EFFECTS OF CYTOKINES ON CEREBRAL NEUROTRANSMISSION

Comparison with the Effects of Stress

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1. INTRODUCTION

1.1. Responses Associated with Stress

Stress is normally associated with coactivation of the sympathoadrenal system (sympathetic nervous system plus the adrenal medulla) and the hypothalamo-pituitary-adrenocortical (HPA) axis. However, extensive work in the past 30 years has indicated that responses also occur in the central nervous system. The major response occurs in noradrenergic (NA) neurons. Most studies have also noted responses in dopaminergic (DA) and serotoninergic (5-HT) systems (Dunn & Kramarcy, 1984; Stone, 1975). Whether or not adrenergic (adrenaline-containing) neurons respond is not resolved, although there is evidence that adrenergic neurons (along with NA and 5-HT neurons) are involved in the regulation of hypothalamic corticotropin-releasing factor (CRF) secretion which initiates HPA activation (Plotsky, Cunningham, & Widmaier, 1989). The NA response is widespread and appears to affect to similar extents both the locus coeruleus (A6) system innervating the dorsal structures (cortex, hippocampus, cerebellum, etc.), and the nucleus tractus solitarius (A1/A2) system innervating the ventral structures (e.g., the hypothalamus). The DA response is also widespread with all the major neuronal systems (nigrostriatal, mesolimbic, mesocortical) showing responses, but the magnitude of the response is particularly large in the mesocortical system (i.e. in the

prefrontal and cingulate cortices). The 5-HT response is not markedly regionally specific (although some (e.g., Kirby, Allen, & Lucki, 1995) have reported regional differences). There is also a robust elevation of concentrations of tryptophan (the natural precursor of 5-HT) in all regions of the brain. This is quite uniform in magnitude, and does not appear to be related in any obvious way to the extent of the serotonergic innervation of a region (Curzon, Joseph, & Knott, 1972; Dunn, 1988a). There may be changes in the metabolism and secretion of many other neurotransmitters (e.g., acetylcholine, and γ-aminobutyric acid (GABA), see Dunn & Kramarcy, 1984), but the evidence that these are a specific or universal response in stress is less compelling than for the catecholamines and 5-HT. There are also responses in certain peptidergic systems. CRF secretion is critical in the activation of the HPA axis (Vale, Spiess, Rivier, & Rivier, 1981), and some extrahypothalamic CRF neurons are activated too (Merlo Pich, Lorang, Yeganeh, Rodriguez De Fonseca, Raber, Koob, & Weiss, 1995). A number of other peptides are also affected in stress.

1.2. Neurochemical Responses to Infection

Before discussing the responses to cytokines, it is useful first to compare the neurochemical and physiological responses to infections and to endotoxin (LPS) with those described above for more commonly studied stressors. When we studied the effects of influenza virus infection in mice, we observed a progressive activation of the HPA axis (Dunn, Powell, Meitin, & Small, 1989). This observation was consistent with scattered reports in the literature, and with our own previous observations of animals that became sick during experiments from a variety of causes (frequently unknown). It is important that this HPA activation was continuous and not transient as it is to stressors such as electric shock. Secondly, we observed an increased metabolism of NA (i.e., production of 3-methoxy,4-hydroxyphenylethylenglycol, MHPG) in all brain regions studied. But, unlike the response to footshock or restraint, the magnitude of the response was significantly greater in the hypothalamus (Dunn et al., 1989), and appeared to be associated with a preferential activation of the ventral noradrenergic system which originates largely from nucleus tractus solitarius, although it receives a contribution from the locus coeruleus. DA metabolism was not significantly affected. Tryptophan concentrations and 5-HT metabolism (i.e., production of 5-hydroxyindoleacetic acid, 5-HIAA) were elevated as observed following footshock or restraint. The earliest time at which these changes appear is around 24 h after infection. Subsequent studies have shown similar changes associated with infection with other viruses and bacteria (Beisel, 1981; Ben Hur, Rosenthal, Itzik, & Weidenfeld, 1996; Guo, Qian, Peters, & Liu, 1993; Kass & Finland, 1958; Miller, Spencer, Pearce, Pisell, Tanapat, Leung, Dhabhar, McEwen, & Biron, 1997; Weidenfeld, Wohlman, & Gallily, 1995). We conclude that there is a marked similarity between the neurochemical and physiological responses to physical and psychological stressors, and infections or other illnesses as depicted in Table 1. The responses are not identical; the major differences being that infections and illness are associated with larger NA responses in the hypothalamus than other brain regions, and a lack of DA responses.

1.3. Neurochemical Responses to Endotoxin (Lipopolysaccharide, LPS)

It has long been known that administration of LPS activates the HPA axis (Bliss, Migeon, Eik-Nes, Sandberg, & Samuels, 1954). In our studies, intraperitoneal (ip) injec-