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# NEUROENDOCRINE MARKERS OF CNS DRUG EFFECTS

E.C. JOHNSTONE & I.N. FERRIER
Division of Psychiatry, Clinical Research Centre, Watford Road, Harrow HA1 3UJ

## Introduction

The idea that there is a relationship between symptoms referable to the nervous system and endocrine effects has its origins in antiquity. The direct investigation of such relationships is, of course, of much more recent origin and the principal focus of such investigation has tended to be anterior pituitary hormone secretion (APHS) (Martin, Reichlin & Brown, 1977). Such studies have been greatly aided by the development of specific and sensitive radio immunoassays for anterior pituitary hormones (Berson & Yallow, 1968). Neuro-pharmacological studies, allied with histochemical and immunofluorescence techniques, have established that biogenic amines and other neurotransmitters play a crucial role in the modulation of APHS through an action on the hypothalamic hypophysiotrophic neurones (Fuxe & Hokfelt, 1969).

There is a complex system of innervation of the hypothalamus by monoaminergic neurones. Noradrenergic and serotonergic nerves cells are mainly situated in the brain stem (locus coeruleus and raphe nuclei respectively) and terminate in several hypothalamic nuclei. The dopaminergic system is situated mainly in the medial basal hypothalamus (the so-called tubero-infundibular dopaminergic system). It has been shown that there is a close anatomical relationship between these monoamine systems and the hypothalamic neurones containing releasing factors for APHS (Martin, 1973; McNeill & Sladek, 1978). The role of monoamines and other putative neurotransmitters in modulating APHS is outlined in Table 1.

It has been hypothesised that schizophrenia (Randrup & Munkvad, 1972), affective illness (Schildkraut, 1965; Lapin & Oxenkrug, 1969), Huntington's chorea (Bird & Iversen, 1974) and Parkinson's disease (Bernheimer, Mirkmayer, Hornykiewicz, Jellinger & Seitelberger, 1973) are all disorders of neurotransmission. On the basis that any disturbance of neurotransmission underlying these disorders might also involve hypothalamic neurotransmission much research has been focused upon APHS in these conditions. Furthermore, if drugs which have therapeutic actions in these conditions do so because of their effects upon neurotransmitters it is possible that these effects would be associated with changes in APHS which could be used as an index of clinical effects. It is obvious that the investigation of APHS in association with the clinical study and treatment of the above diseases has considerable potential. There are, however, certain limitations to the study of APHS as an index of more central events. These include the following—

(A) APHS varies widely in relation to temporal factors, e.g.
  (1) Luteinising hormone (LH), follicle stimulating hormone (FSH), adrenocorticotrophic hormone (ACTH) and growth hormone (GH) have markedly episodic secretory patterns (Martin *et al.*, 1977).
  (2) LH, FSH and prolactin (PRL) vary considerably in relation to the state of maturity of the individual and with the menstrual cycle (Yen, 1977).
  (3) PRL, ACTH and GH have sleep-related secretions which may respond differently to pharmacological stimuli (Rubin, 1977).

(B) Feedback effects from target organ hormone secretion are of major importance in APHS e.g. gonadotrophins—oestrogen/testosterone, and TSH–$T_4$/$T_3$.

(C) There is a wide variation in normal levels of these hormones even when (A) and (B) are taken into account. Thus, direct comparison with a normal range may lead to problems of interpretation.

(D) Non-specific stimuli may be the important determinant affecting APHS at the time of the study, e.g. stress on PRL and ACTH, nutritional status on LH and glucose intake on GH (Noel, Suk, Stone & Frantz, 1972; Himsworth, Carmel & Frantz, 1972; Strain & Strain, 1978).

If indeed, the functional psychoses are disorders of neurotransmission it might be expected that the clinical states might be reflected in changes in APHS. Such findings have been reported in the affective disorders (Ettigi & Brown, 1977). In schizophrenia LH has been found to be low in unmedicated chronic patients (Brambilla, Guerrini, Guastalla, Rovere & Riggi, 1975; Johnstone, Crow & Mashiter, 1977) and relationships between FSH and prolactin secretion and clinical state have been found (Johnstone *et al.*, 1977).

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(E) The systemic administration of neuropharmacological agents provides little evidence as to their site of action (Grahame-Smith, 1976).

In spite of these limitations, there is a considerable body of work concerning the relationship between endocrine effects and drugs acting upon the central nervous system.

It may be classified as follows:—

(a) Endocrine effects of drugs used to treat psychiatric disorders.
(b) Endocrine effects of drugs used to investigate psychiatric disorders.
(c) Endocrine effects of drugs of abuse.

## Endocrine effects of drugs used to treat psychiatric disorders

### *Neuroleptics*

Neuroleptics have the effect of reducing the florid 'positive' symptoms of schizophrenia such as delusions and hallucinations. This group of drugs includes the phenothiazines, butyrophenones and thioxanthenes. They have several properties such as α-noradrenergic receptor blocking and anticholinergic activity but the principal property which they share is blockade of dopaminergic transmission by an action on postsynaptic dopamine receptors. It appears that the dopamine blocking ability of these drugs relates closely to their clinical efficacy in the treatment of acute schizophrenia (Creese, Burt & Snyder, 1976) and is the major factor in inhibiting pituitary lactotrophic cells (Muller, Nistico & Scapagini, 1977). There is evidence to suggest that dopamine may act directly as the primary prolactin inhibiting factor (PIF) (Ben-Jonathan, Oliver, Weiner, Mical & Porter, 1977). It has been shown that PRL secretion is elevated after neuroleptic administration in animals (de Wied, 1967), in normal subjects (Kleinberg, Wharton & Frantz, 1971, Friesen, Guyda, Hwang, Tyson & Barbeau, 1972) and in schizophrenic patients (Beumont, Corker, Friesen, Gelder, Harris, Kolakowska, MacKinnon, Mandelbrote, Marshall, Murray & Wiles, 1974, Wilson, Hamilton, Boyd, Forrest, Cole, Boyns & Griffiths, 1975). With two possible exceptions, all drugs which are known to be effective neuroleptics cause an elevation of prolactin secretion. Clozapine

**Table 1** Role of monoamines, other putative neurotransmitters and physiological stimuli in regulating the secretion of anterior pituitary hormones

| *Pituitary hormone* | *Hypothalamic releasing hormone* | *Physiological stimuli* | *Role of putative neurotransmitters* | | | | |
|---|---|---|---|---|---|---|---|
| | | | *Dopamine* | *Noradrenaline* α | *Noradrenaline* β | *5-HT* | *Others* |
| Prolactin | Prolactin inhibiting factors, PIF | Suckling +ve<br>Stress + ve sleep + ve<br>Pregnancy +ve | −ve | — | — | +ve | opiates +ve<br>? ACH |
| | ? Prolactin releasing factor/?TRH | | | | | | |
| Growth hormone | Growth hormone release inhibiting factor (somatostatin) | Stress +ve<br>Sleep +ve | +ve | +ve | −ve | +ve | opiates +ve<br>GABA −ve |
| | Growth hormone releasing factor | Glucose↑ −ve | | | | | |
| ACTH | Corticotrophin releasing factor (CRF | Sleep +ve<br>Stress +ve<br>Cortisol ↑ −ve | −ve (?) | +ve | −ve | −ve | opiates −ve |
| LH | Luteinizing hormone releasing hormone (LHRH) | Puberty +ve<br>Testosterone/oestrogen − ve | −ve (?) | +ve (?) | — | −ve (?) | opiates −ve<br>−ve ACh |
| FSH | ? LHRH | Menopause +ve | | | | | |
| TSH | Thyrotrophin releasing hormone (TRH) (somatostatin − ve) | Cold + ve, cortisol↑ − ve<br>Stress + ve, oestrogen + ve − ve<br>T4/T3↑ −ve | | — | — | −ve | opiates −ve |

References: Muller *et al.* (1977), Martini & Besser (1977).

elevates prolactin to only a slight extent (Gruen, Sachar, Altman, Leifer, Frantz & Halpern, 1978a; Gruen, Sachar, Altman, Langer, Tabrizi & Halpern, 1978b; Meltzer, Goode, Schyre, Young & Fang, 1979). This drug does appear to have anti-psychotic activity (Meltzer *et al.*, 1979) but clinical studies have been limited by the fact that its administration is associated with the development of agranulocytosis (Idanpaan-Hakkila, Alhava & Olkinvora, 1977) and it has therefore been withdrawn from some European countries. Propranolol is a $\beta$-adrenergic receptor blocking agent which has been used in very high dosage in the treatment of schizophrenia (Yorkston, Gruzelier, Zaki, Hollander, Pitcher & Sergeant, 1977). Because of the cardiovascular effects of this drug double-blind studies are difficult to achieve and its anti-psychotic efficiency is not certainly established. It has been suggested that at the dosages used in the treatment of psychoses, propranolol does elevate prolactin secretion (Nasrallah, Freed, Rogol & Wyatt, 1977) but the evidence on this matter is conflicting (Hanssen, Heyden, Sundberg, Wetterburg & Enroth, 1978; Ridges, Lawton, Harper, Ghosh & Hindson, 1977).

It is generally held that the action of neuroleptics on PRL secretion is a direct one on the pituitary. Stereospecific dopamine receptors are found in the pituitary (Friend, Brown. Jawahir, Lee & Seeman, 1978) but not in the hypothalamic median eminence (Brown, Seeman & Lee, 1976). *In vitro* studies show that neuroleptics elevate prolactin secretion from cultured pituitary cells and block dopamine induced inhibition (McLeod & Lehemeyer, 1974). Domperidone (a drug with dopamine receptor blocking activity which does not cross the blood brain barrier) is a powerful inducer of prolactin secretion (Cocchi, Gil-ad, Parenti, Stefanini, Locatelli & Muller, 1980).

It has been shown that the administration of neuroleptics leads to a reproducible and dose-dependent elevation of PRL secretion in the individual subject (Langer, Sachar, Gruen & Halpern, 1977) but these relationships are much weaker if groups of patients are studied. A positive relationship between the antipsychotic effect of neuroleptics and the associated elevation of PRL secretion has been demostrated (Meltzer & Fang, 1976; Langer *et al.*, 1977; Cotes, Crow, Johnstone, Bartlett & Bourne, 1978; Siris, van Kamman & de Fraites, 1978) but the relationship is not strong and the effect is only obvious at low doses of neuroleptics as a ceiling effect develops (Gruen *et al.*, 1978a). There is a time lag (Cotes *et al.*, 1978) between the rapid elevation of PRL and the slower anti-psychotic effects associated with neuroleptics and this may point to processes of importance in clinical response other than straightforward dopamine blockade. Relationships have also been demonstrated between (a) extra pyramidal symptoms, neuroleptic serum levels and PRL level after neuroleptic administration (Kolakowska, Wiles, McNeilly & Gelder, 1975) and (b) the rate of fall in PRL after cessation of neuroleptic therapy and extrapyramidal symptoms (Brown, Laughren & Robzyk, 1979) but these studies require confirmation.

It has been suggested (Beumont, 1979) that monitoring PRL levels is a possible method of assessing drug compliance in psychotic patients and that for this purpose it may be superior to the assessment of serum levels of neuroleptics or their metabolites. To some extent, this is so, but there are limitations to the value of this estimation in routine clinical use. It has been shown that many elderly men maintained on oral neuroleptics have normal PRL levels and this applies to a smaller percentage of female patients (de Rivera, Lal, Ettigi, Mantella, Miller & Freisen, 1976). This finding is not due to non-compliance because normal PRL levels have been found in men on depot neuroleptics (Huws & Groom, 1977) in whom significant serum levels of neuroleptics were measured (Ferrier *et al.*, unpublished observations). Drug interaction may be a relevant factor in studies of PRL levels. For example, concurrent medication with anticholinergics is said by some authors (de Rivera *et al.*, 1976) but not by others (Lawson & Gala, 1975) to be associated with higher prolactin levels.

There are much conflicting data on the effect of neuroleptics on growth hormone secretion. The basis of these differences appears firstly to be a significant species difference between primate and sub-primate species (Weiner & Ganong, 1978) and secondly the varying $\alpha$-receptor blocking activity of different neuroleptics (Willoughby, Brazeau & Martin, 1977). Markedly fluctuating values, which may be due to sampling during spontaneous GH secretory episodes, are a problem in some patients (Rubin, 1977). The administration of pimozide, the most specific dopamine blocking agent among neuroleptics, is associated with a reduction in growth hormone both basally and in response to certain physiological stimuli (Martin, 1973; Liuzzi, Panerai, Chiodini, Secchi, Cocchi, Botalla, Silvestrini & Muller, 1976; Schwimm, Schwark, McIntosh, Milstrey, Wills & Kobberling, 1976). A summary of the relevant available findings is given in Table 2.

The role of dopamine in the control of LH secretion is uncertain. Direct pharmacological studies (McCann, Fawcett & Krulich, 1974) have indicated an excitatory role but this has been contradicted by histofluorescence studies (Fuxe & Hokfelt, 1969). Dopamine appears to release luteinising hormone releasing hormone (LHRH) from hypothalamic fragments *in vitro* (Bennett, Edwardson, Holland, Jeffcoate & White, 1975), but has also been shown to have a role in the degradation of LHRH (Marcano de

Cotte, Menezes, Bennett & Edwardson, 1980). Most studies show no effect of neuropleptics on LH or FSH in patients (Table 3) but there is some evidence that when LH levels are low neuroleptic treatment is associated with a return to the normal range (Brambilla *et al.*, 1975). This has also been demonstrated for FSH (Brambilla *et al.*, 1975). A summary of relevant available findings is given in Table 3.

Testosterone levels were unchanged by neuroleptic medication in a study where these were given for sexual deviance (Murray, Bancroft, Anderson, Tennant & Carr, 1975). Brambilla *et al.* (1975) found that testosterone levels rose in chronic schizophrenic patients after the introduction of a neuoleptic drug but Cotes *et al.* (1978) found that levels of testosterone in acute schizophrenic patients were unrelated to clinical state or neuroleptic medication and Beumont *et al.* (1974) found a rise in testosterone levels after withdrawal of long term neuroleptics in eight schizophrenic males.

Neuroleptics cause variable effects, predominantly excitatory on ACTH secretion in sub-primate species probably via a noradrenergic action (de Wied, 1967). There is no conclusive evidence in man for a consistent effect of neuroleptics on ACTH secretion.

Recent studies (Healy & Burger, 1977; Scanlon, Rees-Smith & Hall, 1978) have shown small but clear-cut elevations in TSH after acute challenge with metoclopramide, a dopamine receptor blocking agent which has probable anti-psychotic effects (Stanley, Lautin, Rotrosen & Gershon, 1979) although it is not clinically used for this purpose. No longer term changes in TSH/thyroid secretion have been noted (Shader & Dimascio, 1970) and otherwise effects of neuroleptics on this system are not described.

*Lithium*

The therapeutic efficacy of lithium in manic depressive illness both as an acute treatment (Cade, 1949; Mendels, 1976) and as a prophylactic agent (Baastrup & Schou, 1967) has been clearly established. The mechanism of action of this drug is poorly understood and many inconsistent neurotransmitter changes have been reported. Although an effect on post-synaptic dopamine receptors has recently been demonstrated (Gallager, Pert & Bunney, 1978) another study (Lal, 1978) found that lithium had no

**Table 2** Effect of neuroleptics on growth hormone secretion

| *Type of patient and nature of study* | *Result* | *Authors* |
|---|---|---|
| Normal subjects given haloperidol | Basal GH reduced GH response to hypoglycaemia reduced | Kim *et al.* (1971) |
| Normal subjects given chlorpromazine | Basal GH reduced GH response to hypoglycaemia reduced | Sherman *et al.* (1971) |
| Psychiatric patients of mixed sex, age and diagnosis chronically taking phenothiazines | Basal GH normal GH response to hypoglycaemia adequate | Beumont *et al.* (1974) |
| Patients with chronic schizophrenia given haloperidol | GH secretion unchanged | Brambilla *et al.* (1975) |
| Patients with acute schizophrenia treated with α-flupenthixol β-flupenthixol or placebo | No relationship between GH levels and neuroleptic medication or anti-psychotic effect | Cotes *et al.* (1978) |
| Three groups of subjects untreated schizophrenics, schizophrenics on chlorpromazine, normals | No differences between groups in basal GH or in GH response to hypoglycaemia | Beg *et al.* (1979) |

effect upon the GH response to the dopamine agonist apomorphine or the PRL response to the dopamine receptor blocker haloperidol and that there was no alteration in the basal levels of these hormones. Long term administration of lithium has effects on thyroid functioning causing, in up to 20% of cases, hypothyroidism associated with raised TSH (Lindstedt, Nilssen, Walinder, Skott & Ohman, 1977). Long term lithium treatment may also be associated with a raised secretion of antidiuretic hormone (Padfield, Park, Morton & Braidwood, 1977) and indeed may produce a clinical picture of diabetes insipidus (Singer, Rotenberg & Puschett, 1972). These hormonal changes are thought to be due to peripheral effects on cyclic AMP (Forrest, Cohen, Torretti, Himmelhoch & Epstein, 1974) and to bear no relationship to central effects or clinical efficacy.

*Antidepressants*

Drugs with antidepressant properties cover a wide spectrum of neuropharmacological agents with a wide spectrum of differential effects on monoamines (Iversen & Mackay, 1979). In general, the administration of antidepressants does not lead to consistent hormonal change nor to endocrinological side effects. Although Turkington (1972) found elevated prolactin in patients treated with tricyclic antidepressants this has not been replicated by other workers (Meltzer, Piyakalmala, Schyre & Fang, 1977; Gruen *et al.*, 1978b; Widerlov, 1978). An exception to this is clomipramine which has a strong action in inhibiting uptake of 5-hydroxytryptamine. The administration of this drug on an acute and a chronic basis causes increased prolactin secretion (Jones et al., 1977). The administration of L-dopa, L-tryptophan and 5-hydroxytryptophan, the precursors of dopamine, noradrenaline and 5-hydroxytryptamine is associated with increased PRL secretion in man and in animals (Checkley, 1980). These drugs have been used as antidepressants but their efficacy is uncertain (Johnstone, 1980). Nomifensine is an inhibitor of endogenous catecholamine uptake and a weak dopamine agonist. It has been shown to reduce

**Table 3** Effects of neuroleptics upon secretion of luteinizing hormone

| *Type of patient and nature of study* | *Result* | *Authors* |
|---|---|---|
| Normal males given sulpiride | Prolactin raised LH unchanged | Thorner *et al.* (1971) |
| Males and post-menopausal females on neuroleptics and after withdrawal or neuroleptics | Normal levels unaffected by drugs | Beumont *et al.* (1974) |
| Premenopausal females with and without normal menstrual cycles on neuroleptics. Neuroleptics withdrawn in 4 cases. | Normal levels in subjects with normal cycles Absent midcycle LH peak in amenorrhoeic subjects restored on withdrawal of neuroleptics. | Beumont *et al.* (1974) |
| Chronic schizophrenic patients initially untreated and then given haloperidol | Initially low levels rose following haloperidol administration | Brambilla *et al.* (1975). |
| Normal females aged 20–25 years given pimozide at mid-cycle | LH levels reduced compared with previous cycles | Leppaluoto *et al.* (1976) |
| 38 acute schizophrenic patients treated with α-flupenthixol, β-flupenthixol and placebo | LH levels unrelated to clinical state or drug treatment | Cotes *et al.* (1978) |

prolactin following the administration of a single 200 mg dose (Muller, Genazzi & Murru, 1978; Masala, Magna, Devella, Delitala & Novasio, 1980) although results of another study do not support this (Dunne, Walker, Cowden & Ratcliffe, 1979). Antidepressants show few consistent effects upon growth hormone secretion. 5-hydroxytryptophan increases GH secretion (Imura, Natakai & Yoshimi, 1973) but its antidepressant activity has been very little studied (Persson & Roos, 1967).

The TSH response to TRH is blunted in some cases of depression (Prange, Wilson, Lara, Alltop & Breese, 1972; Coppen, Peet, Montgomery & Bailey, 1974). This response has been postulated as a means of classification (Gold, Pottash, Davies, Ryan, Sweeeney & Martin, 1979) and a predictor of response to antidepressants (Langer et al., 1980) but as it may persist after recovery (Kirkegaard, Nørlem, Laundsen, Bjørun & Christiansen, 1975), it cannot be used as a marker of clinical effect. In general most studies have failed to show consistent relationships between TSH response to TRH and clinical features (Paykel & Rowan, 1979).

No consistent effects of antidepressants upon the secretion of other anterior pituitary hormones have been found.

*Anxiolytics*

These drugs are generally considered to be free of neuroendocrine effects (Beumont, 1979). Two recent studies of benzodiazepines which are the most commonly used anxiolytics (Blackwell, 1973) have shown results of theoretical interest to the general topic of neuroendocrine markers of central nervous system drug effects. In the first of these studies it was found that the administration of diazepam 10 mg gave a consistent rise in GH (Syvalahti & Kanto, 1975) and that this effect was blocked by pimozide and sodium valproate but not methysergide (Koulu, Lammentausta, Kangas & Dahlstrom, 1979). Since GABA is thought to be inhibitory to GH release this does not accord with diazepam's putative GABA agonist activity (Snyder, Enna & Young, 1977).

The second of the studies concerned the effects of benzodiazepines upon basal and stress related ACTH secretion. Diazepam has been shown to reduce ACTH output in man (Rees, 1970) and to reduce basal cortisol secretion in animals at low doses although in high doses cortisol secretion in animals is increased (Barlow, Knight & Sullivan, 1979). In neurotic male subjects a high correlation was found between ACTH and cortisol secretion and arousal as measured by galvanic skin response. In these patients there was an ACTH and cortisol response to acute stress. After 4 weeks treatment with diazepam the initial high correlation was lost, the ACTH responses were reduced and more variable and the cortisol response was abolished (Ferrier *et al.*, unpublished observations).

*Cyproheptadine*

This drug is an antagonist of histamine and 5-hydroxytryptamine. Its properties in increasing weight were found fortuitously when its antihistaminic actions were being utilized in the treatment of hay fever and asthma in children (Lavenstein, Dacanay, Horvath, Lasagna & van Metre, 1961). This finding has been replicated in patients with many diagnoses (General Practitioner Clinical Trials, 1970) and although the drug has been used in the treatment of anorexia nervosa systematic studies of its value in that condition have been few (Halmi & Goldberg, 1978). Endocrinological effects of cyproheptadine in man have been little studied but it has been found to reduce the growth hormone response to hypoglycaemia in normal volunteers (Bivens, Lebovitz & Feldman, 1973) and to suppress sleep related GH and cortisol release (Chihara, Kato, Maeda, Matsukara & Imura, 1976).

## Endocrine effects of drugs used to investigate psychiatric disorders

Neuroendocrine tests are increasingly being used as a means of investigating neurotransmission in psychiatric conditions and in other disorders of the CNS. The considerable body of information concerning this topic has been reviewed by Checkley (1980), Rotrosen, Angrist, Gershon, Parquin, Branchley, Oleshansky, Halpern & Sachar (1979), Langer, Sachar, Nathan, Tabriezi, Perez & Halpern, (1979) and Annunziato (1979). Studies confined to particular disorders concern acromegaly (Thorner, Chait, Aitken, Bender, Bloom, Mortimer, Sanders, Stuart-Mason & Besser, 1975), Huntington's chorea (Caraceni *et al.*, 1977) and Parkinsonism (Parkes, Debono & Marsden, 1976). A summary of the more consistent findings in normals and patient groups employing the drugs described below is given in Table 4.

(a) *Dopamine agonists*

There are several drugs in this category used in endocrinological research and the details of their modes of action are shown in Table 5. In addition to these drugs dopamine infusions are increasingly being employed. Apomorphine and bromocriptine both lower prolactin in cell culture lines, animals, normal subjects and hyperprolactinaemic patients (Besser, Parke, Edwards, Forsyth & McNeilly, 1972; McLeod & Lehemeyer, 1974; Martin, Lal, Tolis & Friesen, 1974; Lawson & Gala, 1975). Lisuride (Delitala, Wass, Stubbs, Jones, Williams & Besser, 1979) and

**Table 4** Endocrine responses to centrally acting drugs used in the investigation of psychiatric and other conditions

| *Condition* | *Authors* | *Dopamine agonists Bromocriptine (Bromo), levodopa (L-D) Apomorphine (Apo)* | *α-noradrenergic receptor agonists Clonidine* | *Amphetamines* |
|---|---|---|---|---|
| Normal | See text | PRL↓GH↑<br>? LH ACTH→ | GH↑ PRL→<br>ACTH→LH→ | GH↑ PRL?<br>ACTH↑ LH→ |
| Schizophrenia | Pandey *et al.* (1977)<br>Ettigi *et al.* (1976)<br>Langer *et al.* (1976) | ? enhanced GH↑ and reduced PRL↓ to Apo in some acute patients<br>Blunted GH↑ and PRL↓ to Apo in many chronic patients | — | Normal GH responses |
| Huntington's chorea | Caraceni *et al.* (1977)<br>Chalmers *et al.* (1978) | Enhanced GH↑ to Bromo but reduced PRL↓<br>Normal responses | — | — |
| Parkinson's disease | Hyppa (1978)<br>Shaw *et al.* (1976)<br>Parkes *et al.* (1976)<br>Malarkey *et al.* (1974) | Enhanced PRL↓ and GH↓ to Bromo<br>Reduced GH↑ to Bromo<br>Reduced GH↑ to Bromo Normal to L-D<br>Reduced GH↑ to L-D | — | — |
| Acromegaly | Thorner *et al.* (1975) | GH↓ PRL↓ | — | — |
| Affective illness | Coppen & Ghose (1978)<br>Gold *et al.* (1976)<br>Mendels *et al.* (1974)<br>Checkley (1980)<br>Checkley (1979)<br>Langer *et al.* (1976) | Normal PRL↓<br>Normal PRL↓<br>Normal GH↑ | ? Reduced GH↑ in depression | Reduced cortisol↑ in depression<br>Reduced GH↑ in depression |

lergotrile (Thorner, Ryan, Wass, Jones, Bouloux, Williams & Besser, 1978) inhibit basal prolactin. L-dopa has also been found to lower prolactin although this effect is less consistent (Lal, Martin, de la Vega & Friesen, 1975). Amphetamines, however, have weak and inconsistent effects upon PRL in both animal (Ravitz & Moore, 1977) and human studies (Wells, Silverstone & Rees, 1978; Slater, de la Vega, Shyler & Murphy, 1978). Dopamine infusions reduce PRL secretion from pituitary cell cultures (Birge, Jacobs, Hammer & Daughaday, 1970) animals, including stalk-sectioned monkeys (Diefenbach, Carmel, Frantz & Ferin, 1976) and from human subjects (Leblanc, Lachein, Abu-Fadel & Yen, 1976; Leebaw, Lee & Woolf, 1978). All dopamine agonists block the prolactin response to TRH *in vitro* (Dibbett, Bondreau, Bruni & Meites, 1974) and *in vivo* (Besses, Burrow, Spaulding & Donabedian, 1975).

It seems probable that these agents act directly on the pituitary dopamine receptor although additional effects on the hypothalamus cannot be ruled out and are supported by some evidence (Kamberi, Mical & Porter, 1971). It is possible that dopamine metabolism in the median eminence (Gudelsky & Moore, 1976) and dopamine receptors of the pituitary (Friend *et al.*, 1978) differ in pharmacological responses from central dopamine synapses. Functionally, however, many of the responses of this 'hypothalamic-pituitary dopamine system' resemble those more centrally (Lal, Harvey & Bikadoroff, 1977). One of the problems of using PRL reduction after dopamine agonists as a way of assessing dopamine receptor function is that there is a very narrow range between normal levels and both the lower limit of detection of the assay system and the level below which even massive doses of the drug do not produce any further depression of PRL level. Langer *et al.* (1979) have suggested studying the suppressive effects of dopamine agonists after a dose of neuroleptic to raise PRL to half maximum but this method raises interpretative difficulties of its own. Another problem is that the nausea and emesis which dopamine agonists may produce is stressful. The abolition of these problems by the administration of the peripherally acting dopamine receptor blocker domperidone itself produces marked endocrine effects.

GH secretion is stimulated in man by the administration of dopamine agonists (Lal, de la Vega, Sourkes & Friesen, 1973; Camanni, Massara, Belforte & Molinatti, 1975; Thorner *et al.*, 1978; Delitala *et al.*, 1979) and this effect is blocked by dopamine receptor blockers (Lal, Martin, *et al.*, 1975; Thorner *et al.*, 1978; Delitala *et al.*, 1979) except in the case of L-dopa where the GH response is blocked by 5-HT antagonists (Smythe, Compton & Lazarus, 1976). The rise in GH produced by amphetamine does not differ between the (+) and (−) isomers (Langer & Matussek, 1977) and this, together with the fact that the effect is not blocked by pimozide suggests that this response is noradrenergic (Sachar, Gruen, Altman, Halpern & Frantz, 1976). Dopamine infusion has been reported to increase the secretion of GH in some studies (Burrow, May, Spaulding & Donabedian, 1977, Leebaw *et al.*, 1978)

**Table 5** Actions of dopamine agonists used in endocrinological research

| *Drug* | |
|---|---|
| 1. Apomorphine | Potent dopamine receptor agonist, effective on dopamine sensitive adenylate cyclase system, ? selectively labels presynaptic dopamine receptors, decrease in dopamine turnover, ? increases 5-HT turnover. |
| 2. Ergot derivatives | |
| a) bromocriptine | High affinity for dopamine receptor sites, no stimulation of dopamine sensitive adenylate cyclase system *in vitro*, reduce dopamine turnover. Probable effect on 5-HT receptors but ? effect on 5-HT turnover. |
| b) lisuride | |
| c) lergotrile | |
| 3. Levodopa | Increases synthesis of dopamine and noradrenaline and 5-HT |
| 4. Amphetamines | Indirect presynaptic agent—releases biogenic amines,—noradrenaline and dopamine and blocks re-uptake—increase in turnover of dopamine, noradrenaline and ? 5-HT. |

References: Muller *et al.* (1977), Fuxe, (1979).

but not in others (Leblanc *et al.*, 1976; Camanni, Massara, Belforte, Rosatello & Molinatti, 1977). Direct acting dopamine agonists and dopamine infusion have no effect on ACTH secretion (Lal *et al.*, 1973). Methylamphetamine induces ACTH secretion but this effect is blocked by α-adrenoceptor blockers and enhanced by β-adrenoceptor blockers suggesting that the effects of amphetamine are mediated by noradrenergic synapses (Rees *et al.*, 1970).

In animal studies systemic dopamine agonists have been shown to reduce LH and LH pulsatile release (Arendash & Gallo, 1978; Drouva & Gallo, 1977), but the effects are small and there is much dispute in this area. It is established that apomorphine (Lal *et al.*, 1973) lergotrile (Thorner *et al.*, 1978) and lisuride (Delitala *et al.*, 1979) have little effect on LH but there are disputes regarding the effects of L-dopa and bromocriptine (Hayek & Crawford, 1971; Lachelin, Leblanc & Yen, 1977; Strauch, Valche, Mahoudeau & Bricair, 1977). However, some workers have found that dopamine infusions lower LH in humans although their results on male subjects differ (Leblanc *et al.*, 1976; Leebaw *et al.*, 1978).

No consistent data on FSH and TSH have been noted.

(b) *Drugs acting at noradrenergic synapses*

(1) *α-adrenoceptor agonists* It appears that drugs of this type e.g. clonidine stimulate the release of GH but have little effect on PRL secretion (Lal, Tollis, Martin, Brown & Guyda, 1975; Gil-Ad, Topper & Laron, 1979). There is some evidence that amphetamine acting through an α-adrenergic mechanism elevates ACTH secretion (Rees *et al.*, 1970) as does the specific α-agonist methoxamine (Nakai, Imura, Yoshumi & Matsukura, 1973). However clonidine which is more specific appears to have no such action (Lal, Tollis *et al.*, 1975). No consistent effects on LH, TSH or FSH are noted.

(2) *α-adrenoceptor blockers* This group of drugs appears to block the GH response to most physiological stimuli (Checkley, 1980) but not to sleep (Lucke & Gilke, 1971). No consistent effects on PRL are noted. The ACTH response to amphetamine and to hypoglycaemia is blocked by α-receptor blocking drugs (Rees *et al.*, 1970; Nakai *et al.*, 1973). In animals, α-adrenoceptor blockade produces lower LH levels and a reduction in LH episodic secretion (Weich, 1978; Plant, Nakai, Belchetz, Keogh & Knobil, 1978) but this effect is not noted in man.

(3) *β-adrenoceptor blockers* There is uncertainty about the effect of these drugs on PRL but stress effects particularly associated with hypotension may be paramount here. β-adrenoceptor blockage appears to enhance the GH response to most physiological stimuli, (Checkley, 1980) and also the ACTH response to amphetamine and hypoglycaemia (Rees *et al.*, 1970; Nakai *et al.*, 1973) suggesting that β-receptors have an inhibitory role in these responses. Of itself, β-adrenoceptor blockade appears to be associated with little endocrinological effect.

(c) *Drugs acting on opiate receptors*

In both rats and primates clearcut effects with morphine and enkephalin analogues have been seen after intravenous, intraventricular and intrahypothalamic administration with elevations of PRL and GH and reductions in LH, TSH and ACTH (Lien, Feruchel, Garsby, Sarantako & Grant, 1976; Shaar, Frederickson, Doninger & Jackson, 1977). These effects were blocked by naloxone (Shaar *et al.*, 1977) and indeed reverse by naloxone administration alone (Bruni, van Vogt, Marshall & Meites, 1977; Gold, Redmond & Donabedian, 1978). In man morphine causes an elevation of PRL and GH but there appears to be an interaction with dopamine receptors (Tollis, Hickey & Guyda, 1975). Long acting enkephalin analogues produced the same picture with a reduction in LH and cortisol and in this case the effect was reversed by naloxone (Stubbs, Delitala, Jones, Jeffcoate, Edwards, Ratter, Besser, Bloom & Alberti, 1978). Naloxone administration *per se* has disputed actions on PRL and GH (Janowsky, Judd, Huey, Portman & Parker, 1979; Rubin, Swezy & Bluschke, 1979) although it is likely that pharmacodynamic and dose effects are important causes of these contradictions. Recently, it has been shown that intravenous heroin produces an acute fall in LH levels with a loss of the normal episodic LH pattern (Mirin, Mendelson, Ellingboe & Myer, 1976). This effect was blocked by pre-treatment with the specific opiate antagonist naltrexone. Naltrexone administration alone caused increased LH levels with an increased number of secretory LH bursts in normal subjects (Mendelson, Ellingboe, Keuhnle & Mello, 1978).

## Endocrine effects of drugs of abuse

The difficulties of using endocrinological effects as an index of drug actions described in the introduction apply to drugs coming under this heading as they do to the other groups but there are additional difficulties peculiar to this group. Persons who abuse drugs are inclined to be unreliable, may give misleading information about their drug intake and if they abuse one drug may well abuse others (Brambilla, Resele, de Maio & Nobile, 1979). Furthermore, the drug in question, and alcohol is the best example of this, may have other effects such as

the production of liver damage which may have endocrinological effects. The marked anxiety and other physiological changes which may be associated with withdrawal of some drugs have to be taken into account in designing studies in this area.

(a) *Alcohol*

Alcohol is widely abused in western society. Various studies of its endocrine effects have been conducted but their results tend to be conflicting (Table 6).

(b) *Amphetamine*

The acute effects of amphetamine have been discussed in the previous section. Although amphetamine is chronically abused and is sometimes taken on a long term basis for therapeutic purposes, abuse is not now common and therapeutic use is rare. Thus, its endocrinological effects other than as an investigative tool have been little studied. Its effects on GH have been studied in a group of narcoleptic subjects, some of whom had been on amphetamine for up to 20 years (Parkes, De Bono, Jenner & Walters, 1977). Although GH responses to amphetamine were reduced in the narcoleptic subjects this reduction did not appear to be due to previous amphetamine treatment.

(c) *Cocaine*

Cocaine has a multiplicity of effects on neurotransmitters including the blocking of re-uptake of dopamine, 5-hydroxytryptamine and noradrenaline although it has other effects (Post, 1975). Although it is abused widely in South America its use is not widespread in Europe and its endocrinological effects in man have not been established. It is known

**Table 6** Endocrinological effects of alcohol

| *Subjects* | *Hormonal effect* | *Reference* |
|---|---|---|
| 13 male alcoholics | Basal LH increased. LH response to LHRH raised in those with LH outside normal range. 17 OHA normal. | Wright *et al.* (*1976*) |
| 7 male alcoholics (2–7 days off alcohol) *v* 5 or 6 male controls | Basal GH reduced and GH and cortisol responses reduced in alcoholics | Chalmers *et al.* (1977) |
| 16 normal males given alcohol | Acute rise in LH and fall in testosterone following alcohol administration. | Mendelson *et al.* (1977) |
| 174 abstinent alcoholics of whom half resumed intake during study | Testosterone reduced during alcohol administration | Persky *et al.* (1977) |
| 22 chronic alcoholic males. 14 normal males all given LHRH (in normals before and after 3 days acute alcohol ingestion) | In alcoholics basal testosterone reduced LH and FSH raised and prolactin normal. LHRH response reduced in alcoholics: administration of alcohol to normals produced rise in LH, fall in testosterone. | Van Thiel (1978) |
| 33 male alcoholics in withdrawal tested 2 and 9 days of alcohol | Basal GH raised, PRL low blunted response to TRH basal testosterone and cortisol normal. At second testing GH normal PRL normal TRH response more nearly normal | Loosen *et al.* (1979) |

to produce a slight reduction in serum prolactin in rats (Ravitz & Moore, 1977).

(d) *Heroin*

The effects of heroin have been studied in patients currently abusing the drug, patients maintained on methadone and in abstinent former addicts. The results are shown in Table 7.

Thus, there may be dysfunction of pituitary gonadal axis in heroin/methadone users but the results are not consistent.

(e) *Marihuana*

A reduction in plasma testosterone was found to occur following chronic intensive marihuana use (Kolodny, Masters, Kolodner & Toro, 1974) and these authors also found that very heavy use of marihuana was associated with reduced FSH secretion. Both Mendelson, Kuehnle, Ellingboe & Babor (1974) and Schaefer, Gunn & Dubowski (1975) found normal testosterone levels in abusers of marihuana. Benowitz, Jones & Lerner (1976) studying normal volunteers found a reduced GH response to hypoglycaemia following 14 days administration of delta-9-tetrahydro-cannabinol.

Again there is a suggestion of dysfunction in the pituitary gonadal axis but the results are not consistent. Apart from the lack of consistency of these results the abnormalities which are found tend to represent a change within a wide normal range and even if they were replicable could not be used as an endocrine maker of the drug effect.

## Conclusion

The fact that it has been established that the neurotransmitters which are thought to be involved in the cause of serious psychiatric and other disorders, and are known to be affected by the treatments used for these disorders, are important in the control of the secretion of anterior pituitary hormones which can now be accurately measured in small samples, is obviously of great interest. The possibility is raised that endocrine changes could be used as a readily measurable index of effects upon neurotransmission of centrally acting drugs. As yet, this is a future hope rather than a present reality. The exact nature of the neuronal control of some hormones is unclear, their secretion may be influenced by non-specific factors which are difficult to control, and some of the drugs have a variety of actions. Even where these problems apply only to a very limited extent as is the case with regard to the rise in prolactin produced by the dopamine blocking agents used to treat schizophrenia, the practical value of this 'endocrinological marker' is doubtful. As noted, some patients taking these drugs on a chronic basis no longer have elevated prolactin levels (de Rivera *et al.*, 1976; Huws & Groom, 1977) but even if the acute situation only is considered, although a correlation between clinical effect and the rise in prolactin can be found, some patients with very high levels show no clinical response and some improve without active medication (Cotes *et al.*, 1978). Thus, despite the considerable theoretical interest of the topic, these techniques do not yet have a place in routine clinical practice.

**Table 7** Endocrinological effects of heroin

| *Subjects* | *Hormonal effect* | *Reference* |
|---|---|---|
| Heroin addicts; methadone maintained; former methadone maintained abstinent addicts; normal controls (all male) | Testosterone within normal range | Cushman (1973) |
| Heorin addicts; methadone users; controls (all male) | Testosterone reduced in methadone users but not in heroin addicts | Cicero *et al.* (1975) |
| Heroin addicts; high dose methadone users; low dose methadone users; normal controls (all male) | Testosterone reduced in heroin addicts and high dose methadone users but not in low dose methadone users. | Mendelson *et al.* (1975) |
| Heroin addicts (all male) | Reduced basal FSH, LH & testosterone | Brambilla *et al.* (1977) |
| Heroin addicts and controls both given GnRH (all male) | Basal LH and FSH low in addicts response to GnRH reduced in addicts | Brambilla *et al.* (1979) |

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