EFFECTS OF ACTINOMYCIN D (ACT. D) AND CYCLOHEXIMIDE (CX) ON DEVELOPMENT OF CYTOPATHIC EFFECTS IN MRC-5 CELLS

Inhibitor (μg/ml)	Cytopathic effect			^{35}S-methionine incorporation	^{3}H-uridine incorporation
	Polio	Echo 3	VLA		
Control	+	+	+	100%	100%
Act. D (0·5)	+	+	+	NT	30%
Act. D (1)	+	+	+	NT	15%
Act. D (2)	+	+	+	NT	8%
CX (0·5)	±	±	+	28%	NT
CX (1)	−	−	+	22%	NT
CX (2)	−	−	+	12%	NT
CX (5)	−	−	+	5%	NT

NT = not tested.

medium from cytopathic cultures was mixed with anti-interferon serum and then added to fresh cells, it was still not possible to transmit the CPE. Therefore, it seems unlikely that the CPE is produced by virus growth and replication. Two additional points are worthy of note. The VLA appears to become cell associated within 2 h, after which time the cells can be washed and incubated in fresh medium without development of the CPE being prevented. The CPE usually develops within 16 h (in one case in 8 h)—i.e., much more quickly than is the case with most viruses, in which CPE normally takes from 12 h (e.g., poliovirus) to 10 days (e.g., cytomegalovirus) to develop.

Further studies of the structure of the VLA and its effect on cellular metabolism are in progress, but its relation to disorders of the nervous system is unclear. Clearly the existence of a cytotoxic agent in the CSF of patients with psychiatric and other CNS diseases could be aetiologically significant, but other explanations (e.g., the agent is a secondary consequence of some types of CNS damage) are possible.

Our recent studies suggest either that the CPE is not due to a virus or, if it is due to a virus, it is not a consequence of replication. CPE can be produced by a non-replicating virus (e.g., adenovirus in cell cultures)[4] but the CPE might be due to a toxic factor, perhaps associated with a cellular particle which would account for its apparent size.

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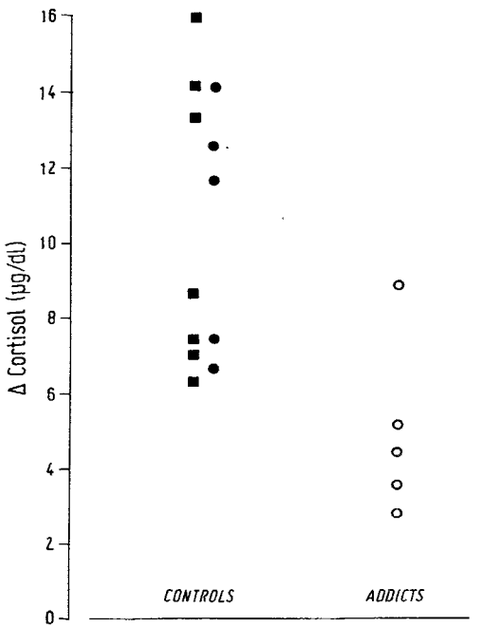
METHADONE INDUCED HYPOADRENALISM

SIR,—Corticotropin (ACTH) and beta-endorphin are formed from the same precursor protein, stored in the same cells, and probably released concomitantly under all physiological conditions.[5,6] Chronic opiate use may deplete the ACTH/beta-endorphin system, the basis for this hypothesis being blunted response of cortisol to infused naloxone.[7,8] Methadone infusion in man lowers plasma cortisol,[9] supporting a feedback suppression of the ACTH/beta-endorphin system by exogenous opiates.

To evaluate hypothalamic-pituitary-adrenal (HPA) function in opiate addiction, we administered 1–24α ACTH (0·25 mg i.m.) to five chronic methadone-addicted patients stabilised on methadone and to twelve age matched controls. Plasma cortisol was measured in duplicate by radioimmunoassay at 15 min and immediately before 1–24α ACTH, and at 15, 30, and 60 min after the injection. Cortisol release (Δcortisol) was obtained by subtracting the mean of the two baseline cortisol values from the peak plasma cortisol at 15, 30, or 60 min. Our data demonstrate a significantly blunted ($p<0·01$) cortisol release after 1–24α ACTH in methadone addicts (Δcortisol = 4·9±1·3, mean±SD) compared with controls (10·5±1·1) (see figure) and other published normal values.[10–12]



Cortisol release in addicts and controls (healthy volunteers) after 1–24α ACTH. ■ = 7 female controls; ● = 5 male controls; ○ = 5 addicts.

There was no difference between baseline cortisol levels in the patients and controls.

These findings are consistent with deficient ACTH production and subsequent secondary hypoadrenalism in methadone addicted individuals. Results support our previous report of a blunted ACTH release after naloxone in opiate addicts,[7,8] and suggest that these patients have ACTH and concomitant beta-endorphin deficiencies. Secondary hypoadrenalism in chronic methadone addicts could explain some of the signs and symptoms frequently encountered in these patients, such as fatiguability, weakness, anorexia, weight loss, depression, and gastrointestinal dysfunction. These symptoms often persist long after detoxification and are commonly associated with recidivism. It would be important to assess whether hypoadrenalism in detoxified methadone addicts eventually returns to normal, and whether it follows the time course of protracted abstinence symptoms. Further delineation of this drug-induced endocrine lesion in opiate addicted patients should improve their medical care and further clarify the functional relationship between the endorphin and HPA axis.

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