-B proteins have become significantly more phosphorylated than c-Jun and Jun-D. In addition, post-translational phosphorylation of the C-terminus of Fos has been shown to be necessary for autorepression of the c-*fos* promoter (Ofir et al., 1990). Because post-translational phosphorylation of IEGPs regulates both their stability—and therefore half-life (Jackson et al., 1992)—and their transcriptional activity (Pulverer et al., 1991; Franklin et al., 1992; Chou et al., 1992; Bannister et al., 1993), it represents an important cellular regulatory mechanism that controls IEG function.

The studies performed in PC12 cells were also significant, because they were the first to show that IEGs could be rapidly induced in nondividing cells by nonmitogenic signals. They also suggested that c-*fos* might play a general role in the signal transduction pathway from receptor activation by first-messengers (be they neurotransmitter molecules or growth factors), to appropriate gene responses. Indeed, for neurobiologists, they also raised the possibility that c-*fos* and other IEGs might be induced during the course of normal neuronal function in vivo.

E. Multiple Second-Messenger Pathways Induce Immediate-early Gene Expression by Acting on Distinct Upstream Regulatory Elements

The previous two sections have demonstrated that IEG induction occurs in cultured (3T3 fibroblasts or PC12) cells in response to growth factors and neurotransmitters. The earliest example of neurotransmitter-mediated induction of c-*fos* involved the opening of VSCCs after membrane depolarisation induced by nicotinic receptor activation in PC12 cells (Greenberg et al., 1986). The resulting increase in intracellular Ca^{2+} was believed to lead to the increase in c-*fos* expression. Increased intracellular Ca^{2+} produced by other methods also resulted in c-*fos* expression, suggesting that increases in the concentration of intracellular Ca^{2+} leads to the activation of cellular mechanisms that then regulate the expression of IEGs (Morgan and Curran, 1986; Curran and Morgan, 1986). Activation of Ca^{2+}-permeable NMDA glutamate receptors in cultured cerebellar granule cells also resulted in increased c-*fos* expression (Szekely et al., 1987).

In contrast, growth factor-mediated induction of c-*fos* gene expression in PC12 cells, i.e., NGF (Morgan and Curran, 1986), does not require the entry of extracellular Ca^{2+} ions. The pathway from growth factor activation of its receptor to c-*fos* induction seem, in part, to involve PKC (protein kinase C) activation, inasmuch as the induction of c-*fos* in both 3T3 cells and adipocytes is reduced by phorbol-ester pretreatment of cells that can deplete cellular PKC activity (Stumpo and Blackshear, 1986). The protein kinase inhibitor, 2-aminopurine, which has unknown specificity, has also been shown to block c-*fos* induction in 3T3 cells induced by serum (Zinn et al., 1988).

Together, these early studies suggested that at least two significantly different signalling pathways activate c-*fos* expression, one involving the activation of the inositol-phosphate-PKC pathway, the other involving an increase in intracellular Ca^{2+} ions.

1. The serum-response element. Several regulatory regions located in the 5′ untranslated region of c-*fos* have been demonstrated to play a role in controlling the induction of its expression. Using deletion analysis of upstream regulatory regions of the c-*fos* gene, a region was described that was necessary for c-*fos* induction by se-

rum, growth factors, and PKC-activators (phorbol 12-myristate 13-acetate) in 3T3 cells. This "promotor" was termed the SRE (Treisman, 1985).

The SRE responds to both PKC-dependent and independent signals (Gilman, 1988). The SRE has previously been identified as the dyad symmetry element, is centered at -308, and is approximately located between nucleotides -332 and -277 relative to the 5′ cap site (Treisman, 1985, 1986; Sheng et al., 1988). In addition, a SRE-2 sequence can be found adjacent to the approximately 20 SRE base-pairs *downstream*. It resembles sequences seen in the metallothioneine and HSP70 genes that are serum-responsive and consists of several sequence repeats.

It has been shown that, rather than performing synergistically, the two regions act independently of one another, and SRE-2 binds its own TFs (Visvader et al., 1988). Less is known about the SRE-2 than the SRE. Another binding site for a growth factor-inducible protein complex of unknown nature and function has also been described; it is located approximately 40 base-pairs *upstream* of the SRE and is called the SCM (Hayes et al., 1987). The sequence motif $CC[AT]_6GG$, also known as a CArG box, can be found at the centre of the SRE.

The SRE has been shown to bind a protein termed the SRF (Treisman, 1987; Norman et al., 1988). SRE mutations that block SRF binding, or depletion of SRF from cell nuclei after antibody microinjection, block the response of the c-*fos* SRE to growth factor stimulation, suggesting that SRF binding is important for SRE activity (Triesman, 1992).

The SRF is a 67-kD nuclear polypeptide that is expressed in most cells but whose transcription is also transiently increased after serum stimulation (Norman et al., 1988). The SRF amino-terminal region contains a conserved casein kinase II phosphorylation consensus that is phosphorylated in vivo, causing an approximately three-fold increase in the DNA binding affinity of the SRF for the SRE (Janknecht et al., 1992). The SRF binds to the SRE as a dimer (Norman et al., 1988), probably in association with several other proteins, including a 62-kD protein p62/direct binding factor (Ryan et al., 1989) and p62/TCF (Shaw et al., 1989; Herrera et al., 1989). p62/TCF only binds to the SRE as part of a complex with the SRF (Shaw et al., 1989; Graham and Gilman, 1991; Treisman, 1992). The p62/TCF may be composed of one or other of the two binding proteins Elk-1 and SAP-1, inasmuch as both of these proteins have DNA binding properties identical to the p62/TCF (Hipskind et al., 1991; Dalton and Treisman, 1992).

Mutagenesis studies suggest that the p62/TCF may have a role in serum stimulation of the c-*fos* SRE. Indeed, formation of the ternary complex is necessary for PKC-dependent—but not PKC-independent—signals acting through the SRE. These results suggest that PKC-independent signals do not require p62/TCF binding to the SRE, and it has been suggested that SRF may act alone or with accessory proteins to respond to PKC-independent signals (Graham and Gilman, 1991). In addition, the p62/TCF has been shown to be phosphorylated by MAP kinase. Phosphorylation of p62/TCF by MAP kinase results in enhanced TCF about the SRE (Gille et al., 1992). Therefore p62/TCF may be viewed as an adapter that allows SRF to respond to other second-messenger pathways (PKC and MAP kinase-dependent pathways), (Graham and Gilman, 1991).

Other proteins that bind to the SRE include direct binding factor/MAPF1, SRE-ZBP, NF-IL-6, E12 and Phoxl. At this stage however, the significance of their binding is unknown, although one of these proteins, NF-IL-6, may allow regulation of the SRE by cAMP and thus be an adapter in the mold of p62/TCF (Metz and Ziff, 1991), whereas the presence of the Phoxl homeodomain protein has similar effects on SRF DNA binding as phosphorylation by casein kinase II.

Although the c-*fos* SRE has received much attention, the series of biochemical events that are responsible for activation of c-*fos* transcription through the SRE after stimulation of the cell by growth factors are still not fully understood (Sassone-Corsi and Verma, 1987). For example, it has been shown that the SRF is bound to the SRE before, during, and after growth factor stimulation of cells (Herrera et al., 1989). Therefore it is not known whether in the simplest case DNA binding of the SRF to the SRE in conjunction with other proteins activates c-*fos* transcription or whether post-translational modification of the SRF and binding of other growth factor-activated proteins, such as p62/TCF, Phoxl or NF-IL-6, to the complex is required to increase transcription of the c-*fos* gene. Within the next few years, we are likely to see these mechanisms further elucidated.

2. The calcium/cyclic-adenosine monophosphate response element. Although several second-messenger signals seem to activate c-*fos* transcription via the SRE, another regulatory element located at nucleotide -60 relative to the 5′ cap site has been identified. Named the CaRE/CRE, this regulatory DNA region functions as both a calcium- and cAMP-responsive element, increasing transcription of the c-*fos* gene in response to intracellular increases in the levels of either of these second-messenger molecules (Fisch et al., 1987; Sheng et al., 1988).

The CaRE/CRE contains the consensus sequence *TGACGTTT*, which is very similar to the previously characterised CRE promotor sequence found in the upstream regions of cAMP-inducible genes (*TGACGTCA*). The CaRE/CRE does not confer inducibility of the c-*fos* gene to growth factors or phorbol esters that activate PKC-dependent signalling pathways (Sheng et al., 1990). Central to activation of the CaRE/CRE by Ca^{2+} ions or cAMP is the DNA binding TF CREB (Montminy et al., 1990; Sheng et al., 1991). This constitutively expressed, post-translationally activated TF was first identified by DNA footprinting experiments that at-

tempted to characterise the DNA binding factors that interacted with the CRE of cAMP-inducible genes (Montminy and Bilezikjiun, 1987). Treatment of cells with the drug forskolin, which increases intracellular levels of cAMP, increased the transcriptional efficacy of the CREB protein, although the DNA binding of CREB was not affected.

CREB is a 43-kD protein, 341 amino acids in length. CREB has been purified using cyanogen bromide [.. TGACGTCA..]$_n$-activated silica beads (Montminy and Bilezikjiun, 1987; Yamamoto et al., 1988). Cloning of CREB suggests that multiple CREB cDNAs exist (Hoeffler et al., 1988; Gonzalez and Montminy, 1989). From structural analysis of the amino-acid sequence, it was determined that three functional domains exist within CREB. The three domains are (*a*) the trans-activation region, which contains sites for phosphorylation, (*b*) the DNA binding domain, which consists primarily of basic amino acids, and (*c*) the leucine-zipper dimerisation domain (Montminy et al., 1990). The CREB protein binds to the CaRE/CRE either as a monomer or as a homodimer, however the affinity for DNA is significantly reduced in the monomer form. Dimerisation occurs by way of its leucine-zipper domain.

The transcriptional ability of CREB is activated by phosphorylation. Both PKA, which is activated by cAMP binding (Gonzalez and Montminy, 1989), and CaM kinases I and II (Sheng et al., 1991), which are activated by Ca^{2+}, phosphorylate CREB on the same Serine-133 residue that is located within the transactivation domain. Potential phosphorylation sites on CREB for PKC also exist within this domain. Phosphorylation results in activation of CREB, which then leads to increased c-*fos* expression (Sheng et al., 1990). In this manner, both cAMP and Ca^{2+} second-messenger pathways converge synergistically within the cell to induce the expression of c-*fos* (Sheng and Greenberg, 1990).

In addition to the CaRE/CRE site with which CREB interacts, at least one other Ca^{2+}/cAMP-responsive element exists within the *c-fos* promotor, because internal mutations of the CaRE/CRE do not abolish calcium inducibility of an otherwise intact c-*fos* gene (Sheng et al., 1990). Furthermore, it has been shown that a CaRE/CRE-like region exists upstream of the SRE. Located approximately at nucleotide -350, the function of this region remains unknown (Sassone-Corsi et al., 1988b).

Other gene regions that may be involved in certain aspects of the control of c-*fos* induction have also been identified. One of these identified elements is the AP-1/TRE-like site that lies adjacent to the 3′ side of the SRE. The fact that the presence of this element is conserved by many SREs in other genes suggests that it will have some functional role to play. Indeed, this site does seem to bind members of the AP-1 (Fos/Jun), CREB/ATF protein family of TFs (Triesman, 1992). In addition to this site, a region of the c-*fos* promoter located between base-pairs -102 to -71 relative to the 5′ cap site, has been shown to bind the protein-product of the retinoblastoma susceptibility gene (RB-1). By binding to the retinoblastoma control element, this protein-product negatively regulates the induction of c-*fos* by serum (Robbins et al., 1990). An estrogen-responsive element has also been located to the untranslated 3′-flanking region of the c-*fos* gene, 5 kb downstream from the c-*fos* promoter and 1.5 kb downstream of the poly(A) signal.

F. Regulation of Gene Expression by Immediate-early Gene Proteins

1. Fos and c-Jun and related proteins bind to the activator protein-1/TPA response element site in deoxyribonucleic acid. Cellular proto-oncogenes encode proteins at three major sites: the cell membrane, the cytosol, and the nucleus. Because of the nuclear localisation and DNA binding ability of some proto-oncogenes, it was suggested that they might act as DNA binding TFs to directly control gene expression. Early work that had been published indirectly supported this suggestion. For example, the possibility that Fos protein affected transcription was initially suggested by experiments reporting that a *v-fos* expression vector stimulated transcription from a cotransfected mouse α_1 (III) collagen gene promoter (Setoyama et al., 1986) and that the Fos protein or a Fos-related antigen formed a complex with the promoter region of the adipocyte-specific aP2 gene (Distel et al., 1987). Continued work with adipocyte aP2 gene promotor regions demonstrated that Fos and Fos-associated proteins (the most abundant Fos-associated protein having a molecular weight of 39 kD) bound to a DNA-specific sequence that was identical to the previously identified AP-1 site. The AP-1 site (or TRE site) had been identified in the promoters of the human metallothioneine gene and simian virus 40 (Lee et al., 1987a) and was involved in the activation of cellular genes by the tumour promotor substance 2-tetradecanoyl-phorbol-13-acetate (Lee et al., 1987b; Angel et al., 1987). The AP-1/TRE site contained the octomer consensus sequence *ATGACTCA* and bound a DNA binding factor designated AP-1. AP-1 was subsequently found to contain the proto-oncogene homolog of the avian tumour virus gene v-*jun* (Bohmann et al., 1987).

It therefore seemed that the protein products of both c-*fos* and c-*jun* bound to the same DNA sequence. When the 39-kD Fos-associated protein was identified as the product of the c-*jun* proto-oncogene, it became obvious that the products of the two proto-oncogenes were *major components* of AP-1. Thus, it was postulated that Fos and c-Jun bound together forming a complex, previously identified as AP-1, which then associated with transcriptional control elements containing AP-1/TRE binding sites (Rauscher et al., 1988). The stable Fos and c-Jun complex can be reproduced in vitro (Sassone-Corsi et al., 1988a).

By binding to c-Jun, Fos directly modulates c-Jun transcriptional ability by forming a heterodimer of Fos

and c-Jun proteins (Kouzarides and Ziff, 1988). Although c-Jun proteins can form homodimers (c-Jun/c-Jun) that bind to, and weakly transactivate, gene expression from AP-1/TRE sites, Fos proteins do not form homodimers and hence can not bind to the AP-1/TRE sites to transactivate gene expression. However, in a Fos/c-Jun heterodimer, not only is the Fos protein able to regulate gene transcription, but the transactivating potential of c-Jun is significantly increased.

2. The leucine zipper. Formation of the dimer is possible because both Fos and c-Jun proteins contain a conserved structural motif, or binding region, called the "*leucine zipper*", which allows strong protein-protein interactions to occur (Kouzarides and Ziff, 1988, 1989). The leucine-zipper structure is found within proteins of the b-zip family. TFs in this family include Myc, the yeast TFs GCN4, and yAP-1, CCAAT-enhancer binding protein, and CREB. The leucine zipper is an α-helical domain in which four or five leucine residues occur at regular seven-residue intervals. These leucine residues locate on the same rotational position of the α-helix because of this regular spacing and thus form a linear crest of leucine residues that protrudes from the side of the protein helix. Proteins that have a leucine-zipper domain bind to each other because of hydrophobic interactions between the linear leucine crests of the two molecules. Although substitution of one leucine residue does not alter dimer formation, substitution of two leucine residues will greatly reduce or entirely eliminate formation of the Fos/c-Jun dimer. Although it has been demonstrated that Fos and c-Jun interact through the leucine zipper, the mere presence of a leucine zipper (i.e., among b-zip proteins) is not sufficient for dimer formation. Because the positions of the leucines in all zippers are invariant, the amino-acid residues between the leucines, which differ significantly between different b-zip family members, may determine permissable and nonpermissable protein-protein interactions.

3. Interactions with deoxyribonucleic acid. Currently, five Fos (c-Fos, Fos-B(L), FosB(S), Fra-1, Fra-2) and three Jun (c-Jun, Jun-B, Jun-D) family members have been identified. They all contain leucine-zipper domains and can associate together to form various heterodimers. Jun, but not Fos, proteins also form homodimers (Vogt and Bos, 1990). These different homodimers and heterodimers have unique transactivating abilities at the AP-1/TRE site and therefore have differing effects on gene expression (see next section). The DNA binding regions of Fos and Jun proteins interact with the dyad symmetry DNA consensus sequence *ATGACTCA*. In the AP-1 complex, both Fos and Jun proteins directly bind to DNA. These DNA binding regions lie adjacent to the leucine zipper and contain a high density of basic amino acids (Abate et al., 1990). In addition to enabling dimerisation, the leucine zipper is believed to hold the basic amino-acid DNA contact surface in the correct three-dimensional orientation and to stabilise this orientation. When the dimer binds to DNA, it causes DNA bending. Protein-induced DNA bending participates in the regulation of transcription by facilitating the assembly of initiation complexes (Kerppola and Curran, 1991a, b). Although the AP-1/TRE site is palindromic, it seems that Fos/Jun binding does not recognise the AP-1/TRE site in a symmetrical way. This probably occurs because of DNA bending during the binding phase (Kerppola and Curran, 1991a, b) and is consistent with mutation studies that also suggest asymmetric binding of Fos/Jun to the AP-1/TRE site (Risse et al., 1989).

Recently, a cellular protein termed IP-1 has been identified. IP-1 is a constitutively expressed, labile protein of 30 to 40 kD that is found in both the cytoplasm and nucleus of cells. IP-1 can specifically block the DNA binding of AP-1 (i.e., Fos/Jun complex) to the AP-1/TRE site and therefore represents a potential anti-oncogene (Auwerx and Sassone-Corsi, 1991; Auwerx and Sassone-Corsi, 1992). The ability of IP-1 to block Fos/Jun binding is modulated by phosphorylation. In the nonstimulated cell, IP-1 exists in a nonphosphorylated form and acts as a basal repressor of transcription from the AP-1/TRE site. Upon stimulation of PKA or PKC signal transduction pathways, IP-1 becomes phosphorylated and therefore inactivated. In addition, a report has shown that nuclear TF CREB and the associated DNA binding factor CREM also bind to the AP-1/TRE site and inhibit trans-activation by Jun proteins (Masquilier and Sassone-Corsi, 1992). Both CREB and CREM recognise both the CRE site and the CaRE/CRE site of the c-*fos* gene. These proteins also seem able to bind to the AP-1/TRE site because of the sequence homology between it and the CRE. Indeed, the CRE and the AP-1/TRE sequences only differ by one nucleotide: an additional guanidine nucleotide is found in the CRE (i.e., *TCACgTCA*). This report demonstrates that CREB/CREM proteins disrupt Fos/Jun stimulated *trans*-activation from the AP-1/TRE site (*ATGACTCA*). Neither protein seems to dimerise with Fos or Jun proteins (Lamph et al., 1990; Masquilier and Sassone-Corsi, 1992), suggesting that inhibition occurs by competitive binding of CREB and CREM dimers to the AP-1/TRE site: this results in displacement of the Fos/Jun dimer (Masquilier and Sassone-Corsi, 1992). Cross-family dimerisation of Fos and Jun with ATFs/CREB also alters DNA binding specificity (Hai and Curran, 1991).

It has recently been demonstrated that CREB will inhibit the transcriptional ability of certain ATFs (i.e., ATF-4) at a given promoter by mechanisms that do not involve heterodimerisation with the ATF or binding to a CRE within the promoter. Rather, CREB may down-regulate the expression of another TF that is necessary for the transcriptional ability of the ATF (Lemaigre et al., 1993). It will be interesting to see whether CREB and ATFs interact with IEGP TFs in a similar manner. Ligand-activated TFs, i.e., the glucocorticoid and thyroid hormone receptors, also interact with Fos/Jun com-

plexes to modulate their transactivational ability (Lucibello et al., 1990; Lopez et al., 1993; Schmidt et al., 1993). Inasmuch as Fos and Jun proteins can also bind to the CRE site (Hoeffler et al., 1989; Sassone-Corsi et al., 1990), it is clear that cell stimulation will result in multiple interactions between the three major varieties of cellular TFs and DNA.

4. Specificity of response. Whereas Fos and Jun proteins have near identical DNA binding activities within their families because of conservation of basic amino-acid sequences that confer DNA binding ability (Nakabeppu et al., 1988) outside of the DNA binding domains, there is more limited sequence identity between family members (Nakabeppu and Nathans, 1991). Therefore, the transactivational ability of the various dimers that form at the AP-1/TRE site differs markedly, depending upon their composition. A number of reports have shown that Fos family members do not form homodimers and therefore cannot bind to or effect transcription from the AP-1/TRE site. However, Jun homodimers do form, and some dimers (c-Jun/c-Jun, Jun-D/Jun-D) are able to bind to AP-1/TRE sites and weakly stimulate transcription (Suzuki et al., 1991; Chiu et al., 1989; Nakabeppu and Nathans, 1991).

In contrast, Jun-B homodimers (Jun-B/Jun-B) are almost inactive and only activate transcription from promoters containing multiple AP-1/TRE sites (Chiu et al., 1989; Nakabeppu and Nathans, 1991). Therefore, the binding of (the inactive) Jun-B protein to c-Jun or Jun-D results in the formation of Jun heterodimers (Jun-B/c-Jun and Jun-B/Jun-D) with lower transactivational ability than c-Jun/c-Jun and Jun-D/Jun-D homodimers (Chiu et al., 1989; Schutte et al., 1989). Thus, Jun-B inhibits the transactivational ability of c-Jun and Jun-D. We assume that the Jun heterodimer formed between c-Jun and Jun-D (c-Jun/Jun-D) would have transcriptional activity comparable to the c-Jun and Jun-D homodimers.

In comparison, the binding of Fos and Fos-B(L) proteins with Jun family members to form Fos/Jun heterodimers (i.e., Fos/c-Jun, Fos/Jun-B, Fos/Jun-D, Fos-B(L)/c-Jun, Fos-B(L)/Jun-B, Fos-B(L)/Jun-D) results in a dramatic increase in the transcriptional ability of the Jun proteins (Nakabeppu and Nathans, 1991; Suzuki et al., 1991). The other members of the Fos family form Fos/Jun heterodimers with widely differing transactivational abilities, depending on their composition. For example, Fos/Jun heterodimers containing the Fos-B(S) protein (Fos-B(S)/c-Jun, Fos-B(S)/Jun-B, Fos-B(S)/Jun-D) have little or no transcriptional ability (Nakabeppu et al., 1991). Fos/Jun heterodimers containing Fra-1 and Fra-2 proteins show differing transcriptional ability, depending on the Jun protein they contain. For example, although the transcriptional ability of Jun-D is increased in the Fra/Jun-D heterodimers (Fra-1/Jun-D, Fra-2/Jun-D), the transactivational ability of Jun-B (Fra-1/Jun-B, Fra-2/Jun-B) is unchanged from that seen in the Jun-B homodimer (Jun-B/Jun-B), whereas the transactivational ability of c-jun in the heterodimers (Fra-1/c-Jun, Fra-2/c-Jun) decreases below that found in the c-Jun homodimer (c-Jun/c-Jun), (Suzuki et al., 1991).

We have used these results to construct summary table 1, which shows the relative transactivational ability of various Jun/Jun and Fos/Jun heterodimers to activate reporter genes from an AP-1/TRE-containing promoter in vitro.

The Krox-20 (Chavrier et al., 1988) and Krox-24 (Lemaire et al., 1988) TFs are characterised by their "*zinc-finger*" DNA binding domains. Zinc-fingers are DNA binding domains that were first identified in TF, TF IIIA. Zinc fingers consist of tandemly repeated units of 28 to 30 amino-acid residues, containing two cysteine and two histidine residues at invariant positions. This unit of amino-acid residues centres around a Zn^{2+} ion coordinated by the four invariant residues (two cysteine/two histidine). This complex is called a zinc-finger and is able to bind DNA in a sequence-specific manner dependent upon the sequence of three base-pair variant amino-acid residues that come to lie next to the DNA (Pavletich and Pabo, 1991) and exist between the invariant "zinc-finger structural" residues. Several TFs, in addition to Krox-20 and Krox-24, use zinc-fingers as DNA binding domains, for example, Spl, SW15, and TF IIIA. Both Krox-20 and Krox-24 recognise the same sequence *GCGTGGGGCG* in DNA (Christy and Nathans, 1989; Charvier et al., 1990; Lemaire et al., 1988).

TABLE 1

Descending order of transactivational ability of various Fos/Jun hetero- and Jun/Jun homo-dimers from an AP-1 containing promoter.CAT fusion gene

Transactivational ability	Dimer
High	Fos/c-Jun,[1,2] Fos/Jun-D,[1,2] FosB(L)/c-Jun,[2] FosB(L)/Jun-D[2]
Medium	Fos/Jun-B,[1,2] FosB(L)/Jun-B[2] Fra-1/Jun-D,[1] Fra-2/Jun-D[1]
Medium-Low	c-Jun/c-Jun,[1,2,3,4] Jun-D/Jun-D[1,2] c-Jun/Jun-D†
Low-Not detectible	FosB(S)/Jun-B,[2] FosB(S)/c-Jun[2] FosB(S)/Jun-D,[2] Fra-1/Jun-B[1] Fra-1/c-Jun,[1] Fra-2/Jun-B[1] Fra-2/c-Jun,[1] Jun-B/Jun-B[1,2,3] c-Jun/Jun-B[3,4]

Transcriptional activation experiments were performed in cultured F9 teratocarcinoma cells. Cells were transfected with an AP-1 containing promoter linked to a chloramphenicol acetyltransferase marker gene (AP-1.CAT fusion plasmid). Transactivational ability of various dimers at the AP-1 site was measured by assaying CAT enzyme activity induced by cotransfection of Fos and Jun expression plasmids with the AP-1 containing promoter.CAT fusion plasmid.

References: [1] Suzuki et al., (1991); [2] Nakabeppu and Nathans, (1991); [3] Chiu et al., (1989); [4] Deng and Karin, (1993); † No ref. Estimated transactivational ability. Note that unlike Jun family members, Fos family members (Fos, FosB(S), FosB(L), Fra-1, Fra-2) do not form homo- or heterodimers with each other.

In view of what is currently understood, it is easy to see how a small number of immediate-early gene proteins can, *by combinatorial control*, lead to the formation of a large number of AP-1 TF complexes with differing transcriptional abilities. Full characterisation of two parameters is required to understand the role that these proteins play within the cell after growth factor or neurotransmitter binding.

The first parameter to be determined is the specific IEG proteins that are formed after stimulation of the cell by *that* growth factor or neurotransmitter. The second parameter to be determined is this: how the relative expression of proteins induced by *that* growth factor or neurotransmitter changes over time. These parameters must be characterised, because the composition of the AP-1 TF complex is dynamic, and its composition will determine the genetic response of the cell.

II. Immediate-early Genes and the Central Nervous System

A. Basal Expression within the Central Nervous System

IEG TFs show constitutive expression within the CNS. For certain members of the IEGs, constitutive expression is low. For example, low but noticeable Fos-like immunostaining is apparent within the nuclei of adult nerve cells scattered throughout the amygdala, striatum and piriform cortex, and hippocampus (Dragunow et al., 1987; Morgan et al., 1987; Dragunow and Robertson, 1988a), although hippocampal Fos-like immunoreactivity may be caused by constitutive expression of Fras in dentate gyrus (Hughes et al., 1992). In addition, Fos-B protein is also expressed constitutively in rat brain, and low levels of expression can be found in cerebral cortex, striatum, amygdala, hippocampus, and dentate gyrus (Dragunow, 1990).

In contrast, the expression of Krox family members is high within the CNS. Both *krox*-24 mRNA (*zif* 268 mRNA; Schlingensiepen et al., 1991) and protein (Mack et al., 1990) are expressed at high levels within forebrain neurons. Highest levels of expression can be seen in deep layers of the neocortex (layers IV and VI) and hippocampus (CA1) (Schlingensiepen et al., 1991; Hughes et al., 1992). Krox-20 protein is also expressed at high levels basally within the superficial layers of the neocortex (layers II and III), caudate-putamen, globus pallidus and nucleus accumbens, but not hippocampus (Herdegen et al., 1993a). Currently, reports regarding basal expression of *krox*-20 mRNA are contradictory (Mack et al., 1992; Bhat et al., 1992b). The c-Jun protein is expressed at high levels within neurons of the dentate gyrus of the hippocampus (Hughes et al., 1992) and piriform cortex (Hughes et al., unpublished observations); c-*jun* mRNA is expressed weakly in cerebral cortex, with strongest expression in piriform cortex, dentate gyrus, and CA2-CA3 layers of hippocampus (Mellstrom et al., 1991). The mRNAs coding for *jun*-B and *jun*-D are expressed at high levels throughout the brain in hippocampus (dentate gyrus and CA1/CA3), striatum, thalamus, cortex, amygdala, and cerebellum (Mellstrom et al., 1991).

B. Induction within the Central Nervous System

Numerous recent studies have demonstrated that various treatments to the nervous system result in increased expression of IEG mRNA and protein in both neurons and non-neuronal cells. For example, seizure activity (chemically and electrically induced), kindling, brain-injury (i.e., mechanical, HI, spreading-depression), sensory stimulation (noxious, visual, olfactory, somatosensory), stress, learning, and the induction of LTP result in increased expression of IEGs within the nervous system. This section briefly discusses these topics and refers the reader to appropriate reviews where they exist.

1. Electrically and drug-induced seizure activity. Chemically and electrically induced seizures rapidly increase the expression of IEGs in mouse and rat brain. In the first two studies demonstrating seizure-mediated induction of c-*fos*, the convulsant drug pentylenetetrazole was found to induce c-*fos* mRNA and protein firstly in nuclei of neurons of the dentate gyrus, pyriform and cingulate cortices, and, subsequently, throughout cortex, hippocampus, and limbic system (Morgan et al., 1987; Dragunow and Robertson, 1987a). The time-course of c-*fos* mRNA induction in vivo was protracted compared with that in serum-stimulated fibroblasts and in PC12 cells treated with NGF. Induction of c-*fos* mRNA was refractory to additional seizure-mediated induction, whereas Fos protein-like immunoreactivity remained induced throughout the brain. Fos-like immunoreactivity was only found to be increased in neurons and not glia (Morgan et al., 1987). The benzodiazepine midazolam that prevented seizure activity also prevented Fos induction (Dragunow and Robertson, 1987a). Fos induction generally only occurred in those areas that experienced seizures (Le Gal La Salle and Naquet, 1990).

Additional studies have shown that a coordinated induction of IEGs occurs in the brain after seizure activity (Saffen et al., 1988; Sonnenberg et al., 1989a). c-*jun*, *jun*-B, *zif* 268, and *jun*-D mRNAs are also induced in rat brain neurons when animals are administered convulsant drugs or given electroshock-induced seizures (Saffen et al., 1988; Cole et al., 1990a). The increase in proto-oncogene mRNA is paralleled by an increase in AP-1-like DNA binding activity that persists on average for at least 6 to 8 h after initiation of seizures (Sonnenberg et al., 1989a, b). Fos protein induction occurs briefly within the first few hours and is not present 6 to 8 h after seizure-initiation, although AP-1-like DNA binding persists at these timepoints. This suggests that two Fos-related species of molecular weight 35 (possibly

Fra-1; Cohen and Curran, 1988) and 46 kD (possibly Fra-2; Nishina et al., 1990), which show delayed induction with respect to Fos, might participate with late-expressed Jun proteins to form Fra/Jun dimers.

These results and those of others suggest that seizure activity results in the formation of a dynamic AP-1 complex whose composition changes with time, Fos/Jun dimers initially, whereas Fos-B/Jun or Fra/Jun dimers predominate at later time points (Sonnenberg et al., 1989a; Gass et al., 1992a). Krox-20 protein, such as Krox-24 (zif268), is also induced by seizure activity (Bhat et al., 1992b; Hughes et al., 1994). Other forms of seizures have also been shown to induce IEG expression within the nervous system. Kainic-acid (Popovici et al., 1988), bicuculline (Gass et al., 1992a), pilocarpine or lithium and pilocarpine (Barone et al., 1993), MK801 and pilocarpine (Hughes et al., 1993c; Hughes et al., 1994), and audiogenic-induced seizures (Le Gal La Salle and Naquet, 1990) result in increased expression of IEGs. It has recently been suggested that, like 2-deoxyglucose use, Fos induction could be used as a general marker of neuronal activity (Dragunow and Faull, 1989a; Sagar et al., 1988). Inasmuch as seizure-induced c-*fos* induction does not occur in newborn rats given a convulsant dose of kainic-acid before postnatal day P13, this suggests that mechanisms responsible for seizure-mediated c-*fos* induction are not present at birth (Schreiber et al., 1992b), (For a review of seizure-mediated IEG induction see Morgan and Curran, 1991a).

2. *Kindling*. Kindling is an animal model of seizure development or epileptogenesis, whereby periodic (i.e., daily or twice daily) applications of an initially subconvulsive focal electrical stimulation eventually lead (over a period of days or weeks) to the formation of a generalised seizure. Focal electrical stimulation (usually to the amygdala or hippocampus, two brain areas that show kindling) results in a brief focal seizure or AD. The AD is an absolute prerequisite for kindling to occur. ADs in both the hippocampus and amygdala result in the induction of IEGs. Within the hippocampus, a single kindling AD results in the strong induction of Fos, Fos-B, Fras, c-Jun, Jun-B, Jun-D, and Krox-24 proteins in dentate granule cells and Fos, Jun-D, and Krox-24 proteins in somatostatin-containing neurons of the dentate hilus. Induction is transient, with basal levels reached for all IEGs investigated by 48 h (Dragunow and Robertson, 1987b; Dragunow et al., 1992; Hughes et al., submitted). In addition, mRNAs coding for c-*fos*, c-*jun*, and *NGFI-A* (*zif268/krox-24*) are also induced by kindling ADs within the hippocampus (Shin et al., 1990; Simonato et al., 1991; Hughes et al., submitted; Dragunow et al., 1989b). Amygdala kindling also induces increased expression of c-*fos* mRNA and Fos protein (Dragunow et al., 1988; Clark et al., 1991a; Teskey et al., 1991) c-*jun*, *jun-B*, *krox-24* mRNA and protein, and Krox-20 protein in rat brain (Hughes et al., 1994).

The distribution of IEG expression depends upon the stage of kindling and the length of the AD (Clark et al., 1991a; Tesky et al., 1991). We have found that in naive rats (except for a single test stimulation that was used to check electrode placement), a single amygdala AD results in unilateral increases in IEG expression, moderately within amygdala (basolateral/lateral/medial/cortical and basomedial nuclei) and claustrum/endopiriform nucleus and maximally in piriform and perirhinal cortices of the ipsilateral hemisphere (Hughes et al., 1994).

3. *Focal brain-injury and spreading depression*. Wounding of a fibroblast monolayer in vitro by scratching a line into a confluent layer of NIH 3T3 cells leads to a rapid induction of Fos-like immunoreactivity in cells lining the wound (Verrier et al., 1986). In rodents, injury to the cortex produced by insertion of a drill bit 2 mm into underlying cortex (Dragunow and Robertson, 1988b; Dragunow et al., 1990c), suction removal of cortex (Sharp et al., 1990), or disruption of pia-arachnoid (Herrera and Robertson, 1990a) leads to unilateral induction of c-*fos* mRNA and Fos and Fra proteins in neurons of the injured cortex but not of the undamaged hippocampus. After injury ipsilateral cingulate, piriform and neocortex show increased levels of both c-*fos* mRNA and Fos protein. Within the neocortex the induction of Fos-like immunoreactivity (antibody detects Fos and Fras) is laminar, with highest induction seen in layers 2,3,5, and 6 (Dragunow and Faull, 1990; Dragunow and Robertson, 1988b; Dragunow et al., 1990b, c).

Induction of c-*fos* (30 min) and Fos (1 h) occurs rapidly in cortex. Fos is essentially absent at 4 h. Induction of Fra is persistent remaining for at least 24 and possibly 72 h (Sharp et al., 1990). In addition, injury leads to induction of Fos-like immunoreactivity in ependyma lining the lateral and occasionally the third ventricle, in glial-like cells around the wound margin (but not distal to the wound), and in cells of the pia (Dragunow and Robertson, 1988b; Dragunow et al., 1990c; Sharp et al., 1990). Fos-like immunoreactivity was expressed maximally in glial cells between 12 to 24 h, but was gone by 72 h after injury, suggesting that injury-mediated expression of Fos-like immunoreactivity is more persistent in nerve versus glial cells (Dragunow et al., 1990a).

Unilateral induction of Fos proteins in nerve cells throughout the injured hemisphere may result from injury-induced cortical spreading depression. Literature supporting this idea demonstrates that direct application of KCl (potassium chloride) to neocortex, which induces spreading depression, results in Fos protein induction in a pattern very similar to that seen after mechanical cortical injury (Herrera and Robertson, 1990b; Herrera, et al., 1993). Induction in non-nerve cells may be induced by injury-released factors at the injury site (Dragunow and Robertson, 1988b; Dragunow et al., 1990c). Focal brain injury to the hippocampus produced by needle insertion and saline injection results in induction of c-*fos*, *jun-B*, c-*jun* and *krox*-24 (*zif* 268)

mRNA, and protein (Hughes et al., 1993a) and Krox-20, Fos-B, and Jun-D protein in nerve cells of the dentate gyrus (Dragunow and Hughes, 1993). In contrast, in non-nerve cells, Fos, Krox-24, c-Jun, Jun-B and Jun-D, but not Krox-20 or Fos-B proteins, are induced in cells around the wound margin, lining the ventricles or in the pial surfaces of the brain (Dragunow and Hughes, 1993).

4. Hypoxic-ischemic stroke. A number of studies have investigated the expression of IEGs in HI brain injury, although the results have been contradictory. HI in the infant rat brain was associated with induction of Fos in neurons only in the neocortex on the nonligated side of the brain (because of seizures). Induction of Fos-like immunoreactivity was, however, induced in glial-like cells on the ligated side (Gunn et al., 1990). Other studies have found both strong and weak induction of other IEGs and IEGPs in the injured brain after HI (Abe et al., 1991b; An et al., 1992; Onodera et al., 1989; Wessel et al., 1991; Ikeda et al., 1990; Popvici et al., 1990; Gubits et al., 1993; Gass et al., 1992b); induction occurred only in areas surrounding the ischaemic core (Uemura et al., 1991b) or in neurons resistant to injury (Uemura et al., 1991a). The reasons for these differences are probably associated with differences in the animal models used, the severity of the strokes, and the possibility of seizure activity or spreading depression, all of which could confound the results (Gunn et al., 1990; Gass et al., 1992b). Additional work in this area is required to present any clear picture.

5. Nerve transection. Transection of nerve fibres can induce complex changes in the axotomised neuronal cell body, including increased expression of growth associated proteins, cytoskeleton proteins, and neuropeptides. More recently, it has been identified that rapid but long-lasting increases in specific IEGs and IEGPs also occurs in the axotomised neuron cell body after nerve transection. In most studies, Jun mRNA and proteins (c-Jun and Jun-B and Jun-D) are strongly induced in axotomised neurons, whereas the induction of other IEGs only occurs in rare cases, and always in combination with Jun-family members (Jenkins and Hunt, 1991; Herdegen et al., 1992; Leah et al., 1991, 1993; Jenkins et al., 1993; Haas et al., 1993; Dragunow, 1992; Rutherford et al., 1993).

6. Long-term potentiation and memory formation. Brief episodes of tetanic activation of the perforant path input to the dentate gyrus result in a persistent increase, or long-term potentiation, in the synaptic efficacy of this monosynaptic excitatory pathway (Bliss and Lomo, 1973). LTP is a persistent activity-dependent form of synaptic plasticity that stands as a good candidate for the mechanism involved in associative memory. The mechanisms underlying the persistence of LTP are believed to rely on de-novo protein synthesis (Otani et al., 1989; Fazeli et al., 1993).

Studies performed to date have either investigated the induction of IEGs in anaesthetised or awake rats (For review see Dragunow et al., 1989b; Abraham et al., 1992). In awake animals, various stimulus paradigms resulting in LTP reliably increase the expression of Fra proteins but not c-*fos* mRNA, Fos or Fos-B proteins (Dragunow et al., 1989a; Demmer et al., 1993; Jeffery et al., 1990), c-*jun*, *jun*-B and *jun*-D mRNA and proteins and *zif* 268 mRNA and Krox-20 and Krox-24 proteins in dentate gyrus neurons (Richardson et al., 1992; Williams et al., 1995).

In the dentate gyrus of anaesthetised rats, induction of LTP reliably results in increased expression of *zif* 268 mRNA, less reliable induction of *jun*-B and c-*jun* mRNA, and little or no induction of c-*fos* mRNA or Fos protein (Douglas et al., 1988; Schreiber et al., 1991a; Cole et al., 1989, 1990b; Wisden et al., 1990). The lesser induction of IEGs in anaesthetised animals is thought to be because of the effects of anaesthesia, which also reduces LTP persistence (Jeffery et al., 1990). Correlational studies show that Krox-24 (Abraham et al., 1993) and Krox-20 (Williams et al., 1995) are most likely to be involved in stabilising LTP.

Learning-related phenomenon also induce IEG formation in the brain (Kaczmarek, 1993a, b). For example, hippocampal c-*fos* mRNA levels in rats are increased three-fold immediately after training to attain foot-shock-motivated brightness discrimination in a Y-maze. The elevated levels of c-*fos* mRNA had returned to basal levels after 2 h (Tischmeyer et al., 1990). The levels of both c-*fos* and c-*jun* mRNA are also seen to rise in the forebrains of chicks learning a discrimination behaviour. Chicks that have previously learnt the behaviour and are just repeating it show lower expression of c-*fos* and c-*jun* mRNA, suggesting that the learning of the discrimination task itself, and not the behaviour, is responsible for enhanced expression of c-*fos* and c-*jun* mRNA (Anokhin and Rose, 1990). In addition, imprinting (McCabe et al., 1993), exposure of chicks to a rich environment (Anokhin et al., 1991) or training of chicks in a one-trial passive avoidance task (Rose, 1991; Anokhin et al., 1991), leads to increased expression of c-*fos* mRNA and Fos-like immunoreactivity within a specific region of the chick forebrain, the intermediate medial hyperstriatum ventrale.

The majority of neurons (96.5%) that express Fos also express the gamma protein kinase C isoenzyme (PKCγ), suggesting that a connection may exist between learning, the intermediate medial hyperstriatum ventrale, and Fos expression. That is, learning could activate PKC, which would then lead to Fos production (Ambalavanarr et al., 1993). Songbirds hear the songs of other individuals of their species and respond by modifying their own vocal and social behaviour. Young birds learn their songs by imitating models that they hear (Mello et al., 1992). It is significant then that species-specific song presentation to songbirds has also been seen to causes large increases in the expression of *ZENK* mRNA (*zif* 268) in similar forebrain structures that have been

identified in chick learning processes. In the songbird these areas include the hyperstriatum ventrale and caudal neostriatum. Presentation of other auditory stimulation was less effective or ineffective in increasing *ZENK* expression. (Mello et al., 1992). Furthermore, behavioural training of a two-way passive avoidance response induces c-*fos* and *zif*268 mRNA in rat hippocampus and visual cortex during training (Nikolaev et al., 1992a, b): this seems to be related to learning and not to motor activity or reaction to pain during training (Nikolaev et al., 1992a, b).

Others reports have shown a delayed expression of c-*fos* in rat sensory cortex after sexual learning in male rats (Bialy et al., 1992), increased expression of c-Fos and Krox-24, but not c-Jun, protein in accessory olfactory bulb during the formation of an olfactory memory in mice (Brennan et al., 1992), and increased expression of c-*fos* and c-*jun* mRNAs specifically within the hippocampus of mice during learning of a bar-pressing task (Heurteaux et al., 1993). Apamin, a bee venom neurotoxin that can improve learning and memory retention, enhanced the learning-induced increase in IEG expression within the hippocampus (Heurteaux et al., 1993). Increased expression of Fos-like immunoreactivity in brain nuclei is also associated with conditioning and pseudo-conditioning of the rabbit nictitating membrane reflex (Irwin et al., 1992). In addition, performance in an escape task induces c-Fos in the motor cortex of rats (Castro-Alamancos et al., 1992).

7. Stress. Various forms of stress lead to increased expression of IEGs within the brain (Ceccatelli et al., 1989). For example, immobilisation stress or the general stress response after capsaicin administration strongly increases expression of IEGs in two brain regions: the central amygdaloid nucleus and PVN. Stress associated with capsaicin administration induces c-*fos*, c-*jun*, and *jun*-B in both central amygdaloid nucleus and PVN, whereas *jun*-D expression is selectively increased in the PVN (Honkaniemi et al. 1992). Immobilisation stress will also induce Fos-like immunoreactivity in both of these regions (Covenas et al., 1993; Honkaniemi, 1992).

The stress associated with earclipping has also been shown to increase c-*fos* mRNA in mouse brain (Nakajima et al., 1989a). Handling and a single injection of isotonic saline has been reported to result in increased c-*fos* mRNA levels in various brain regions, including the PVN, amygdala, hippocampus, and neocortex (Sharp et al., 1991b). Other IEG mRNAs (i.e., *fos-B*, *jun*-B, c-*jun*, *zif*268 and *fra*-1), as detected by Northern blotting, may also be increased in brain by injection stress 1 h after injection of saline (Perisco et al., 1993).

8. Sensory stimulation (noxious, non-noxious, olfactory and visual) and circadian rhythms. Both noxious (Fitzgerald, 1990) and non-noxious (sensory) peripheral stimuli induce c-*fos* expression in spinal dorsal horn neurons. For example, physiological stimulation of rat primary sensory neurons (hair brushing, gentle joint manipulation) causes the expression of c-Fos protein-like immunoreactivity in nuclei of postsynaptic neurons of the dorsal horn (Hunt et al., 1987). Activation of small diameter cutaneous sensory afferents by noxious chemical or heat stimulation strongly induces Fos, mainly in superficial layers I and II of the dorsal horn where the majority of unmyelinated nociceptive afferents terminate, although lower induction occurs in layers III to V. This effect is reasonably general being independent of the noxious agent applied, although some stimuli increase Fos-like immunoreactivity more in layers III and IV than do others (Strassman and Vos, 1993). In contrast, activation of low-threshold cutaneous afferents by hair-brushing and gentle joint manipulation induced weaker Fos expression in layers II to IV (and rarely in layer I), a finding consistent with termination zones for Aδ and C primary afferent fibres (Hunt et al., 1987). Noxious peripheral stimulation also results in Fos induction in thalamic areas known to process nociceptive information (Bullitt, 1989, 1990). In addition, non-noxious sensory stimulation produced by tactile stimulation of face whiskers induces Fos in somatosensory cortex (Mack and Mack, 1992).

Differential induction of IEGs has been reported to occur in dorsal horn neurons after noxious (hot water) stimulation of the hind paw. Specifically, c-*fos*, c-*jun* and *NGFI*-A (*zif*268/*krox*-24), but not *jun*-B or *jun*-D mRNA, is induced in neurons located mainly in laminae I and II, but also in V and X (Wisden et al., 1990). In another study, c-*fos* and *jun*-B, but not c-*jun* or *jun*-D, mRNAs were induced mainly in superficial layers of the dorsal horn after either peripheral injection of Freund's adjuvant (inflammation model) or heat stimulation of hindpaws (Naranjo et al., 1991).

c-Jun protein can be induced in layers I and II of dorsal horn (with slight induction in layer III) by repeated squeezing of the plantar surface of rat hind-paw (Herdegen et al., 1991). Opiates modify induction of c-*fos* in the spinal cord of the rat after noxious stimulation. Injection of morphine (10 mg/kg i.v.) reduced to 14% and 23% of control the number of Fos-positive neurons seen in deep (III-VI and X) and superficial (I and II) layers of spinal dorsal horn, respectively, after hot water (52°C) noxious stimulation of rat right hind paw (Tolle et al., 1990).

In addition, olfactory information and sensory processing of odours have been shown to influence IEG expression. For example, Fos-like immunoreactivity increases in accessory olfactory structures of female rats exposed to male odours (Dudley et al., 1992), whereas c-*fos* mRNA increases dramatically in cells of the glomerular layer and underlying granule, mitral, and tufted cells of the main olfactory bulb in response to brief exposure of male rats to peppermint or isoamyl acetate odours (Guthrie et al., 1993).

Visual input also controls IEG expression. For example, the high constitutive expression of *krox*-24 mRNA

and protein in visual cortex depends on ongoing visual input. Blockade of afferent visual activity with intraocular injections of tetrodotoxin results in rapid, dramatic reductions of *krox*-24 mRNA and protein in this area (Worley et al., 1991). Indeed, mono-ocular visual deprivation and Krox-24 immunohistochemistry reveals ocular dominance columns in monkey visual cortex (Chaudhuri and Cynader, 1993). Brief visual experience induces c-*fos*, *jun*-B and *krox*-24 (*egr*-1) but not c-*jun* mRNAs in cat visual cortex (Beaver et al., 1993, Rosen et al., 1992b), whereas light also induces a Fos-like nuclear antigen in retinal neurons (Sagar and Sharp, 1990). The induced IEGs might be involved in the process whereby visually elicited activity controls visual cortical development (i.e., visual system plasticity).

Light pulses that alter the phasing of the internal circadian clock result in IEG induction within the SCN of the hypothalamus (Rea, 1989; Rusak et al., 1990). The SCN seems to contain a light-entrainable circadian pacemaker that is responsible for the generation of a wide range of circadian physiological and behavioural rhythms in mammals. Bilateral destruction of the SCN abolishes, whereas transplantation of fetal SCN restores, circadian rhythmicity in rodents (Rusak and Zucker, 1979; Rea, 1989). It seems that gene expression is important for both the generation and control of circadian rhythms (Kornhauser et al., 1992).

Photic induction of IEGs occurs in subjective night but not subjective day. This finding links IEG induction with phase entrainment, inasmuch as the phase of the circadian clock is only sensitive to photic entrainment during subjective night. The induction of IEGs is predominantly located within the ventrolateral subdivision of the SCN, although weaker induction occurs in rostral SCN dorsal and lateral borders (Rea, 1989; Rusak et al., 1990; Abe et al., 1992). Photic exposure of rodents during subjective night can induce Fos-like immunoreactivity (Rea, 1989; Rusak et al., 1990; Earnest et al., 1990; Abe et al., 1991a, 1992), c-*fos* mRNA and *NGFI*-A (*zif*268) mRNA (Rusak et al., 1990, 1992), and *jun*-B, *jun*-D and c-*jun* mRNAs (Rusak et al., 1992). The increase in c-*jun* mRNA is small, however (Kornhauser et al., 1992), and preliminary results suggest that c-Jun protein may not be induced in SCN by photic stimulation (Rusak et al., 1992).

Recently, it has also been demonstrated that the constitutively expressed TF CREB becomes phosphorylated on Serine-133 (and therefore transcriptionally activated) in SCN in response to photic stimulation. Inasmuch as IEG promoters contain CREB binding sites, it is possible that CREB-P controls IEG expression in SCN in response to photic stimulation. Photic stimulation-induced CREB phosphorylation only occurs during subjective night, supporting this possibility (Ginty et al., 1993).

9. Sleep/sleep deprivation. Cholinergically-induced rapid eye movement sleep can induce Fos-like immunoreactivity in dorsolateral pontine regions associated with rapid eye movement sleep, such as the lateral dorsal tegmental and pedunculopontine tegmental nuclei, LC, dorsal raphe, and pontine reticular formation (Shiromani et al., 1992). In addition, sleep deprivation induces Fos-like immunoreactivity (Pompeiano et al., 1992) and c-*fos* and *NGFI*-A mRNAs and, less consistently, *jun*-B but not c-*jun* mRNA in rat brain (O'Hara et al., 1993).

10. Cardiovascular control and immediate-early gene induction. In studies attempting to identify central circuits involved in cardiovascular control in rats, a lowering of blood pressure either by stimulation of the aortic depressor nerve (McKitrick et al., 1992) or by substantial blood-volume removal (Dun et al., 1993; Badoer et al., 1992) causes Fos protein induction in nucleus tractus solitarius, area postrema, ventrolateral medulla, nucleus ambiguus, medullary reticular formation, parabrachial nucleus, LC, supraoptic nucleus, inferior olive, subfornical organ, organ vasculosum, hypothalamus, central nucleus of the amygdala, bed nucleus of the stria terminalis, and islands of Calleja (McKitrick et al., 1992; Dun et al., 1993; Badoer et al., 1992). Electrical stimulation of the vagus nerve or mechanical stimulation of the carotid sinus (stretching) leads to increased expression of c-*fos* and *NGFI-A* mRNA in nucleus tractus solitarius and paratrigeminal nucleus (Rutherford et al., 1992b). In addition, it has been shown that circulating angiotensin II (iv infusion of 30 to 55 pmol/kg/min over 2 h) induces Fos in the subfornical organ and organum vasculosum of the lamina terminalis (McKinley et al., 1992).

III. Activation of Specific Neurotransmitter Receptors Results in Increased Immediate-early Gene Expression within the Central Nervous System

A. Glutamate Receptors: N-methyl-D-aspartate/non-N-methyl-D-aspartate

Activation of both NMDA and non-NMDA receptors results in increased expression of IEGs within the nervous system. MK801 is a noncompetitive antagonist of the NMDA receptor. The distribution of MK801 binding sites closely parallels the distribution of Fos-positive cells found within the rat brain after administration of the convulsant metrazole, suggesting that activation of NMDA receptors by seizure activity may lead to Fos production within these neurons (Morgan et al., 1987). Glutamate receptor agonists (acting on both NMDA and non-NMDA receptors) also increase the expression of Fos in brain (Sonnenberg et al., 1989b; Abbud et al., 1992; Page and Everitt, 1993; Sugimoto et al., 1993; Saitoh et al., 1991).

Although antagonists of the NMDA receptor, such as MK801, have been reported to have little effect on IEG induction produced by electroshock (Cole et al., 1990a) or lindane-induced seizures (Vendrell et al., 1992), prior

administration of MK801 (1 to 1.5 mg/kg) will attenuate (by 50%) the increase in expression of c-*fos* mRNA in hippocampal dentate gyrus neurons produced by a single hippocampal kindling AD (Labiner et al., 1989; Labiner et al., 1993). In accordance with these results, we have found that MK801 significantly, but differentially, attenuates the rise in IEG mRNA and protein in rat dentate gyrus neurons produced by a single AD. MK801 strongly attenuates the rise in c-*fos* mRNA and protein (25 ± 5%, 38 ± 4%) and *krox*-20 protein (30 ± 5%), has a lesser effect on *jun*-B mRNA and protein (66 ± 4%, 59 ± 3%) and c-*jun* mRNA and protein (60 ± 15%, 67 ± 7%) but does not markedly attenuate *krox*-24 mRNA or protein (85 ± 2, 92 ± 6%). These results suggest that seizure-mediated induction of IEGs in neurons occurs through both NMDA receptor-dependent and -independent mechanisms. In addition, these results suggest that different members of the IEG family (i.e., the *krox*-24 gene and the c-*fos* and *krox*-20 genes) differ in their responsiveness to induction by NMDA receptor-dependent and independent signalling pathways (Hughes et al., submitted). It is likely that NMDA receptor-independent signalling pathways may involve activation of non-NMDA glutamate receptors, L-type VSCCs (Murphy et al., 1991; Lerea et al., 1992), or receptors sensitive to platelet-activating factor (Marcheselli et al., 1990). Blockade of the NMDA receptor with MK801 before induction of LTP in the hippocampus (Cole et al., 1989; Dragunow et al., 1989a; Cole et al., 1990b) or before traumatic mechanical brain injury to the cortex or hippocampus (Dragunow et al., 1990b; Dragunow et al., 1990c; Herrera and Robertson, 1990a; Sharp et al., 1990; Hughes et al., 1993a) totally prevents the increased expression of IEGs in neurons. However the increased expression of IEGs seen in glia after brain injury (Dragunow et al., 1990a; Dragunow and Hughes, 1993) is not significantly affected, suggesting that NMDA receptor-independent signalling pathways induce IEGs in glia after mechanical brain injury (Dragunow and Faull, 1989b; Dragunow et al., 1990a).

NMDA receptor blockade has also been shown to abolish induction of Fos produced by cortical spreading depression (Herrera and Robertson, 1989; Herrera and Robertson, 1990b), induction of Fos in cells of the arcuate nucleus-median eminence after systemic injection of NMDA (MacDonald et al., 1990), and induction of c-*fos* mRNA in cortex after excitotoxin stimulation of cortical inputs (Wood and de Belleroche, 1991). In addition, NMDA receptors are involved in regulating central expression of IEGs at a more physiological level. NMDA receptor blockade partially prevents light-induced c-*fos* and *NGFI*-A mRNA expression in rat retina (Gudehithlu et al., 1993) and, in addition, blockade of both NMDA and non-NMDA receptors inhibits the photic-mediated induction of Fos protein in ventrolateral, but not dorsolateral or dorsomedial, suprachiasmatic nucleus (Abe et al., 1991a, 1992), whereas blockade of NMDA receptors abolishes the synaptic activity-dependent high constitutive expression of *zif*268 in rat cortex (Worley et al., 1991). In contrast, the constitutive expression of Krox-20 protein in superficial layers of the neocortex does not seem to be dependent upon activation of NMDA receptors (Dragunow et al., unpublished observations). Lactation has recently been shown to inhibit hippocampal and cortical activation of Fos-like immunoreactivity by NMDA (40 mg/kg i.v.) but not kainate (1.5 to 2.5 mg/kg i.v.) (Abbud et al., 1992).

B. Cholinergic Receptors

1. Muscarinic. Administration of the nonselective muscarinic agonist pilocarpine (1 to 100 mg/kg i.p.) has been shown to result in increased expression of c-*fos* mRNA (Weiner et al., 1991) and Fos-like immunoreactivity in rat brain (Hughes and Dragunow, 1993; Bernard et al., 1993; Hughes and Dragunow, 1994). In addition, another nonselective muscarinic agonist oxotremorine (0.5 mg/kg i.p.) also increases Fos-like immunoreactivity in rat brain (Bernard et al., 1993). Upon administration of pilocarpine, particularly intense Fos protein induction occurs in many rat forebrain structures, including the primary olfactory (piriform) cortex, nucleus accumbens, amygdala, hippocampus, neocortex, and supraoptic nucleus of the hypothalamus. Lesser induction is seen in the striatum, septum, inferior colliculus, thalamus, hypothalamus, and in several brainstem nuclei. Within the neocortex, induction follows a laminar pattern being highest in layers 4 and 6 with lower induction seen in layers 2 and 5 (Hughes and Dragunow, 1993; Bernard et al., 1993; Hughes and Dragunow, 1994). Induction of Fos within the hippocampus is localised to Ammon's horn (CA1 and CA2) with only faint staining seen in the upper blade of the dentate gyrus (Hughes and Dragunow, 1993; Hughes and Dragunow, 1994).

The distribution of Fos protein induced by pilocarpine in the striatum is predominantly medio-ventral in rostral and medio-dorsal in caudal striatum. Very few Fos-positive cells are seen in lateral striatum (Hughes and Dragunow, 1993; Bernard et al., 1993). The distribution of medio-dorsal located Fos-positive cells in the striatum seems patchy, possibly suggesting matrix/striosomal compartmentalisation. Inasmuch as few neurons double-label for Fos and calbindin, a matrix protein, it seems that Fos induction occurs predominantly in neurons of the striosomal compartment (Hughes and Dragunow, 1993). However, whereas both oxotremorine and pilocarpine seem to preferentially induce Fos-like immunoreactivity in the striosomal compartment of the striatum, lesser induction also occurs within the matrix compartment (Bernard et al., 1993). Within olfactory and amygdaloid areas the highest levels of Fos induction are seen in piriform cortex, bed nucleus of the accessory olfactory tract, endopiriform nucleus, taenia tecta, anterior cortical, medial, posteriomedial cortical, and intercalated nuclei of the amygdaloid body. High levels are

also seen in the cortex-amygdala transition zone and the amygdala-hippocampal area (Hughes and Dragunow, 1993).

Coadministration of atropine (10 mg/kg) to pilocarpine-treated rats effectively reduces Fos protein induction in hippocampus and neocortex to vehicle-injected control levels, suggesting that induction of Fos protein is mediated by muscarinic cholinergic receptors (Hughes and Dragunow, 1993). Atropine (5 and 40 mg/kg i.p.) also abolishes Fos labeling induced by oxotremorine (Bernard et al., 1993). Systemic administration of pirenzepine is less effective than atropine in reducing pilocarpine-induced Fos-like immunoreactivity, possibly because of its poor penetration of the blood brain barrier (Hughes and Dragunow, 1993), however when injected centrally (200 μg i.c.v.) pirenzepine totally abolishes Fos induction (Hughes and Dragunow, 1994).

It has also been shown that the muscarinic antagonists atropine and scopolamine induce Fos-like immunoreactivity in rat brain. Atropine (2.5 to 40 mg/kg i.p.) and scopolamine (0.2 to 50 mg/kg i.p.) induce Fos-like immunoreactivity in striatum, nucleus accumbens, cingulate cortex, septum and olfactory tubercle, but not in neocortex, substantia nigra, or pallidum. Within the striatum, most Fos-immunoreactive nuclei are located in neurons of the dorsal and medial striatum and are preferentially located within the matrix, although some are also seen in striosomes (Bernard et al., 1993).

In addition, it has recently been shown that administration of pilocarpine produces increased expression of c-*fos*, *jun*-B, and *krox*-24 (*zif*268) mRNA and protein and Krox-20 protein in neurons of the hippocampus and neocortex (Hughes and Dragunow, 1994). Induction occurs in a similar spatial pattern to Fos protein induction after pilocarpine. Induction of c-*fos*, *jun*-B, *krox*-20, and *krox*-24 gene expression occurs rapidly (30 min to 1 h) after administration of pilocarpine with cortical induction preceding induction in hippocampus. By 8 h the expression of IEGPs is near baseline.

Systemic administration of either atropine (10 mg/kg) or scopolamine (5 mg/kg) reduces induction of all IEGs to levels seen in vehicle-injected rats. In addition, central unilateral injection of pirenzepine (200 μg i.c.v.) abolishes IEG induction in hippocampus and cortex, suggesting that activation of central muscarinic (M1 but not M2) receptors results in increased expression of IEGs in rat brain neurons. Furthermore, pilocarpine administration does not detectibly induce the expression of c-*jun* mRNA or protein or jun-D protein in neurons of the neocortex or hippocampus, suggesting that activation of central pirenzepine-sensitive muscarinic receptors results in the induction of a specific pattern of immediate-early gene expression in neurons (Hughes and Dragunow, 1994).

These results are in contrast to in vitro studies that have shown that carbachol, a nonselective muscarinic agonist, increases c-*jun* mRNA (Trejo and Brown, 1991) and c-Jun protein in addition to c-*fos*, possibly *fos*-B, and *jun*-B mRNA in human 1321N1 astrocytoma cells. The expression of *jun*-D, *fra*-1, and *fra*-2 mRNAs seemed unaltered (Trejo et al., 1992). In addition, in cultured cerebellar granule cells, carbachol seemed unable to increase c-*fos* mRNA levels (Szekely et al., 1989). In cultured Neuroblastoma × Glioma Hybrid NG108–15 cells, however, carbachol does seem to increase *zif*268 mRNA expression (Katayama et al., 1993).

Within rat cortex, Northern blots show that a single intraperitoneal injection of lithium chloride significantly augments pilocarpine-induced c-*fos* mRNA expression (Weiner et al., 1991). This effect has also been demonstrated in PC12 cells (Kalasapudi et al., 1990; Divish et al., 1991), where it can be shown that, although lithium augments phosphatidyl inositol biphosphate$_2$-mediated c-*fos* expression induced by activation of either muscarinic cholinergic receptors or phorbol esters that directly activate PKC, lithium does not augment c-*fos* expression induced by receptor (prostaglandin E_1) or post-receptor (forskolin, 3-isobutyl-1-methyl xanthine) activators of cAMP (Divish et al., 1991).

In addition, in human 1321N1 astrocytoma cells in which PKC has been down-regulated by prolonged exposure to phorbol esters, carbachol no longer stimulates c-*fos* or c-*jun* expression, suggesting a critical role for PKC in these responses (Trejo and Brown, 1991). In contrast, an earlier paper suggested that activation of PKC-independent pathways by carbachol could also increase c-*fos* expression in this cell line, inasmuch as carbachol retained the ability to stimulate c-*fos* expression in PKC-deficient cells (Blackshear et al., 1987). Interestingly, if cytosolic Ca^{2+} levels are buffered in 1321N1 cells, c-*fos* expression induced by muscarinic receptor activation is augmented, whereas c-*jun* expression is attenuated. Furthermore, activation of c-*fos* expression by phorbol esters is potentiated by the Ca^{2+} ionophore ionomycin while c-*jun* expression is repressed, suggesting that concomitant rises in intracellular Ca^{2+} will potentiate the induction of c-*fos*, but repress the induction of c-*jun* after muscarinic receptor activation (Trejo and Brown, 1991). It has also recently been shown that lithium alone increases Fos-like immunoreactivity in parabrachial nucleus, area postrema, and nucleus of the tractus solitarius (Yamamoto et al., 1992), and we have observed that i.c.v. injection of polymyxin B (PMB, a selective inhibitor of PKC) abolishes pilocarpine-mediated induction of IEGs in hippocampus (Dragonow et al., unpublished observations).

Taken together, these observations suggest that activation of central pirenzepine-sensitive muscarinic receptors linked to phosphatidyl inositol biphosphate$_2$ hydrolysis and PKC activation results in a transient temporal, spatially distinct, combination specific, pattern of IEG expression in rat brain. Within the rat retina blockade of muscarinic receptors with atropine has been demon-

strated to partially reduce light-induced expression of both c-*fos* and *NGFI-A* mRNA (Gudehithlu et al., 1993).

2. *Nicotinic*. Nicotine has previously been shown to induce c-*fos* in differentiated PC12 cells (Greenberg et al., 1986). Induction by nicotine relies upon a flux of Ca^{2+} ions into the cell through VSCCs. Nicotine at a dose of 2 mg/kg i.v. (1 h cannula infusion in free-moving rats) induces Fos immunoreactivity in specific rat brain regions that include primary visual structures, including the superficial grey layer of the superior colliculus and medial terminal nucleus of the accessory optic tract and in the rostral subnucleus of the interpeduncular nucleus (Ren and Sagar, 1992). Induction occurred within 60 min of infusion initiation and was reduced at 180 and 240 min. The nicotinic receptor antagonist mecamylamine (5 mg/kg i.p.) significantly reduced Fos expression in these areas. Subcutaneous injection of nicotine at the same dose has been shown to result in induction of Fos in these structures as well as in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and in the medial habenula (Sagar et al., 1990).

It is likely that nicotine acts presynaptically, possibly in the retina, to stimulate the release of an unidentified neurotransmitter that then increases Fos expression in the superior colliculus and medial terminal nucleus of the optic tract; blockade of retinal activity with intravitreal injections of tetrodotoxin blocks nicotine-induced Fos immunostaining in these regions. The site at which nicotine acts to increase Fos in the interpeduncular nucleus is unknown at present, but this nucleus contains both pre- and post-synaptic nicotinic receptors. Because i.v. nicotine fails to induce Fos expression in several areas that have high densities of nicotine-binding sites (i.e., substantia nigra, ventral tegmental area, and thalamus), it has been suggested that in these areas activation of presynaptic nicotine receptors causes the release of neurotransmitters that are unable to induce Fos in the post-synaptic cell (i.e., release of γ-aminobutyric acid in the thalamus is unlikely to induce Fos immunostaining) (Ren and Sagar, 1992). However, in another study, nicotine (0.4 to 1.4 mg/kg sc) was shown to induce Fos-like immunoreactivity, mostly in nondopaminergic neurons of the ventral tegmental area (Pang et al. 1993).

Fos induction has also been demonstrated in PVN, nucleus tractus solitarius, LC, supraoptic nucleus, central nucleus of the amygdala, cingulate gyrus of the cortex and dentate gyrus of the hippocampus 60 min after a single i.v. injection of 0.1 mg/kg nicotine (Matta et al., 1993). Nicotine at 2 mg/kg i.p. also induces rapid expression of c-*fos*, *jun*-B, and *NGFI*-A mRNA and a slower increase of c-*jun* and *jun*-D mRNAs in rat superior cervical ganglion (Koistinaho et al., 1993). c-*fos* mRNA also was induced in rat brain after nicotine administration, suggesting that increased transcription of the c-*fos* gene is responsible for increased levels of Fos protein (Sharp et al., 1993). Activation of nicotinic receptors also seems to be required for light-induced IEG expression in hamster SCN, with the nicotinic receptor antagonist drug mecamylamine significantly reducing light-induced Fos-like immunoreactivity, predominantly in dorsomedial SCN (Zhang et al., 1993).

C. Adrenergic Receptors

Treatments that cause brain NE release can be shown to increase the expression of c-*fos* in rat brain. For example, stress associated with restraint handling and saline injection increases expression of c-*fos* and *zif*268 genes (Gubits et al., 1989; Bing et al., 1991). This increase can be abolished by pharmacological blockade of β-adrenoceptors with propranolol (10 mg/kg i.p.), (Bing et al., 1991). Agents that release NE by blocking presynaptic autoinhibitory α_2 receptors (i.e., yohimbine, 5 mg/kg i.p.) also strongly induces c-*fos* mRNA (Gubits et al., 1989) and *zif*268 mRNA in rat brain (Bing et al., 1991). Induction of c-*fos* and *zif*268 mRNA after NE release produced by yohimbine can be partially prevented by administration of propranolol and prazosin (α_1 receptor antagonist, 5 mg/kg i.p.) in combination (Bing et al., 1991).

Yohimbine induces Fos-like immunoreactivity in areas of rat brain that contain a high density of α_2-receptor binding sites such as the LC, bed nucleus of stria terminalis, the central nucleus of the amygdaloid complex, the PVN, the nucleus tractus solitarius, and ventrolateral medulla oblongata (Tsujino et al., 1992). Yohimbine also increases Fos-like immunoreactivity in neocortex and piriform cortex, Islands of Calleja, and supraoptic nucleus (Bing et al., 1992b).

Within the neocortex induction seems laminar (Bing et al., 1992b). Induction is predominantly mediated by β-adrenoceptors, inasmuch as propranolol is more effective than prazosin in reducing the increased cortical expression of Fos-like immunoreactivity produced by yohimbine (Bing et al., 1992b). Although the majority of neocortical β-adrenoceptors exist on astrocytes (Stone et al., 1990), Fos-like immunoreactivity seems to be located almost exclusively in neurons (Bing et al., 1992a).

The effect of stress associated with saline injection alone had little effect on the number of cells that showed Fos-like immunoreactivity, however restraint stress produced strong Fos-like immunoreactivity in neocortical cells. Propranolol significantly reduced the induction of Fos in neocortex produced by restraint stress (Bing et al., 1992b). The majority of noradrenergic fibres that innervate the neocortex originate from the LC, where their neuronal cell bodies reside. Lesioning of the LC using the neurotoxin 6-OHDA effectively abolishes noradrenergic innervation of the neocortex. Lesioning of the LC also markedly attenuates the induction of Fos-like immunoreactivity in rat neocortex produced by either restraint stress or the α_2-adrenoceptor antagonist yohimbine, suggesting that it is a release of NE after restraint stress or yohimbine administration that re-

sults in increased Fos production in neocortical neurons (Stone et al., 1993). Lesioning of the LC with the neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine has also been shown to markedly suppress the high constitutive expression of *zif*268 mRNA that is found in rat neocortex. Basal expression of *zif*268 in hippocampus (CA1) was not altered by LC lesion.

These results show that constitutive expression of *zif*268 in neocortex, but not hippocampus, is dependent upon tonic activity of the forebrain noradrenergic neurotransmitter system (Bhat and Baraban, 1992). Furthermore, within the rat pineal gland, both c-*fos* and *jun*-B mRNA can be regulated by activation of noradrenergic receptors. Although both phenylephrine (α_1-agonist) and isoproterenol (β-agonist) induce similar levels of expression of *jun*-B mRNA in pineal neurons (although isoproterenol was somewhat more effective), the expression of c-*fos* mRNA is differentially regulated by these two drugs. The α-agonist phenylephrine causes a far more significant increase in pineal c-*fos* mRNA levels than does isoproterenol (Carter, 1993). Activation of α_2-adrenoceptors by the highly selective α_2-agonist medetomidine has also been shown to suppress the increase in c-Fos, Fos-B, c-Jun, Jun-B, and Krox-24 proteins seen in the dorsal horn of the spinal cord after peripheral noxious stimulation. Supression was stronger in the deep (III to VI) rather than superficial (I and II) laminae of the dorsal horn (Pertovaara et al., 1993).

D. Serotonin Receptors

Fenfluramine is an indirect 5-HT agonist. It increases 5-HT availability at nerve terminals by enhancing 5-HT release but blocking 5-HT uptake. Systemic administration of fenfluramine (25 mkg/kg i.p.) results in marked increases in Fos-like immunoreactivity in striatum (but not nucleus accumbens), parvocellular division of the hypothalamic PVN, and in the central amygdaloid nucleus (Richard et al., 1992). In addition, it also seems to induce Fos-like immunoreactivity in the bed nucleus of the stria terminalis, midline thalamic nuclei, habenular nuclei, lateral parabrachial nucleus, and nucleus of the solitary tract (Li and Rowland, 1993).

At parenteral doses of 2 or 8 mg/kg, the 5-$HT_{2/1C}$ receptor agonist DOI causes a highly localised expression of Fos in frontal, parietal, cingulate, and piriform cortex as well as in claustrum, mamillary bodies, globus pallidus, amygdala, nucleus accumbens, and dorsomedial striatum. Within the primary somatosensory cortex, induction occurs within layer Va, which is reported to receive innervation from the dorsal raphe nucleus. Chronic lithium treatment of rats enhances cortical induction of Fos by DOI (Leslie et al., 1993b). No induction of Fos was found in hippocampus, although 5-$HT_{2/1C}$ receptors can be found here.

The 5-$HT_{2/1C}$ antagonist, ritanserin (0.4 mg/kg), markedly attenuated the increased Fos expression produced by DOI. Induction of Fos protein by DOI first became evident after 30 min, reached a maximum level at 3 h, and declined to background or near background levels by 24 h. Induction occurred only in neurons, because, although many neurons double-labeled for Fos and neuron-specific enolase, no neurons could be seen to double-label for Fos and glial fibrillary acidic protein (a glial-specific marker) (Leslie et al., 1993a).

The 5-HT_{1A} receptor agonist 8-OH-DPAT also slightly increases Fos protein levels in cortex. Chronic lithium did not seem to enhance Fos expression induced by 8-OH-DPAT. This lack of effect may occur because 5-HT_{1A} and 5-HT_{2A} receptors are linked to different second-messenger systems. The 5-HT_{2A} receptor is linked to the hydrolysis of phosphoinositides, whereas the 5-HT_{1A} receptor activates adenylate cyclase (Leslie et al., 1993b). Serotonin systems also seem necessary (in conjunction with dopamine systems, see next section) for the induction of IEGs in striatum by cocaine, with selective denervation of 5-HT projections to the striatum attenuating the increased expression of c-*fos* and *zif*268 mRNA produced in striatum by cocaine administration (Bhat and Baraban, 1993).

E. Dopamine Receptors

Recent studies have shown a link between dopaminergic neurotransmission and the IEGP Fos/Fras in rat basal ganglia neurons. For example, in 6-OHDA-lesioned rats, administration of the dopamine precursor, levodopa, produced a large induction of Fos/Fras in striatal neurons (Robertson et al., 1989a). This effect was later found to be caused by D_1, but not D_2, dopamine receptor agonism (Robertson et al., 1989b), although D_2 receptors do seem to play a small part in the induction of c-Fos after levodopa injection (Morelli et al., 1993a). In contrast, D_2 receptor agonists induce Fos/Fras in pallidal neurons after dopamine-depletion (Paul et al., 1992).

D_1-agonists induce Fos specifically in striato-nigral projection neurons (Robertson et al., 1990, 1992; Cenci et al., 1992) that contain dynorphin and substance P, but not enkephalin (Zhang et al., 1992). Activation of D_1-receptors is involved in c-*fos* induction in dopamine-depleted striatum (Simson et al., 1992; Johnson et al., 1992). More recently, it has been shown that combined treatment of dopamine-depleted rats with D_1- and D_2-selective agonists produces a synergistic induction of c-*fos* in the striosomal compartment and in the dorsolateral caudoputamen (Paul et al., 1992). This c-*fos* induction (and turning behaviour) is blocked by D_1 or D_2 antagonists and also by the NMDA receptor antagonist MK801 (Paul et al., 1992). In contrast, MK801 potentiates induction of Fos by the D_1 agonist SKF 38393 in the dorsolateral aspect of the depleted striatum (Morelli et al., 1992). The reason for these different results is unclear, however, recently it has been demonstrated that transection of glutaminergic cortico-fugal fibres reduces amphetamine- and apomorphine-induced Fos expression (Cenci and Björkland, 1993), supporting previous

results (Paul et al., 1992). In addition it has recently been demonstrated that muscarinic antagonists potentiate D_1-receptor (but not D_2-receptor)-mediated turning and Fos expression in lesioned striatal neurons, suggesting that both glutamate and acetylcholine systems are involved in the D_1-mediated induction of Fos/Fras in the striatum (Morelli et al., 1993b).

Although D_1-agonists induce Fos in the dopamine-depleted striatum, they do not induce it on the intact side (Robertson et al., 1989a, b; also see Dilts et al., 1993, who found that a high dose of apomorphine induced Fos and Fras). It seems that direct-acting dopamine receptor agonists induce Fos through D_1 receptors made supersensitive by dopamine-depletion with 6-OHDA or reserpine (Cole et al., 1992; Robertson et al., 1989a). The reason for this selectivity for supersensitive D_1-receptors is unclear, but it may be subtle neurochemical alterations occurring after dopamine-depletion caused this selectivity (Thomas et al., 1992). However, c-Fos induction seems to provide a biochemical marker of D_1-receptor sensitivity (Asin and Wirtshafter, 1993; Lahoste et al., 1993).

In contrast, dopamine-releasing drugs (indirect dopamine agonists), such as cocaine, amphetamine, and MDMA, induce Fos in intact striatal neurons via D_1-receptor activation (Dragunow et al., 1991b; Graybiel et al., 1990; Snyder-Keller, 1991; Young et al., 1991) and in striato-nigral projection neurons (Cenci et al., 1992). In fact, dopamine depletion abolishes amphetamine-mediated induction of Fos, indicating that it is caused by dopamine release (Robertson et al., 1989b). Interestingly, MDMA- and amphetamine-induced expression of Fos in caudo-putamen is inhibited by MK801 (Dragunow et al., 1991b; Snyder-Keller, 1991) and induction by amphetamine is also slightly inhibited by morphine (Fuxe et al., 1991), which, along with caffeine, also induces Fos expression in the striatum (Chang et al., 1988; Nakajima et al., 1989b; Johansson et al., 1992). A detailed study of the types of striatal neurons expressing Fos after amphetamine and cocaine reveals that induction occurs in DARPP-22-positive neurons but not in enkephalin-positive cells. Fos induction was not seen in neurons that co-expressed enkephalin and DARPP-22. It was therefore suggested that D_1-receptor agonists might induce Fos via DARPP-22 (Berretta et al., 1992).

In addition to inducing c-*fos* gene expression, dopamine-releasing drugs, such as amphetamine and cocaine, also lead to the expression of *jun*-B (Cole et al., 1992; Moratalla et al., 1993), *zif* 268 (Cole et al., 1992; Moratalla et al., 1992), but not c-*jun* (Moratalla et al., 1993; but see Hope et al., 1992). These results suggest that dopamine-releasing drugs induce mainly Fos/Jun-B dimers as well as *zif* 268. *zif* 268 is also expressed at high levels basally in the striatum (and other brain regions), and this basal expression can be reduced by blocking D_1-dopamine receptors (Mailleux et al., 1992) and by noradrenaline depletion (Bhat and Baraban, 1992). Although the 5-HT system does not contribute to basal expression of *zif* 268 in the striatum (Bhat and Baraban, 1992), it seems that the induction of IEGs, including *zif* 268, by dopamine-releasing drugs such as cocaine is partly caused by activation of 5-HT receptors (Bhat and Baraban, 1993).

In contrast to the effects of acute drug administration, chronic administered cocaine leads to a suppression of basal *zif* 268 expression (Bhat et al., 1992a), and of c-*fos*, c-*jun*, *fos*-B, *jun*-B, and *zif* 268 expression, although AP-1 binding activity remained elevated (Hope et al., 1992). Also, repeated treatment of rats with the D_1-agonist A-77636 fails to induce either turning or striatal Fos expression in dopamine-depleted rats (Asin and Wirtshafter, 1993). In contrast, 2.5 mg/kg amphetamine induces a greater expression of Fos in the striatum of rats treated 3 days earlier with amphetamine compared with rats treated 3 days earlier with saline (Norman et al., 1993). The reason for these different results may lie in the different dosing regimes, with short-interval dosing suppressing Fos and causing behavioural tolerance, whereas the 3-day interval leads to behavioural and biochemical sensitisation (Norman et al., 1993).

In addition to dopamine agonists, D_2 but not D_1 dopamine receptor antagonists induce Fos and Fras in rat caudate putamen and nucleus accumbens neurons (Dragunow et al., 1990d; Miller, 1990). Furthermore, dopaminergic denervation with 6-OHDA leads to a long-term increase in Fra, but not Fos, expression in striatal neurons projecting to the globus pallidus (Dragunow et al., 1991a; Jian et al., 1993). This increased Fra expression may account for the inhibitory effect of 6-OHDA lesions on haloperidol induction of Fos (Robertson and Fibiger, 1992), inasmuch as Fras may inhibit c-*fos* transcription. These results suggest that dopamine, acting on D_2 receptors, tonically inhibits Fos and Fras in striatal neurons. Induction of Fos by D_2 antagonists occurs in striato-pallidal enkephalinergic neurons (Robertson et al., 1992).

It has been suggested that the induction of Fos by D_2 antagonists may be because of blockade of dopamine-mediated inhibition of glutamate release onto striatal neurons (Dragunow et al., 1990d). This belief is supported by observations that the D_2 receptor antagonist, haloperidol, increases the release of glutamate into striatum, whereas intra-striatal injection of quinolinic acid, an NMDA receptor agonist, results in increased expression of Fos and Fras (Aronin et al., 1991; Berretta et al., 1992). Furthermore, cortical stimulation that activates cortico-striatal glutaminergic pathways induces Fos in striatal neurons (Fu and Beckstead, 1992). However, whereas block of NMDA receptors with MK801 inhibits haloperidol-mediated induction of Fos in rat striatum, very high doses of antagonist are required, and induction is never completely abolished (Dragunow et al., 1990d). In mouse striatum, MK801 seems more effective (Ziolkowska and Hollt, 1993).

More recently, the muscarinic antagonist scopolamine has also been shown to attenuate haloperidol-induced Fos expression in the striatum, suggesting that D_2 antagonist-mediated induction of Fos in striatum may also be partially mediated by cholinergic mechanisms (Guo et al., 1992). Furthermore, the muscarinic agonist, pilocarpine, induces Fos in striatal neurons (Hughes and Dragunow, 1993). Others reports, however, have found that another muscarinic antagonist, atropine, does not block haloperidol-induced c-*fos* mRNA expression in the caudate (Merchant and Dorsa, 1993). Although pilocarpine induces Fos strongly in the striatum, this occurs most prominently in the posterior caudate (Hughes and Dragunow, 1993), whereas haloperidol induction occurs most strongly in anterior caudate (Dragunow et al., 1990d), suggesting perhaps that the muscarinic system is not involved.

The transcriptional program switched on in striatal neurons by D_2 antagonists such as haloperidol has recently been characterised in detail (Rogue and Vincedon, 1992; MacGibbon et al., 1994; Nguyen et al., 1992). In a comprehensive study measuring both mRNA and protein levels, it has been shown that haloperidol induces c-Fos, Fras, Fos-B, Jun-B, Jun-D and Krox-24, but not c-Jun, in striatal neurons (although see Rogue and Vincedon, 1992, who suggest that c-*jun* mRNA expression is increased). Therefore, it seems that a complex transcriptional gene program is activated by haloperidol in striatal neurons, and it has been suggested that these changes in gene expression may be involved in the extrapyramidal side effects of typical neuroleptic drugs such as haloperidol (MacGibbon et al., 1994).

In contrast to the effects of haloperidol, clozapine, which is an atypical neuroleptic that lacks appreciable extra-pyramidal side-effects, induced Fras, Jun-B, and Krox-24, but not c-Fos or Jun-D (MacGibbon et al., 1994). The inability of clozapine to alter the expression of c-Fos has also been demonstrated by others (Robertson and Fibiger, 1992; Nguyen et al., 1992; Deutch et al., 1992). Furthermore, clozapine, but not haloperidol, produces a strong induction of Fras in the islands of Calleja. It is possible that the changes in Fra gene expression in this area of the brain may be involved in producing the therapeutic effects of clozapine on negative symptoms of schizophrenia (MacGibbon et al., 1994).

F. Opiate Receptors

Activation of central opiate receptors by an acute dose of morphine (10 mg/kg s.c.) results in an increase in c-*fos* mRNA and Fos-like immunoreactivity in rat caudate-putamen. c-*fos* mRNA was significantly increased at 45 min, but not at 90 min, after morphine administration. Fos protein was also increased 3 h after morphine administration in caudate-putamen but not in olfactory tubercle, which does not express the μ-type of opiate receptor. Coadministration of naloxone blocked the morphine-mediated increase in c-*fos* mRNA (Chang et al., 1988). Morphine has also been shown to reduce, by up to 80%, the number of Fos-positive neurons induced in spinal cord dorsal horn after peripheral noxious stimulation (Tolle et al., 1990).

G. Adenosine Receptors

Blockade of central adenosine receptors with the adenosine-receptor antagonist caffeine can transiently induce c-*fos* mRNA in mouse brain. Caffeine, at a subconvulsive dose (100 mg/kg i.p.), caused a significant rise in the levels of c-*fos* mRNA in caudate-putamen and olfactory tubercle. Coadministration of the adenosine A_1 receptor agonist, N^6-cyclohexyladenosine, did not block C-*fos* stimulated by caffeine administration, however the selective adenosine A_2 receptor agonist, 5′-N-ethylcarboxamide adenosine (0.1 mg/kg i.p.), significantly reversed c-*fos* expression induced by caffeine. These results suggest that blockade of central adenosine A_2 receptors by caffeine results in c-*fos* mRNA expression in mouse brain (Nakajima et al., 1989b), although recent work suggests alternative mechanisms (Johansson et al., 1992).

H. Neuropeptide and Hormone Receptors

Various neuropeptide and hormone systems seem able to regulate the expression of IEGs. For example, an estrogen-responsive element exists in the c-*fos* gene, and estrogen (0.375 mg/kg s.c.) has been shown to increase the expression of c-*fos* mRNA in ovariectomised rats in midbrain and hippocampus, but not in cerebellum. Induction of c-*fos* mRNA was maximal at 30 min in midbrain and at 60 min in hippocampus (Cattaneo and Maggi, 1990). A single subcutaneous injection of estradiol (0.1 mg/kg) also induces Fos-like immunoreactivity in noradrenergic neurons of the A2 cell group of the nucleus tractus solitarius 3 h after injection (Jennes et al., 1992).

Administration of recombinant growth hormone (1.33 mg i.v. = 4 units) to hypophysectomised rats results in c-*fos* expression in specific brain regions. Induction of c-*fos* gene expression occurs in the arcuate nucleus of the hypothalamus after a single dose of growth hormone. After a second dose of growth hormone, c-*fos* induction also occurs within the periventricular nucleus of the hypothalamus. Induction in both areas was transient, being maximal at 60 min and decreasing thereafter until basal levels were reached at 120 min (Minami et al., 1992).

Peripheral administration of CCK (8 μg/kg i.p.) induces c-*fos* expression in rostral and caudal parts of the nucleus of the solitary tract and in the PVN of the hypothalamus. Because induction was blocked by administration of the peripheral CCK-A antagonist, Devazepide (L364, 718), it is likely that CCK induces Fos-like immunoreactivity in CNS regions by activating peripheral systems that project to these areas (Chen et al., 1993). The CCK analog caerulein has also been

shown to reduce seizure-mediated (pentylenetetrazole, 50 mg/kg i.p.) induction of c-*fos* and *zif*268 mRNA in hippocampus and dentate gyrus, but not in piriform cortex (Miyoshi et al., 1992).

Peripheral bombesin, like CCK, results in induction of Fos-like immunoreactivity in area postrema, medial portion of the nucleus tractus solitarius, and in the PVN of the hypothalamus. Smaller increases in Fos-like immunoreactivity were seen in the central part of the amygdala, parabrachial nucleus, and supraoptic nucleus (Bonaz et al., 1993a). Furthermore, peripheral administration of Peptide YY (300 μg/kg i.p.) increases fos-like immunoreactivity in area postrema, nucleus tractus solitarius, central amygdala, and thalamus (Bonaz et al., 1993b).

Intracerebroventricular injection of somatostatin or vasopressin leads to increased expression of c-*fos* mRNA in granule cells of the cerebellum but not in cortex or limbic brain regions such as the hippocampus. It is not known whether this transient induction of c-*fos* in cerebellum is a direct effect of the two neuropeptides on granule cells or whether induction is secondary to the phenomenon of "barrel rotation" that both drugs produce in rats (Kamegai et al., 1993). Central injection of vasopressin also increases Fos-like immunoreactivity in the central nucleus of the amygdala, ventrolateral septum, parvocellular divisions of the PVN of the hypothalamus, dorsal tuberal nucleus, and LC (Andreae and Herbert, 1993).

Intraventricular administration of corticotropin-releasing hormone (100 μg) induces c-*fos* mRNA unilaterally in several cerebral cortical structures, most predominantly in the dorsal endopiriform nucleus and in the piriform and insular cortices (Clark et al., 1991b). Another report has shown that corticotropin-releasing hormone also induces c-*fos* mRNA in limbic structures, including the cingulate cortex, lateral septal nucleus, hippocampus, amygdala (i.e., central nucleus), hypothalamic PVN, supraoptic nucleus, dorsomedial nucleus, pontine nucleus, Barrington's nucleus, and LC. The granule cells of the cerebellum, some thalamic nuclei, the bed nucleus of the stria terminalis, and the habenula nuclei also showed increases (Imaki et al., 1993). In addition, the dorsal tuberal nucleus and parabrachial nucleus show increased levels of Fos-like immunoreactivity after corticotropin-releasing hormone administration (Andreae and Herbert, 1993).

IV. Expression of Immediate-early Genes in Non-nerve Cells of the Central Nervous System

It was discovered a number of years ago that mechanical injury to the brain induces Fos in non-nerve cells in white matter tracts (corpus callosum, fornix-fimbria, internal capsule), grey matter (hippocampus, cortex, striatum, thalamus), lateral and third ventricles in ependymal cells, and on the pial surfaces of the brain (Dragunow and Robertson, 1988b). Similar effects were observed after hypoxia-ischaemia (Gunn et al., 1990) and heat-shock (Dragunow et al., 1989c). More recently, it has been shown that this induction does not occur uniformly in non-nerve cells with Fos/Fras, c-Jun, and Krox-24 being strongly induced, Jun-B and Jun-D weakly induced, and Fos-B and Krox-20 not induced (Dragunow, 1990; Dragunow and Hughes, 1993). Although induction in neurons after mechanical brain injury is dependent on NMDA receptor activation and calcium/calmodulin kinase II, induction in non-nerve cells is not (Dragunow et al., 1990b, c). Cyclic AMP seems to be an important signal for IEGP induction in non-nerve cells of the brain (Dragunow and Faull, 1989b). Furthermore, using double-labeling methods, we have discovered that most of the non-nerve cells expressing IEGPs are not glial fibrillary acidic protein-positive astrocytes or glycerol phosphate dehydrogenase-positive oligodendrocytes (Dragunow et al., 1990c). Thus, at present, the identity of the non-nerve cells expressing IEGPs in white and grey matter is unclear. However, a number of these cells seem, from their donut-shaped morphology, to be dividing (Dragunow and Hughes, 1993). Thus, IEGP expression in non-nerve cells after traumatic stimuli may be involved in the proliferation of these cells in response to injury, as has been demonstrated in other cell types (Kovary and Bravo, 1991; Riabowol et al., 1988).

V. Specificity of Immediate-early Gene Induction in Adult Neurons

Because of the apparently widespread inducibility of the Fos IEG (Morgan and Curran, 1991b), many researchers initially questioned the specificity and importance of this molecule to neuronal function. However, the DNA binding activity of IEGPs is complex, inasmuch as they interact with many other TFs (see previous discussion in I.F.3). Therefore, the induction of Fos, measured in isolation by a variety of stimuli, is functionally meaningless, because members of the Fos (c-fos, Fos-B, Fra-1, Fra-2, Fras) and Jun (c-Jun, Jun-B, Jun-D) family of TFs must form homodimers (Jun family only) and heterodimers (e.g., Fos/Jun-D) for transcriptional activity (Morgan and Curran, 1991b). Furthermore, a naturally occurring truncated form of Fos-B can inhibit Fos/Jun transcriptional activity (Nakabeppu and Nathans, 1991), increasing the possible interactions between these various TFs. Also, recent studies have found that Fos/Jun and Jun/Jun dimers bend DNA in opposite directions (Kerpolla and Curran, 1991) and form topologically distinct DNA-protein complexes. Also, Fos and Jun act cooperatively with the glucocorticoid receptor but have opposite effects on transcriptional activity in combination with the glucocorticoid and mineralocorticoid receptors (Diamond et al., 1990, Funder, 1993).

Fos and Jun also interact with other members of the ligand-dependent family of TFs such as the thyroid hormone receptor (Zhang et al., 1991). Furthermore, reti-

noic acid is a negative regulator of AP-1-responsive genes (Schüle et al., 1991), and a phosphorylation-modulated inhibitor of Fos/Jun activity called IP-1 has recently been identified (Auwerx and Sassone-Corsi, 1991). Regulation by methylation has also been reported for the Egr-1 IEG (Seyfert et al., 1990), and this gene is also regulated by protein phosphorylation and dephosphorylation (Cao et al., 1992). Also, phosphorylation of Jun protein by MAP-serine kinases positively regulates its transactivating activity (Pulverer et al., 1991), whereas phosphorylation of Jun by casein kinase II inhibits Jun activity (Hunter and Karin, 1992).

Another level at which c-Jun can be regulated has recently been described (Baichwal et al., 1991). These authors demonstrated the existence of a cell-specific inhibitor of c-Jun activity that was overcome by Src and Ras proteins. A factor called Ref-1 stimulates AP-1 DNA binding activity of Fos and Jun without altering their DNA binding specificity via a novel reduction-oxidation mechanism (Xanthoudakis and Curran, 1992). Jun can also form dimers with Ca^{2+}/cAMP response element binding protein and ATFs (Hai and Curran, 1991) and bind to other cis-acting elements (e.g., CRE, ATF-binding sites). Fos can also interact with a helix-loop-helix-zipper protein (Blanar and Rutter, 1992). Another level of regulation of b-*zip* proteins has recently been described (Wagner and Green, 1993), showing that the Tax protein promotes dimerisation of c-Jun and other b-*zip* proteins, thereby facilitating the DNA binding reaction. Thus, the complexity of these interactions suggests that the IEGPs could potentially mediate a vast array of biological processes in neurons.

To understand the functions of these molecules, we must determine the expression of a range of IEGPs in neurons and uncover the biochemical pathways of their induction. However, the specificity and function of IEGPs may be determined not only by the pattern of IEGPs induced but also by their temporal profile of induction (especially for Fos and Jun family members that form dimers for transcriptional activity) and by the biochemical pathway through which they are induced. For example, the induction of the c-*myc* IEG in the presence of growth factors leads to cell proliferation, whereas c-*myc* induction in growth-arrested cells induces apoptosis (programmed cell death) Bissonnette et al., 1992; Evan et al., 1992; Fanidi et al., 1992; Shi et al., 1992).

Presumably, the biochemical environment in which a particular IEGP is induced will influence its DNA binding activity and its biological effect. For this reason, multiple biochemical induction pathways in neurons may not be solely a redundancy mechanism (Lerea et al., 1992) but may confer specificity and a wide range of functions to IEGPs. For example, Krox-24 is induced in CA1 pyramidal cells by tonic activation of NMDA receptors (Worley et al., 1991; Richardson et al., 1992) and by phasic activation of muscarinic receptors (Hughes and Dragunow, 1994). Because the biochemical environment into which Krox-24 is induced after NMDA receptor activation will be different from that existing after muscarinic receptor activation (e.g., cellular pH, ions, protein kinase activation, other TFs), the biological effect may be quantitatively and/or qualitatively different. Furthermore, because the microenvironment of neurons in different brain regions differs (growth factors, neurotransmitters, TFs, etc.), IEGPs may have different biological effects in different brain regions. Thus, expression of c-Jun in dentate granule cells after long-term potentiation may be involved in LTP stabilisation (Demmer et al., 1993), whereas c-Jun induction in CA1 neurons after hypoxia-ischaemia and SE may be involved in cell death (Dragunow et al., 1993c) (see VII.G.).

As detailed in section III of this review., *activation of different neurotransmitter receptors induces specific patterns of IEG expression in anatomically distinct brain regions*. This suggests that different IEGs are linked to different neurotransmitter receptors (e.g., muscarinic activation induces Jun-B but not c-Jun: see table 2 and fig. 2). This is clearly an important determinant of the specificity of action of IEGs. However, not only are different IEGs linked to different receptors, but also *the degree of activation of the same receptor can influence which IEGs are expressed*. For example, Krox-24 is expressed at high levels in CA1 pyramidal cells of the hippocampus under basal conditions (Hughes et al., 1992), and this induction can be abolished by NMDA antagonists (Worley et al., 1991). However, under the same basal conditions, Fos, c-Jun, Jun-B, Jun-D, and Krox-20 are not expressed, suggesting that their threshold for induction via NMDA receptors is higher. Thus, tonic activation of NMDA receptors is sufficient to induce Krox-24 but not the other IEGPs in CA1 neurons.

CA1 neurons can express c-Fos, c-Jun, and Jun-B after SE, and this is NMDA receptor-mediated (Dragunow et al., 1993c). Similarly, 10 bursts of high-frequency electrical stimulation (leading to LTP) will induce Krox-24 but not c-Fos, c-Jun, Jun-B, or Krox-20 in dentate granule cells, whereas 50 bursts will induce all of these genes via NMDA receptors (Demmer et al., 1993; Abraham et al., 1992, 1993). Thus, low (physiological?) levels of activation of NMDA receptors is sufficient to induce Krox-24 in CA1 and dentate granule cells, but higher (pathological?) levels are required for induction of related genes. Perhaps this differential sensitivity to NMDA receptor activation reflects different second-messenger induction pathways for these different IEGs.

The neurotransmitter receptor-mediated induction of a particular IEG in the same sets of neurons can vary, depending upon the nature of the inducing stimulus. As mentioned above, LTP induction of Krox-24 in dentate granule cells occurs via NMDA receptor activation (Abraham et al., 1992). Similarly, induction of Krox-24 in these same neurons by injury is via NMDA receptors (Hughes et al., 1993a). However, induction of Krox-24 in

TABLE 2
Differential induction of immediate-early gene family members after stimulation of specific neurotransmitter receptors

Neurotransmitter receptor activated	IEG species expressed	Brain Areas	Selected References
NMDA glutamate receptors	Fos, Jun-B, c-Jun, Jun-D, Krox-20, Krox-24	Neocortex, limbic system–dentate gyrus	Hughes et al., 1993a
Muscarinic receptors–pirenzepine-sensitive	Fos, Jun-B, Krox-20, Krox-24 not c-Jun or Jun-D	Neocortex, layer 4/caudate/limbic system CA1	Hughes and Dragunow 1993; Hughes and Dragunow (1994)
Dopamine receptors–predominantly D_1	Fos, Fras, Jun-B, Krox-20, Krox-24 not c-Jun	Striatal-nigral neurons of caudate	Bhat et al., 1992b; Robertson et al., 1989b; Moratella et al., 1993; Cole et al., 1992
Adrenergic receptors–predominantly β	Fos, Jun-B, Krox-24	Fos, Krox-24 in cortex, Jun-B in pineal	Carter, 1993; Bing et al., 1991; Bing et al., 1992b
Dopamine D_2 receptor blockade	Fos, Fras, Fos-B, Jun-B, Jun-D, Krox-24 not c-Jun	Striatal-pallidal neurons of caudate nucleus	MacGibbon et al., (1994); Dragunow et al., 1990d; but see Rogue and Vincedon, 1992
Serotonin receptors	Fos	Caudate/hypothalamus/amygdala/neocortex	Richard et al., 1992; Leslie et al., 1993
NMDA receptor blockade	Fos, Fos-B, Jun-B, Jun-D, Krox-24, none to weak c-Jun expression depending upon area	Cingulate/retrosplenial/deep neocortex/thalamus	Hughes et al., 1993b; Gass et al., 1993, Dragunow and Faull, 1990

Notice that c-jun gene expression is only increased strongly following activation of NMDA glutamate receptors.

dentate granule cells, after brief hippocampal seizures, is not NMDA receptor-mediated, whereas c-Fos induction *is* (Hughes et al., 1994).

This complexity of regulation may be an important determinant of the specificity of action of IEGPs. Another potential factor that may regulate IEG specificity is the time-course of IEGP expression. Recently, it has been demonstrated that prolonged, but not brief, c-Jun induction was required for transactivation by Jun (Trejo et al., 1992). Thus, the temporal profile of IEGP induction may also regulate biological activity. IEGPs show different profiles of induction as shown in the next section of this review.

VI. Temporal Profile of Immediate-early Gene Protein Induction in Adult Neurons

IEGPs show different time-courses of expression and decay after various treatments with Fos, Jun-B, and Krox-24 being induced first (within 1 h) and falling away rapidly to baseline (within 4 h). Induction of Fos-B and Jun-D is more delayed (4 h), but these IEGPs remain elevated for longer periods of time (up to 24 h) (Demmer et al., 1993; Dragunow et al., 1992; MacGibbon et al., 1994; Dragunow et al., 1993c). This suggests that Fos/Jun-B and Fos-B/Jun-D dimers are formed in neurons. Krox-20 is induced rapidly after LTP, but levels remain elevated for over 24 h (Williams et al., 1995). c-Jun induction is delayed (3 to 6 h) and prolonged (24 to 72 h) after SE and HI (Dragunow et al., 1993c). After axotomy, c-Jun induction is more delayed (48 h) and very prolonged (weeks to months) depending upon the brain region affected (Dragunow, 1992; Leah et al., 1993).

VII. Functions of Immediate-early Genes in Neurons

A. Immediate-early Genes as Plasticity/Sensitisation Switches

The nervous system is dynamic in that it changes in response to pharmacological/environmental/pathological stimuli. From the time of the initial discovery of IEGs and associated proteins in brain neurons (Goelet et al., 1986; Morgan et al., 1987; Dragunow et al., 1987) to the present, investigators have hypothesised that these proteins may be involved in this plasticity by linking nerve cell membrane events to the neuronal genome and leading to neuronal phenotype changes (Dragunow et al., 1989b). Physiologically, this plasticity may be involved in learning and memory, and pathologically in drug tolerance/supersensitivity, epileptogenesis, development of depression, development of side effects to antipsychotic drugs, etc., as described in the next section.

B. Immediate-early Gene Proteins in Learning and Memory

1. Krox-20 and Krox-24 as stabilisers of long-term potentiation. LTP is an activity-dependent strengthening of synaptic efficacy that may be involved in memory storage in the brain (Bliss and Collingridge, 1993). Recent studies suggest that there are at least three types of LTP that can be distinguished on the basis of decay rates (Jeffery et al., 1990; Abraham et al., 1993): LTP1 decays with an average decay constant of about 2 h; LTP2 decays with a decay constant of about 4 days, and LTP3 decays with a decay constant of about 23 days (Jeffery et al., 1990). These various types of LTP can be generated in dentate granule neurons by administering increasing

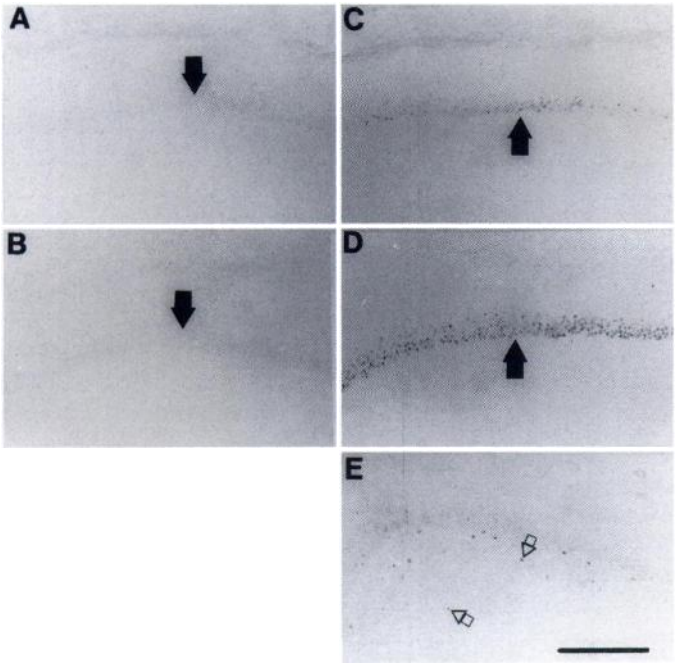

FIG. 2. Differential induction of Jun family members within the CNS. Activation of neuronal muscarinic receptors with the nonselective muscarinic agonist pilocarpine (25 mg/kg i.p.) results in increased expression of Jun-B but not c-Jun protein in hippocampal CA1 pyramidal neurons. *(a)* c-Jun protein expression in a rat 2 h after distilled water (control) injection; 2 h after injection of pilocarpine solution, Jun-B *(c)* but not c-Jun *(b)* or Jun-D proteins are produced in CA1 pyramidal neurons. Twenty-four hours after SE produced by electrical stimulation of the hippocampus (see Dragunow et al., 1993), c-Jun protein is strongly expressed in hippocampal CA1 pyramidal neurons *(d)*, whereas the expression of Jun-B and Jun-D proteins occurs weakly. Closed arrows show CA1. Eight to 24 h after hippocampal SE or after a single hippocampal kindling AD, Jun-D protein is strongly expressed within hippocampal interneurons (open arrows), *(e)* although c-Jun and Jun-B protein are not significantly expressed within these neurons. Scale Bar = 300 μm.

numbers of bursts of pulses (Jeffery et al., 1990). Furthermore, anaesthetising rats with sodium pentobarbital prevents LTP3 expression (Jeffery et al., 1990).

We have recently shown that stimulation that generates LTP3, but not LTP2, will produce a strong induction of Krox-20 and Krox-24 in dentate granule cells via NMDA-receptor activation (Williams et al., 1995; Abraham et al., 1993), although stimulation inducing LTP2 will produce a weak induction of Krox-24 but not Krox-20. Krox-24 expression does not correlate with LTP induction (Richardson et al., 1992; Schreiber et al., 1991a) but correlates with LTP maintenance (Richardson et al., 1992). Members of the Fos and Jun families are also induced in these situations (Nikolaev et al., 1991; Kaczmarek, 1992, 1993a, b; Demmer et al., 1993), but their induction does not correlate with LTP induction or stabilisation (Demmer et al., 1993). These results suggest that Krox-20 and Krox-24 may be involved in the NMDA-receptor-mediated *stabilisation* of the synaptic modifications occurring during LTP, thereby leading to the generation of LTP3. Both of these zinc-finger TFs recognise the *cis*-acting element *GCGTGGGGCG* (Lemaire et al., 1988; Christy and Nathans, 1989).

Krox-24 is expressed at very high levels basally in the neocortex, hippocampus, striatum, and limbic system regions (Hughes et al., 1992), and this basal expression can be abolished by blocking NMDA receptors (Worley et al., 1991; Gass et al., 1993) and by sodium pentobarbital anaesthesia (Richardson et al., 1992). Basal expression in the neocortex is also reduced after noradrenaline depletion (Bhat and Baraban, 1992) and by block of D_1-dopamine receptors (Mailleux et al., 1992). As NMDA, noradrenaline, and D_1-dopamine receptors are all involved in learning and memory (Ohno et al., 1992; Matthies, 1989), basally expressed Krox-24 may be involved in these actions. In particular, basal expression of Krox-24 in CA1 pyramidal cells (Hughes et al., 1992), which is largely NMDA-receptor mediated (Worley et al., 1991), may be involved in new learning, inasmuch as CA1 destruction (Kubo et al., 1993) and NMDA antagonists injected into the hippocampus (Ohno et al., 1992) impair new learning (similar to deficits seen in Alzheimer's disease).

All of the work on LTP and IEGs has been performed in dentate granule cells. LTP also occurs in CA1 pyramidal cells, although the induction of IEGs after LTP in these neurons has not been investigated. However, although dentate granule cells express low levels of Krox-24, CA1 neurons show very high constitutive expression that is mediated by activation of NMDA receptors (Hughes et al., 1992; Worley et al., 1991). NMDA antagonists also block LTP production in granule cells and CA1 neurons (reviewed in Bliss and Collingridge, 1993). Thus, assuming that Krox-24 is also involved in CA1 LTP, this NMDA-mediated high basal expression suggests that LTP may be occurring in CA1 neurons under physiological conditions and that Krox-24 is a constitutively expressed *plasticity switch*. Alternatively, Krox-24 expression may be necessary, but not sufficient, for LTP3 production, inasmuch as NMDA receptor activation alone is not sufficient to induce LTP but requires the co-activation of metabotropic glutamate receptors (Musgrave et al., 1993; Behnisch et al., 1991). It will be important to determine the second-messenger/protein kinases regulating NMDA-receptor-mediated basal expression of Krox-24 in CA1. NMDA receptor activation induces cAMP and tyrosine kinases in CA1 neurons (Bading and Greenberg, 1991; Chetkovich et al., 1991).

Recent studies have shown that a number of second-messenger/protein kinase systems are involved in LTP production (e.g., tyrosine kinases, cAMP/PKA, PKC, casein kinase II, calmodulin kinase II, nitric oxide/carbon monoxide, Stevens and Wang, 1993; Reymann et al., 1988; Silva et al., 1992; Ben-Ari et al., 1992; Frey et al., 1993; Matthies and Reymann, 1993; Slack and Pockett, 1991; Chavez-Noriega and Stevens, 1992; O'Dell et al.,

1991; Charriaut-Marlangue et al., 1991; Zhuo et al., 1993), and in particular, LTP maintenance may involve PKA activation. It will be interesting to determine the effects of blocking these second-messenger pathways on LTP-induction of IEGs, especially cAMP and tyrosine kinases, both of which are turned on by NMDA receptor activation in CA1 neurons, (Bading and Greenberg, 1991; Chetkovich et al., 1991) as is Krox-24 (Worley et al., 1991). Long-lasting LTP produced by cAMP is protein-synthesis dependent (Frey et al., 1993), suggesting that it might involve IEG and late-response gene expression. It will be interesting to elucidate the role of CREB phosphorylation in IEG expression in this cyclic AMP-inducible form of LTP, because CREB is involved in the strengthening of synaptic efficacy in Aplysia (Dash et al., 1990).

Many studies have shown that various neurotransmitters, such as acetylcholine, serotonin, glutamate, platelet-activating factor, noradrenaline, dynorphin, adenosine, and benzodiazepines (Del Cerro et al., 1992; Wagner et al., 1993; Weisskopf et al., 1993; Dunwiddie et al., 1992; Wieraszko et al., 1993; Corradetti et al., 1992; Stanton and Sarvey, 1985; Sekino et al., 1991; Sirviö et al., 1992), regulate LTP induction. It will be fascinating to investigate whether any of these compounds also alter IEG expression in the same direction as LTP processes. Noradrenaline facilitates LTP and learning and induces Fos/Fras in the cortex (Bing et al., 1992a) and in subcortical structures (Tsujino et al., 1992). IEG expression may someday provide a rapid method of screening drugs with potential to influence learning and memory. In this regard, a recent study shows that apamin, which blocks a class of calcium-activated potassium channels and which improves learning, facilitates c-Fos and c-Jun expression in hippocampus (Heurteaux et al., 1993). These authors suggested that this action of apamin on IEGs might account for its memory-enhancing effects.

Tetanisation of pathways generating LTP also generates LTD of synaptic transmission (Abraham and Goddard, 1983). Thus, expression of IEGs might be involved in this process, although we have recently found in preliminary studies that, although blockers of L-type calcium channels block LTD induction (Wickens and Abraham, 1991), they do not affect IEG expression after tetanisation. Thus, IEGs are probably not involved in LTD induction but could play a role in LTD persistence (Abraham et al., 1994). A recent report suggests that Fos and Jun-B may be involved in cerebellar LTD (Nakazawa et al., 1993).

Studies on LTP as well as in many other paradigms show that IEGs are induced in hippocampal and neocortical neurons via NMDA-receptor activation. However, NMDA receptor antagonists, such as MK801, which block IEG induction in the hippocampus after LTP, induce IEGs in layers 4 to 6 of the neocortex and in the thalamus (Dragunow and Faull, 1990; Hughes et al., 1993b). The pattern of IEG expression produced in the neocortex by MK801 is similar to that produced by the muscarinic agonist pilocarpine (Hughes and Dragunow, 1993) and induction in the neocortex can be prevented with atropine (Hughes et al., 1993b). Other NMDA antagonists, such as CGS19755, produce similar effects. NMDA antagonists interfere with learning tasks involving hippocampal function (Ohno et al., 1992), and this might be caused by suppression of hippocampal IEG expression. However, these drugs might be expected to have memory-enhancing effects on learning involving neocortical regions. Although MK801 and pilocarpine induce a similar pattern of IEG expression in the neocortex, only pilocarpine induces IEGs in the hippocampus (Hughes and Dragunow, 1994). Thus, in the neocortex, muscarinic and NMDA receptors seem to be negatively coupled, whereas this is not the case in the hippocampus. Indeed, in the hippocampus, muscarinic and NMDA receptors may be positively coupled (Markram and Segal, 1990, 1992; Feig and Lipton, 1993).

2. Immediate-early gene proteins and the mnemonic effects of acetylcholine: role of hippocampal theta rhythm. Activation of muscarinic receptors in the brain enhances learning and memory and facilitates LTP (Hughes and Dragunow, 1993). Muscarinic receptor activation can also produce LTP in the cortex (Lin and Phillis, 1991). Recent studies have shown that activation of central pirenzepine-sensitive muscarinic receptors induces c-Fos (Hughes and Dragunow, 1993; Pombo-Villar et al., 1992), Jun-B, Krox-20, and Krox-24 (Hughes and Dragunow, 1994) in hippocampal (mainly CA1), limbic system, and neocortical neurons. This action on IEG expression in parts of the brain implicated in learning and memory suggests that the effects of muscarinic drugs on LTP, learning, and memory may be mediated by IEG expression (Hughes and Dragunow, 1993). Therefore, the effects of tacrine to improve cognition in Alzheimer's disease (Holford and Peace, 1992) may also be mediated by IEG expression. Because muscarinic M_1 receptors are spared, whereas glutamate receptors are lost, in the hippocampus of Alzheimer's patients (Jansen et al., 1990), the muscarinic M_1 receptor will remain an important target for anti-Alzheimer's drug development; studies of the role of IEGs in M_1-receptor-mediated effects may be vital to these actions.

One important role for cholinergic neurons in the brain is to generate hippocampal theta rhythm in the hippocampus, and this may be involved in memory processing (Huerta and Lisman, 1993). Learning, arousal, exploration, etc., induce hippocampal theta rhythm via muscarinic receptor activation, and a recent study shows that theta rhythm induced by the muscarinic agonist carbachol induces synapses to a state of heightened plasticity so that even weak stimulation will induce LTP in CA1 neurons (Huerta and Lisman, 1993). This

may be the physiological mechanism whereby muscarinic activation facilitates and muscarinic antagonists impair new learning and memory. Furthermore, this may account for the learning problems in patients with Alzheimer's disease, who experience an early loss of cholinergic systems (Hughes and Dragunow, 1993). Because activation of muscarinic receptors induces both hippocampal theta rhythm and IEGs in CA1 neurons (Hughes and Dragunow, 1993, 1994), the facilitatory effects of cholinergically induced theta activity on new learning might be mediated by IEG expression. This hypothesis would predict that other treatments that induce hippocampal theta (e.g., exploration, stress, learning, urethane anaesthesia) should also lead to IEG expression in an atropine-sensitive manner. Stress and exposure to a novel environment is known to be a potent inducer of IEGs in the hippocampus and neocortex (Schreiber et al., 1991b; Handa et al., 1993; Papa et al., 1993; Kinney and Routtenberg, 1993), supporting this hypothesis. It will be important to determine whether IEG induction is atropine-sensitive.

3. Behavioural learning and immediate-early genes. As reviewed previously, a number of studies have shown that c-Fos is induced in situations where an animal is learning a behavioural task. It has yet to be definitively demonstrated, however, that the c-fos expression is causally related to learning. Furthermore, as suggested, learning-induced increases in Fos expression in the brain might be caused by stress and/or the arousal state of the animal (Nikolaev et al., 1992a, b). As discussed in the previous section, stress/arousal may induce IEGs via cholinergically mediated theta activation. The role of IEGs in learning and memory processes is presently not clear, however, they are likely to serve important roles in learning processes.

C. Immediate-early Gene Proteins as Transducers of Stress into Psychopathology

It was suggested in a recent review that sensitisation to psychosocial stressors may be encoded at the level of gene expression and that IEGPs may play a role in this process (Post, 1992). Eventually, these genetically encoded stressful events may manifest themselves in the form of a major affective disorder. One important therapeutic implication of this hypothesis is that there may be a justification for the prophylactic use of antidepressant drugs to prevent this sensitisation phenomenon (Post, 1992). A number of studies show that stress induces IEGPs in brain neurons (Post, 1992; Deutch et al., 1991). This intriguing hypothesis must await experimental verification. Furthermore, it might be argued that because seizures induce IEGPs (Dragunow et al., 1992), the therapeutic effects of electroconvulsive therapy might be mediated through this action. Thus, IEGPs might be antidepressant rather than prodepressant.

D. Role of Immediate-early Gene Proteins in Drug Dependence

A number of drugs of abuse, such as morphine, ecstasy (MDMA), amphetamine, and cocaine, induce IEGPs in CNS neurons, principally the striatum, but also cortical regions (see references in section on dopamine receptors, III.E). It has been suggested that this action may be involved in the dependence-inducing properties of these drugs (for reviews see Nestler, 1992 and Mackler and Eberwine, 1992). In particular, depending upon the dosing schedule, repeated administration of stimulants such as amphetamine can lead to either behavioural tolerance or sensitisation (Post, 1980). Normally, drugs such as cocaine and amphetamine, which augment dopaminergic transmission, would be expected to decrease neurochemical and behavioural sensitivity; indeed, behavioural (Post, 1980) and biochemical (Hope et al., 1992) tolerance occurs with drug administration at closely spaced intervals. However, if these drugs are administered at longer intertrial intervals, behavioural sensitisation occurs (Post, 1980).

Recently, it has been shown that the behavioural sensitisation to cocaine, methamphetamine, and amphetamine can be blocked by inhibitors of protein synthesis (Karler et al., 1993; Shimosato and Saito, 1993) and by NMDA receptor antagonists (Karler et al., 1989; Wolf and Jeziorski, 1993). This suggests that the sensitisation is produced by NMDA-receptor-activated genes. Previous studies have shown that c-Fos induction in caudate neurons by cocaine or ecstasy (MDMA) is NMDA-receptor mediated (Torres and Rivier, 1993; Dragunow et al., 1991b). These results suggest that IEGPs may be involved in the behavioural sensitisation to stimulant drugs. Evidence for this hypothesis is provided by results that show that amphetamine induces significantly greater expression of c-Fos in the striatum of rats injected 3 days previously with amphetamine compared with saline-pretreated rats (Norman et al., 1993). Furthermore, a recent study shows that c-fos antisense, which prevents c-fos induction in the nucleus accumbens, blocks the locomotor stimulant action of cocaine (Heilig et al., 1993). Whether it also blocks the rewarding effects of cocaine is unclear. Similarly, the sensitisation to amphetamine, which might be involved in amphetamine-induced psychosis, might be mediated at the gene level by the IEGPs.

A recent study has shown that morphine-induced tolerance and dependence can be inhibited by the NMDA antagonist MK801 (Trujillo and Akil, 1991; Marek et al., 1990) and by a nitric oxide synthase inhibitor (Kolesnikov et al., 1992). Because MK801 potentiates the rewarding effects of morphine (Carlezon and Wise, 1993), this action of MK801 on morphine-induced dependence cannot be caused by block of the rewarding effects of morphine. Morphine induces c-Fos in the striatum and other brain regions (Chang et al., 1988; Krylova et al.,

1992), and this action is inhibited by MK801 (Krylova et al., 1992), suggesting that morphine tolerance and dependence may involve an NMDA receptor-activated Fos expression.

IEGPs may also be involved in the chronic effects of opiates in the LC (Nestler, 1992). Acutely, opiates decrease the firing of LC neurons and inhibit adenylate cyclase. However, chronic administration of opiates produces tolerance to the inhibitory action on LC neurons, an upregulation of the cAMP system, and an increase in tyrosine hydroxylase (Nestler, 1992). Opiate withdrawal leads to overactivity of LC neurons, suggesting that these effects on the LC may be involved in opiate withdrawal and dependence.

Recent studies have implicated the IEGPs in the molecular mechanism by which chronic opiates up-regulate the cAMP system in LC neurons (Hayward et al., 1990; Nestler, 1992). Opiate withdrawal after chronic treatment induces c-fos in the LC in rats (Hayward et al., 1990). Morphine withdrawal responses of rat LC neurons can be blocked by excitatory amino-acid antagonists (Tung et al., 1990), and it will be interesting to see what effects these drugs have on Fos expression in LC neurons. These effects of opiates on IEGPs may be mediated by CREB-like TFs (Guitart et al., 1992).

Another aspect of the effects of drugs, such as cocaine and morphine, that relates to drug dependence is the classical conditioning of their behavioural effects with specific environmental stimuli, leading to conditioned cravings. This action of these drugs is of major clinical significance, because it can result in abstinent abusers resuming drug use (Brown et al., 1992). Induction of IEGPs in the brain by drugs of abuse might be involved in this classical conditioning via their role in LTP and learning phenomena (see sections V and VI).

Phencyclidine, ketamine, and MK801 also induce IEGPs in neocortical and thalamic neurons (Dragunow and Faull, 1990; Sharp et al., 1991a; Hughes et al., 1993b; Gass et al., 1993), although this action may be more involved in the psychotomimetic effects of these drugs, rather than to their abuse potential (Dragunow and Faull, 1990). Indeed, phencyclidine and related drugs can produce a prolonged psychosis in normal humans and can greatly exacerbate the symptoms of schizophrenia in schizophrenics (Snyder, 1980), and we speculate that perhaps the induction of IEGs in deep layers of the neocortex and in the thalamus is involved in this action.

Clearly, IEGPs are very important molecules in the action of drugs of abuse. This area of research promises to provide major insights into the molecular mechanisms of drug tolerance/sensitisation/dependence.

E. C-Fos as a Regulator of Basal Ganglia Motor Function

As reviewed previously in the section on dopamine receptors (section III.E.), IEGPs are induced in striatal neurons by direct-acting agonists on supersensitive D_1-receptors and by indirect agonists on intact receptors. Induction of c-Fos in dopamine-depleted striatum does not require any turning responses. However, a recent study has shown that c-fos antisense DNA injected into the nucleus accumbens can block the locomotor stimulant action of cocaine (Heilig et al., 1993). We have found that injection of c-*fos* antisense and sense DNA into opposing striata leads 10 hours later to apomorphine- and amphetamine-induced turning toward the antisense-injected side of the brain (Dragunow et al., 1993b). Others have also recently shown amphetamine-induced turning toward the c-*fos* antisense side after striatal injection (Sommer et al., 1993). These results suggest that c-Fos regulates a gene in the striatum that is important for the actions of direct- and indirect-acting dopamine agonists, perhaps the D_1- or D_2-receptor, or for a neuropeptide such as dynorphin (Lucas et al., 1993)—or perhaps c-Fos induction is part of the cascade that mediates D_1-receptor-mediated motor activity, probably a *non*genetic effect because of its rapid onset.

Antipsychotic drugs, such as haloperidol, that produce EPSs, induce c-Fos and Jun-B (as well as Jun-D and Krox-24) in striatal pallidal-projecting neurons, whereas clozapine, a neuroleptic that does not produce EPSs, does not induce c-Fos (MacGibbon et al., 1994). Thus, the production of Fos/Jun-B dimers by haloperidol may initiate long-lasting changes in gene expression that could generate the EPSs. It will be interesting to test whether haloperidol-induced behavioural sensitivity, a model of EPSs in rats (Marin and Chase, 1993), is protein-synthesis-dependent and what effects c-*fos* antisense DNA has on this process. Fos expression in striatal neurons promises to be a sensitive screening method for extrapyramidal side effects of neuroleptic drugs.

F. Role of Immediate-early Genes in Epileptogenesis: Proconvulsive or Anticonvulsive?

The first two studies to show c-Fos expression in CNS neurons used seizures as the inducing stimulus (Morgan et al., 1987; Dragunow and Robertson, 1987b). Because the brain sensitises to seizures after repeated elicitation, an effect called kindling (Goddard et al., 1969), it was suggested that c-Fos may be involved in this sensitisation phenomenon and hence in the development of epilepsy in the brain (i.e., epileptogenesis) (Dragunow et al., 1989b, 1992). As discussed later in the section on target genes (VIII. Potential IEGP Target Genes within the CNS), c-Fos and other IEGPs may regulate the expression of neuropeptides and growth factors after brief seizures and may be responsible for the neuronal or nerve terminal sprouting that occurs after brief seizures. These effects may be epileptogenic and contribute to the development of epilepsy in the brain. Alternatively, IEGPs may induce expression of molecules (e.g., thyrotropin-releasing hormone) that are anticonvulsant

(Post and Weiss, 1992) and may be responsible for post-seizure anticonvulsant effects (Dragunow, 1986).

The NMDA receptor is critical for the development of kindling (Sato et al., 1988), and NMDA receptors are involved in inducing c-Fos, but not Krox-24, in dentate granule cells after brief seizures (Labiner et al., 1993; Hughes and Dragunow, 1994). However, we have recently found that the induction of IEGPs in the piriform/amygdala region after a brief amygdala seizure (Dragunow et al., 1988) is not blocked by an NMDA receptor antagonist (Hughes et al., 1994) at a dose that blocks amygdala kindling. This suggests that IEGP expression is not sufficient for amygdala kindling but could still be a necessary component of the sensitisation process. Thus, the role of IEGPs in epileptogenesis is currently unclear.

G. Immediate-early Genes in Brain Injury: Regeneration or Suicide Genes?

Recent studies have begun to unravel the mechanisms responsible for nerve cell death in the infant and adult brain (Choi, 1990; Pulsinelli, 1992). Brief ischaemia or SE produce a delayed nerve cell death in vulnerable structures such as the hippocampus. Severe ischaemic insults result in quick-onset neuronal and glial death leading to infarction, although around this infarcted region, neurons die via a delayed mechanism. Based upon studies of growth factor-dependent neurons in culture and during brain development, the idea has arisen that some types of nerve cell death in the brain may be genetically programmed (Martin et al., 1988; Altmann, 1992; Johnson et al., 1989; Lockshin and Zakeri, 1990; Oppenheim, 1991; Raff, 1992; Schwartz, 1991). However, before we discuss these data, we will review the evidence for and against the hypothesis that delayed neuronal death in the brain is produced by active gene expression and protein synthesis.

If nerve cell death in the adult brain is caused by PCD, then drugs that interfere with protein synthesis should block nerve cell death, as has been demonstrated for sympathetic neurons in culture (Martin et al., 1988); however, it should be remembered that it is possible for apoptosis/PCD to be produced by constitutively expressed proteins activated post-translationally, e.g., Ca^{2+}-dependent endonucleases). Initial reports showed that inhibition of protein synthesis with either cycloheximide or anisomycin reduced HI-induced DND in vivo in rat and gerbil hippocampus (Goto et al., 1990; Pappas et al., 1992; Shigeno et al., 1990) and in vitro in cultured cerebellar neurons after anoxia (Dessi et al., 1992). In rats, administration of cycloheximide 12 h after HI produces the strongest neuroprotection.

These results suggest that there are proteins synthesised after HI that may be involved in the subsequent DND (so-called "killer proteins"). Moreover, providing trophic support for hippocampal neurons with NGF infusions produces a dose-dependent neuroprotective effect (Shigeno et al., 1991) after transient HI that may interfere with PCD. Protein synthesis inhibitors also prevent the neurotoxic effects of methamphetamine in mice and rats (Finnegan and Karler, 1992), and the neurotoxicity of calcium-channel antagonists in cultured cortical neurons (Koh and Cotman, 1992). Cycloheximide also prevents SE-induced neuronal damage (Schreiber et al., 1992a). Also, bcl-2, which blocks PCD (Hockenberry et al., 1990), prevents apoptosis in cultured sympathetic neurons (Garcia et al., 1992) and in neural cell lines (Zhong et al., 1993a, b).

Furthermore, calcium can activate endonucleases resulting in DNA fragmentation in PC12 cells (Joseph et al., 1993) and in rat brain after focal ischaemia (Tominaga et al., 1993). DNA fragmentation is an important characteristic of PCD/apoptosis (Cohen, 1993). Also, glutamate infusions into the hippocampus of rats produces DNA fragmentation (Kure et al., 1991), and a β-amyloid fragment also causes DNA fragmentation in cultured hippocampal neurons (Forloni et al., 1993). Furthermore, aurintricarboxylic acid, a drug that has been shown to prevent PCD of sympathetic neurons in culture (Bastistou and Greene, 1991), protects hippocampal neurons from NMDA- and ischemia-induced neurotoxicity in vivo and in vitro (Robert-Lewis et al., 1993; Samples and Dubinsky, 1993; Zeevalk et al., 1993), although this effect may be because of direct NMDA receptor effects (Zeevalk et al., 1993).

Not all reports, however, have shown neuroprotective effects of protein synthesis inhibitors. Cycloheximide does not block, and seems to potentiate, excitotoxicity in cortical cultured neurons (Koh and Cotman, 1992), and anisomycin is not neuroprotective in vivo after glutamate receptor-mediated neurotoxicity (Leppin et al., 1992). Glutamate-induced nerve cell death in cerebellar culture is not PCD (Dessi et al., 1993). Furthermore, injections of kainic acid or quinolinic acid into the hippocampus does not induce PCD (Ignatowicz et al., 1991). Also, HI brain damage is not reduced by actinomycin D, anisomycin, or cycloheximide (Deshpande et al., 1992). Indeed, it has been suggested that the neuroprotective effects of protein synthesis inhibitors on hypoxia may be caused by hypothermia (Keissling et al., 1991). Thus, one major problem with the studies of protein synthesis inhibitors is that their peripheral administration produces hypothermia, confounding interpretation of these results. Another problem with these previous studies is that none have monitored protein or RNA synthesis, so that some of the negative results might be caused by a lack of protein synthesis block at the appropriate time-point. Furthermore, although PCD and apoptosis are characterised by endonuclease-mediated DNA fragmentation, it is possible for de novo gene transcription and translation in neurons to contribute to nerve cell death without necessarily producing "classic" PCD/apoptosis; indeed, DNA fragmentation cannot be used as a sole criterion of PCD (Collins et al., 1992). Furthermore, the

effects of protein synthesis inhibitors on cell survival are complicated by the injury-induced stimulation of endogenous neuroprotective mechanisms, i.e., insulin-like growth factor-1, transforming growth factor β1, and BDNF (Gluckman et al., 1992, 1993; Beilharz et al., 1993; Hughes et al., 1993a), which are also RNA- and protein synthesis-dependent (Favaron et al., 1993). With this proviso in mind, it is still clear that if "death genes" exist in neurons and if these genes are required for nerve cell death, then their suppression with RNA and protein-synthesis inhibitors should reduce brain injury.

In contrast to these results, other studies have shown a progressive loss of mRNA during DND in the hippocampus (Maruno and Yanagihara, 1990), and it has been suggested that this suppression of RNA and protein synthesis may cause DND. Furthermore, SE, which induces neuronal death, is also characterised by inhibition of protein synthesis (Dwyer and Wasterlain, 1983). At first appraisal, these two areas of research seem to contradict each other, however, it is possible for overall RNA and protein synthesis to be inhibited by transient HI and SE but for specific mRNAs and proteins to be strongly expressed. Furthermore, a recent study shows that in rat hippocampal slices, anoxia produces an increase in protein synthesis (Charriaut-Marlangue et al., 1992).

The identity of the genes and protein(s) that may give rise to delayed neuronal death is unknown. Possible candidate molecules that may be either directly involved or part of the cascade that generates "neuron death proteins" are the IEGPs (e.g., c-Fos, Fras, Fos-B, c-Jun, Jun-B, Jun-D, Krox-20, Krox-24, Nur77, c-Myc). Recent studies have shown that c-*fos* and c-*myc* are induced during PCD/apoptosis in prostate and in liver (Lockshin and Zakeri, 1990); c-Myc is involved in fibroblast apoptosis (Evan et al., 1992). Also, block of c-Myc expression by antisense oligonucleotides in T-cells blocks activation-induced apoptosis (Shi et al., 1992). Bcl-2 may inhibit apoptosis by inhibiting the actions of c-Myc (Fanidi et al., 1992; Bissonnette et al., 1992). A recent study shows that prolonged c-*fos* expression precedes PCD in vivo and in vitro (Smeyne et al., 1993). The protein c-Jun is induced in astrocytoma cell lines (*a*) after DNA damage produced by chemotherapeutic drugs and ionising radiation (Manome et al., 1993) and (*b*) in response to etoposide-induced DNA damage and PCD in myeloid leukemia cells (Rubin et al., 1991).

The first report of the effects of brain injury on c-*fos* demonstrated that cerebellar injury induced c-*fos* mRNA in neonatal—but not adult—rat brain (Ruppert and Wille, 1987). In contrast to this earlier study, it was subsequently shown that a stab-wound injury to the adult brain induces c-Fos in neocortical neurons (Dragunow and Robertson, 1988b; Dragunow et al., 1990a, b, c) and that this was because of the production of spreading depression via activation of NMDA receptors (Dragunow et al., 1990a, b, c). Neocortical neurons do not die after this type of insult, and a recent study suggests that this may be because of the production of the neuroprotective growth factor BDNF after spreading depression (Kokaia et al., 1993).

Other studies have confirmed these initial results. Hence, c-Fos is induced in CNS neurons by a number of traumatic stimuli, such as mechanical brain injury, and by neurotoxins such as lindane and quinolinic acid, via NMDA-receptor activation (Aronin et al., 1991; Ballarin et al., 1991; Herrera and Robertson, 1989, 1990; Kaczmarek et al., 1988; Sequier and Lazdunski, 1990; Sharp et al., 1989, 1990; Vendrell et al., 1991). NMDA receptors are involved in producing the neuronal damage after traumatic brain injury (Faden et al., 1989). This suggests that c-Fos induction may be involved in the neurotoxic effects of NMDA-receptor activation; c-Fos induction has also been associated with survival and/or maturation of nerve cells in culture (Didier et al., 1989, 1992), although this has been questioned (Bardoscia et al., 1992; Graham and Burgoyne, 1991). Thus, c-Fos may be involved in neuronal injury/repair after neurotoxin administration and traumatic brain injury.

c-Fos has been implicated in PCD during development of the rat cortex (Gonzalez-Martin et al., 1992). Additionally, in rats before postnatal day 13, kainic acid seizures do not lead to c-Fos induction or brain damage, whereas in older rats, kainic acid produces seizures, c-Fos induction, and brain damage, suggesting that c-Fos may be involved in brain damage after kainic acid-induced SE (Schreiber et al., 1992b). Kainic acid-induced SE in adult mice has been associated with prolonged c-fos expression (Smeyne et al., 1993).

We have also been studying the role of IEGs in nerve cell death occurring after SE (Dragunow et al., 1993c). Our model of SE involves delivering electrical stimulation for 1 h to the dorsal hippocampus of rat brain (Young and Dragunow, 1994). This mainly leads to limbic SE that results in hippocampal injury and exactly matches the pattern seen in human brain after SE (DeGiorgio et al., 1992; Young and Dragunow, 1993). However, if SE is induced in the presence of MK801, a blocker of NMDA-type glutamate receptors (block of these receptors does not terminate limbic SE) (Hughes et al., 1993c), hippocampal cell death does not occur (Dragunow et al., 1993c). Thus, although NMDA receptors do not maintain seizures during SE (Hughes et al., 1993c), activation of these receptors during SE is responsible for killing hippocampal neurons.

We recently discovered that (*a*) 24 h after SE, there was a massive expression of the Jun and a smaller expression of the Fos TFs in hippocampal neurons destined to die and (*b*) this expression was blocked in MK801-treated rats undergoing SE (Dragunow et al., 1993c). Because Jun and Fos are TFs, we speculated that they may be involved in the regulation of genes involved in killing hippocampal neurons after SE. This

hypothesis is supported by other studies we have undertaken. For example, c-Jun is selectively expressed in the nucleus of axotomised medial septal neurons (Dragunow, 1992). After axotomy, these cholinergic medial septal neurons undergo atrophy and lose their cholinergic markers (Fischer and Björklund, 1991). This atrophy can be prevented by NGF infusions (Fischer and Björklund, 1991); these infusions also inhibit c-Jun expression in peripheral neurons after axotomy (Gold et al., 1993).

Although many investigators have speculated that c-Jun expression is involved in axonal regeneration in peripheral neurons (Leah et al., 1991; Jenkins and Hunt, 1991), it has been suggested that in the medial septum at least the expression may be neurotoxic (Dragunow, 1992; Dragunow et al., 1993c). This hypothesis is strengthened by our SE studies and by our other studies showing that ischaemic brain injury also induces c-Jun in dying neurons (Dragunow et al., 1993c). In other studies, we have found that colchicine, which causes a selective degeneration of hippocampal dentate granule cells (Goldschmidt and Steward, 1980), also induces c-Jun in these neurons (Leah et al., 1993). Also, c-Jun is induced in dopaminergic neurons after injections of the dopamine neurotoxin 6-hydroxydopamine (Jenkins et al., 1993) and after axotomy of the medial forebrain bundle (Leah et al., 1993).

IEGs may also play roles in brain injury associated with ischaemia. HI in adult rat and gerbil brain induces c-*fos*, c-*jun* and *zif* 268 mRNA and c-Fos protein (Abe et al., 1991b; Blumenfeld et al., 1992; Jørgensen et al., 1989; Onodera et al., 1989; Wessel et al., 1991; Nowak et al., 1990; Gass et al., 1992b; Gubits et al., 1993). In contrast, other studies have found either weak induction of c-Fos after ischaemia (Ikeda et al., 1990; Popovici et al., 1990), or induction in areas surrounding the ischaemic core (Uemura et al., 1991a) or in neurons resistant to injury (Uemura et al., 1991b).

We have also investigated the regulation of IEGPs after HI and found that neurons undergoing delayed neuronal death show prolonged c-*jun* and c-*fos* mRNA and protein expression (24 to 48 h), whereas neurons in infarcted tissue did not express IEGPs (Dragunow et al., 1994). Neurons surviving moderate HI showed only short-lasting IEGP expression (1 to 4 h).

Although these different results may be because of differences in species or to technical differences, we have previously proposed that the results obtained reflect differences in the severity of the ischaemic insult, with milder insults leading to c-Fos expression in ischaemic neurons undergoing DND and more severe insults resulting in rapid neuronal failure, infarction, and death, thereby obscuring any potential c-Fos expression (Gunn et al., 1990). This possibility is supported by a study showing that mild traumatic brain injury produces a stronger induction of c-Fos in CA1 hippocampal neurons than does moderate injury (Phillips and Belardo, 1992). However, in contrast to these reports, hyperglycemia suppresses c-*fos* mRNA expression after transient cerebral ischemia in gerbils (Combs et al., 1992), suggesting that c-Fos may be protective of neurons, inasmuch as hyperglycemia enhances brain injury after ischemia. A recent study in adult rat brain showed that 30-min ischaemia strongly induced c-*fos* and *jun*-B but only weakly induced c-*jun* mRNA (An et al., 1993). Interestingly, 30-min ischemia did not cause any damage. Longer ischaemia (90 min) caused a reduced expression of these genes, but the anatomical distribution of ischemia did not correspond to the pattern of IEG expression.

Permanent middle cerebral artery occlusion in spontaneously hypertensive rats induces c-Fos in the zone around the infarct but not in the infarct itself (Christensen et al., 1993). This induction in the peri-infarct zone was blocked by MK801 but not by a non-NMDA antagonist, indicating that it is NMDA-receptor mediated. Tissue in the peri-infarct zone shows selective neuronal loss that can be prevented by MK801, suggesting that the c-Fos expression may be involved in cell death. Furthermore, this study confirms the previous observation that c-Fos is not induced in infarcted tissue (Gunn et al., 1990).

These studies suggest that perhaps c-Jun and c-Fos are involved in killing neurons during delayed cell death; c-Jun expression is clearly not sufficient to cause nerve cell death, because it is induced in neurons by stimulation (LTP, saline infusion, brief seizures) that does not lead to cell death. However, the duration of its expression after these types of stimulation is brief (2 to 4 h) (Demmer et al., 1993; Abraham et al., 1992; Dragunow et al., 1992; Hughes et al., 1993a), whereas its induction in dying neurons is prolonged (24 to 72 h after hypoxia and SE and many days after axotomy) (Dragunow, 1992; Dragunow et al., 1993c). Prolonged but not brief expression of c-Jun was required for its DNA-activating ability (Trejo et al., 1992), *suggesting that the different time-courses of its expression in dying versus surviving neurons may be critical in determining its biological effects*.

Post-translational modifications may also be involved in determining the biological activity of Jun (Hunter and Karin, 1992). Also, in all the situations where c-Jun is expressed and neurons do not die, we have detected an induction of BDNF, which we have discovered is itself an early-response gene (Hughes et al., 1993a), in the same neurons with a similar time-course of expression (Hughes et al., 1993a; Dragunow et al., 1993a). Because BDNF is neuroprotective (Sendtner et al., 1992; Shimohama et al., 1993), its expression may interfere with any neurotoxic effects of c-Jun, perhaps in a fashion analogous to the prevention of programmed cell death by growth factors. Furthermore, although c-Jun is induced by LTP, saline infusion into hippocampus and brief seizures, treatments that do not kill neurons, this induc-

tion occurs via glutamate receptors (Demmer et al., 1993; Hughes et al., 1993a; Hughes and Dragunow, submitted). In contrast, activation of muscarinic receptors or block of dopamine receptors, which strongly induce Jun-B, Krox-24 and Fos, do not induce c-Jun (Hughes and Dragunow, 1994; Dragunow et al., 1993c; MacGibbon et al., 1994). Thus, *c-Jun expression is closely coupled to glutamate receptor activation*.

Glutamate receptors, particularly the NMDA receptor, play important roles in brain plasticity and neuronal injury (Choi, 1990). Jun expression occurs preferentially in response to glutamate receptor activation. Perhaps low-level glutamate receptor activation produces a transient induction of c-Jun (Demmer et al., 1993; Hughes et al., 1993a), whereas activation of glutamate receptors producing neurotoxicity leads to prolonged c-Jun expression. Thus, prolonged expression of c-Jun (and perhaps c-Fos) may be necessary for nerve cell death (perhaps PCD) in the brain. However, this hypothesis is based entirely on correlational data, and direct tests of this hypothesis await the use of antisense DNA technology (Chiasson et al., 1992; Dragunow et al., 1993b).

In contrast to this cell death hypothesis, other researchers studying axotomy of peripheral neurons have suggested that Jun proteins may play a role in initiating a regeneration program in neurons after axotomy (Leah et al., 1991; Jenkins and Hunt, 1991; Rutherford et al., 1992a; Jenkins et al., 1993; Hass et al., 1993) and that c-Fos may be involved in survival of LC neurons after axotomy (Weiser et al., 1993b). Peripheral neurons regrow axons after axotomy, and this process may be initiated by Jun expression that occurs in the nuclei of the axotomised neurons.

Axotomy of facial and rubrospinal neurons causes increased expression of cytoskeletal proteins and growth-associated protein-43, which are likely to be involved in the regenerative response (Tetzlaff et al., 1991). Furthermore, other genes, such as calcitonin gene-related peptide (Herdegen et al., 1993b; Saika et al., 1991), galanin (Rutherford et al., 1992a), and CCK (Saika et al., 1991) are also induced after axotomy. Calcitonin gene-related peptide seems to be colocalised with c-Jun (Herdegen et al., 1993b).

Expression of c-Jun may be involved in regulating the expression of the regenerative proteins and hence in axonal regeneration. CNS neurons do not regrow after axotomy, and yet they display a robust expression of c-Jun upon axotomy (Dragunow, 1992, Leah et al., 1993). If c-Jun is a crucial signal for the regenerative response, then its expression in CNS neurons suggests that these cells have the capacity to regrow axons but that some other factor may prohibit regeneration.

Axotomy of nigrostriatal neurons with 6-OHDA produces a strong but short (2 weeks) expression of c-Jun in nigral dopamine neurons (Jenkins et al., 1993). Because peripheral nerve transection produces a prolonged expression of c-Jun (Leah et al., 1991), these researchers suggested that this shorter induction in CNS neurons may be the result of other factors in the CNS that are nonpermissive for regeneration. However, it might be argued that because 6-OHDA kills dopamine neurons, the short-lasting expression may be caused by cell death.

After transection of the medial forebrain bundle and mamillary tract, we found that neurons in the substantia nigra, mamillary nuclei, and ventral tegmentum expressed c-Jun (Leah et al., 1993). By 30 days after transection, levels had returned to baseline in the nigra and tegmentum but were still elevated in the mamillary nuclei. These results (apart from the mamillary nuclei) would support the previous hypothesis (Jenkins et al., 1993). However, because the fate of the axotomised neurons was not determined (Leah et al., 1993), interpretation of these results is difficult. Furthermore, it is possible that induction of c-Jun after axotomy of peripheral neurons is an attempt at cell suicide that is prevented by other factors present in the peripheral (but not central) nervous system that overcomes the death pathway. Schwann cells are known to produce growth factors around injured axons and thus may be involved in this process.

Production of c-Jun in axotomised peripheral nervous system and CNS neurons may be initiated by the absence of retrogradely transported growth/survival/maintenance factors (perhaps NGF/fibroblast growth factor for medial septal neurons) (Dragunow, 1992). NGF has recently been shown to reduce c-Jun expression in axotomised peripheral neurons (Gold et al., 1993). Thus, growth factor deprivation may be the signal for c-Jun expression. Because cultured neurons die via apoptosis upon growth factor deprivation (Martin et al., 1988), these results support our hypothesis of the role of c-Jun in nerve cell death (Dragunow et al., 1993c). However, whether or not axotomised CNS neurons undergo apoptosis is unknown.

Clearly, antisense DNA studies are now required to determine the role of neuronal c-Jun expression in neuronal injury/repair/regeneration mechanisms. Also, because CNS axons can be induced to sprout after denervation and seizures (Sutula et al., 1988), it will be interesting to investigate the role of c-Jun expression in these processes. For example, entorhinal cortex lesions lead to a sprouting of medial septal axons into the denervated hippocampus (Fagan and Gage, 1990). If c-Jun is involved in axonal growth rather than nerve cell death, then it might be induced in these sprouting medial septal neurons.

VIII. Potential Immediate-early Gene Protein Target Genes within the Central Nervous System

A number of potential target genes with AP-1-like sequences have been described, including tyrosine hydroxylase, thyrotropin-releasing hormone, CCK, glutamic-acid decarboxylase, PENK, and NGF (White and Gall, 1987; Hengerer et al., 1990; Moochetti et al., 1989;

TABLE 3
Potential target genes for IEGPs in CNS

Target gene potential	Gene	Selected References
Almost certain to be	Prodynorphin	Lucas et al., 1993
Strong possibility	NGF; Tyrosine hydroxylase	Hengerer et al., 1990; Mocchetti et al., 1989; Gall and Isackson, 1989; Goc et al., 1992; Kilbourne et al., 1992; Icard-Liepkalns et al., 1992; Weiser et al., 1993; Nestler, 1992; Jehan et al., 1993; although see Barbany and Persson, 1993
Possible	Proenkephalin; TRH; CCK; GAD; GAP-43; Somatostatin; Interleukins; TNFα; TrkB; NPY; hsp70; NOS; galanin; CGRP	Sonnenberg et al., 1989; Mar, et al., 1992; Konradi et al., 1993; Rosen et al., 1992a; Olenik et al., 1991; Najilerahim; Meberg et al., 1993; Pennypacker et al., 1993; Minami et al., 1991; Merlio et al., 1993; Kubek et al., 1993; Marksteiner et al., 1990; Wanscher et al., 1990; Dragunow et al., 1992; Lanteri-Minet et al., 1993; Fiallos-Estrada et al., 1993; Herdegen et al., 1993b
Unlikely	BDNF	Hughes et al., 1993a

Abbreviations: BDNF-Brain-derived neurotrophic factor, CCK-Cholecystokinin, CGRP-Calcitonin gene-related peptide, GAD-Glutamic acid decarboxylase, GAP-Growth-associated protein, hsp-heat shock protein, NGF-Nerve growth factor, NOS-Nitric oxide synthase, NPY-Neuropeptide Y, TNF-Tumor necrosis factor, TRH-Thyrotropin-releasing hormone, Trk-Tyrosine kinase linked receptor.

Ballarin et al., 1991; Sonnenberg et al., 1989c; Gall and Isaacson, 1989; Icard-Liepkalns et al., 1992; Monstein, 1993; Rosen et al., 1992a; Olenik et al., 1991; Najilirahim et al., 1991; Goc et al., 1992; Weiser et al., 1993a; Wessel and Joh, 1992, although see Zhu et al., 1993) (table 3).

Although the PENK gene has been proposed as an IEGP target (late-response gene) (Sonnenberg et al., 1989c), we have recently found that although hippocampal injury induces IEGPs in dentate granule cells, PENK mRNA is not induced (Hughes and Dragunow, unpublished observations). Also, a recent study demonstrates that PENK mRNA is induced in caudate neurons after haloperidol injection via CREB phosphorylation, but c-Fos is not involved (Konradi et al., 1993). However, in spinal cord cultures using antisense DNA methods, it has been demonstrated that $5HT_{1A}$ receptor agonists induce transactivation of the prodynorphin gene via c-Fos expression (Lucas et al., 1993). This is the first target gene to be unequivocally demonstrated in the nervous system, although it will be important to demonstrate this action in vivo as well as in other brain regions. For example, cocaine induces IEGPs in striatal neurons and leads to dynorphin gene expression (Graybiel et al., 1990). Antisense DNA technology should be able to demonstrate any causal link (Chiasson et al., 1992; Dragunow et al., 1993b).

After brief and long seizures, induction of IEGPs in dentate granule cells (Dragunow et al., 1992) may induce axonal sprouting (Represa and Ben-Ari, 1992; Sutula et al., 1988, 1992) by regulating the expression of various growth-related genes: structural and/or microtubule proteins, growth-associated protein-43, NGFs (Ernfors et al., 1991; Gall and Isaacson, 1989; Meberg et al., 1993), and/or growth factor receptors such as transketolaseB and transketolaseC (Bengzon et al., 1993). Expression of Fos-Fra/Jun-D dimers in somatostatin neurons after seizures (Dragunow et al., 1992) may be involved in regulation of the somatostatin gene after seizure activity. Seizures also induce (*a*) neuropeptides PENK, neuropeptide Y, preprodynorphin, and thyrotropin-releasing hormone and (*b*) glutamate receptors, as well as (*c*) interleukins and TNFα and transketolaseB in dentate granule cells (Pennypacker et al., 1993; Kamphuis et al., 1992; Minami et al., 1991; Merlio et al., 1993; Kubek et al., 1993; Rosen et al., 1992a, 1993; Marksteiner et al., 1990); these may be controlled by the earlier IEGP expression that occurs selectively in these dentate granule cells after brief seizures (Dragunow and Robertson, 1987b; Dragunow et al., 1992).

Injury to the neocortex can rapidly induce IEGPs in neocortical neurons (Dragunow and Robertson, 1988b) and cause a more delayed expression of CCK (Olenik et al., 1991) and glutamic-acid decarboxylase (Najilerahim et al., 1991). Furthermore, there is some evidence for a role for c-Fos in the regulation of the tyrosine hydroxylase gene in LC neurons after axotomy (Weiser et al., 1993a). c-Fos may also be involved in the increase in tyrosine hydroxylase expression that follows chronic opiate injection (Nestler, 1992). A number of genes have been proposed to be IEGP targets after axotomy, including (*a*) heat-shock protein 70 (Lanteri-Minet et al., 1993), which contains an ATF-binding site, (*b*) nitric oxide synthase (Fiallos-Estrada et al., 1993), (*c*) galanin, and (*d*) calcitonin gene-related peptide (Herdegen et al., 1993b; Rutherford et al., 1993; Saika et al., 1991), although there is no direct evidence that any of these are regulated by Jun dimers.

BDNF mRNA is induced in many situations where the Fos, Jun and Krox families of IEGPs are induced; the BDNF mRNA induction is delayed with respect to the IEGP expression: after MK801 injection (Hughes et al., 1993b), after LTP via NMDA receptor activation (Dragunow et al., 1993a), and after hippocampal injury via NMDA receptors (Hughes et al., 1993a). These results

suggest that BDNF may be a target of IEGP expression. However, we (Hughes et al., 1993a) and others (Demello et al., 1992) have found that BDNF expression after hippocampal injury and seizures is not blocked by cycloheximide, a protein synthesis inhibitor that prevents IEGP induction (Hughes et al., 1993a), suggesting that BDNF is not an IEGP target but is itself an IEG.

As an IEG, it seems to have both an interneuronal signalling and DNA binding capacity (Wetmore et al., 1991). Thus, BDNF may also function as a TF in neurons. Interestingly, expression of BDNF after LTP correlates with LTP maintenance (Dragunow et al., 1993a) and BDNF seems to be involved in spatial memory processes (Falkenberg et al., 1992). It may regulate both pre- and post-synaptic activity during LTP by acting as both a retrograde messenger and as a TF (Dragunow et al., 1993a). Thus, it may play a crucial role in LTP stabilisation. However, it is clearly not a target gene for IEGPs. NGF may be a more likely candidate target gene, inasmuch as it is induced by injury in dentate granule cells (Ballarin et al., 1991), although a recent study indicates a clear dissociation between seizure-induced c-Fos and NGF expression after adrenalectomy (Barbany and Persson, 1993). Therefore, apart from the dynorphin gene in spinal cord cultures, no other genes have been definitively demonstrated to be regulated by IEGPs in neurons.

Since their initial identification in brain neurons in 1987 (Dragunow et al., 1987; Morgan et al., 1987), a wealth of studies have investigated IEGPs in both the peripheral nervous system and CNS. These studies suggest important roles for IEGPs in neurotransmitter-regulated gene expression in the brain. However, the full potential of IEGP research awaits tantalisingly to be fulfilled.

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