Appendix C

SURVEY OF C-FOS

C-fos is one of a family of intermediate early genes (IEGs), identified as a proto-oncogene in virology research. These genes are present in many tissues but under basal conditions usually at very low levels. Varied stimuli initiate increased levels of c-fos messenger RNA within minutes that persist for minutes to weeks. The FOS protein c-fos produces is a regulatory protein that forms dimer complexes with another IEG product of c-Jun (a family of JUN proteins), which in turn activates an inducible transcription factor, P1, which binds to a DNA that controls target gene expression. The means by which such mechanisms convert external stimuli into longer-term changes within the cell have been a matter of great scientific interest (some 8,000 titles relating to c-fos were published in the past three to four years.) (Chiasson, 1997; Bozas, 1997, Lane et al., 1998; Inada, 1998).

In some cases, the effects of c-fos expression are protective (Kaina, 1997; Giovanelli, 1998), but they are also implicated in cell death via apoptosis (Inada, 1998).

The study of the effects within the nervous system of inducible transforming factors has been intense and varied. These studies can be expected to improve understanding of the longer-term effects of military agents on the nervous system—eventually. The physiological consequences of acutely or chronically altering the expression of IEG transforming factors in humans or freely behaving animals remains largely unknown (Chiasson, 1997).

Physical (Patronas et al., 1998), physiological (Minson et al., 1997) and pharmacological (Giovanelli, 1998) stimuli presented once or on multiple occasions can alter the "normal" functioning of the brain for the long term (Chiasson, 1997).

Stimuli, such as neurotransmitter-receptor interactions, can be coupled to gene action, leading to changes in neuronal function lasting minutes to a lifetime. Early studies showed that drug-induced seizures, kindled seizures, and noxious stimulation showed regional activation of IEGs within the brain and spinal cord (Chiasson, 1997; Harris, 1997).

IEGs regulate the expression of varied neuropeptides and trophic molecules, such as nerve growth factor or cholineacetyl transferase, suggesting an important role in neuroplasticity: the adapting of the brain to changed circumstances (Chiasson, 1997; Pongrac and Rylett, 1998). There are growing indications that c-fos and other messenger RNAs may have effects in addition to translation (Chiasson, 1997).

C-fos and other IEGs are substantially involved in stress responses, with definite regional differences noted for different forms of stress (Chiasson, 1997; Rachman, 1998; Martinez, Phillips, and Herbert, 1998; Serova et al., 1998; Bozas, 1997, Schreiber, 1991).

Cholinergic mechanisms are often involved in activating c-fos, which in turn can regulate neurotransmitter abundance (Bernard et al., 1993; Pongrac and Rylett, 1998; Cook, 1998; Bucci, 1998).

C-fos is increased when seizures occur (White and Price, 1993) and may play a role in protection from further seizures (Rocha and Kaufman, 1998), although other data using antisense analogs of c-fos suggest the reverse is so in other models (Lu et al., 1997). It has been shown that, with soman-induced seizures in rats, increases in c-fos are later reflected by an increase in a heat shock protein, hsp70, which generally reflects neuronal "distress," while antisense versions of c-fos prevent the appearance of hsp70 (Baille et al., 1997).

Although c-fos and c-Jun are insufficient alone to produce apoptosis, studies in hypoxia-injured animals show that they are saliently involved in selectively vulnerable cells in switching on target genes (APP751) that induce apoptosis (Walton et al., 1998) and tumor necrosis factor. After unilateral mechanical injury to the hippocampus in mice, there is widespread expression of c-fos throughout the brain, followed within 24 hours by the production of interleukin 1 alpha and tumor necrosis factor alpha lasting 6 to 15 days. These factors are also induced in invading macrophages and glial cells. Similar effects do not arise from lesions in striatum or cortex. The physiological significance is unknown (Tchelingerian, 1997).

There are other indications of a role for c-fos in the elusive communications between immune and nervous systems. Vagal afferent neurons are activated following systemic administration of endotoxin, while administration of the interleukin IL 1-beta systemically induces in experimental animals expression of c-fos in afferent vagus neurons, providing an avenue for immune system signaling to the brain (Goehler et al., 1998). Although the focus of this survey has been the central nervous system, the fact that peripheral tissues also demonstrate considerable IEG activity in response to environmental changes should be kept in mind.