ENDOCRINE RESPONSES TO ANAESTHETIC AGENTS

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In recent years the development of new techniques of hormone assay has stimulated studies on the effects of anaesthetics on the endocrine system. Although the endocrine response to anaesthesia is less than that to major surgical procedures, the effects of anaesthesia on metabolism and on the autonomic nervous system are substantial. It would be beneficial if the safety of patients undergoing anaesthesia and surgery could be increased by utilizing the latest developments in this field. It should also be remembered that endocrine disease itself exerts an influence on the course of anaesthesia and surgery. While the preoperative and postoperative management of patients with endocrine disease is of special importance, it will not be discussed here.

This paper lists the information specifically pertaining to the action of anaesthetics on endocrine function in man, particularly that obtained in recent years in the author's laboratories. The subjects to be covered are: (1) the hypothalamic-hypophyseal-adrenal cortical axis (ACTH, cortisol, aldosterone); (2) catecholamines; (3) growth; (4) thyroid; (5) antidiuretic hormones; and (6) testosterone.

THE HYPOTHALAMUS AND PITUITARY

There are many hypothalamic nuclei producing and secreting releasing factors (RF), which stimulate the pituitary to produce corresponding trophic hormones. Releasing factors pass into the portal hypothalamo-hypophyseal circulation, and are thus able to exert their effects rapidly on the anterior lobe of the pituitary while they are in relatively high concentration. The hormones produced stimulate the peripheral endocrine organs, and influence the activity of the corresponding hypothalamic nuclei by either a negative or positive feedback mechanism, and so regulate pituitary function.

The posterior pituitary hormones include oxytocin and vasopressin (antiuretic hormone = ADH).

**Adrenocorticotropicin (ACTH).**

ACTH in human plasma is increased markedly during induction of anaesthesia and throughout surgery. Large amounts of ACTH are released intermittently, with two or three steep peaks in plasma levels (Oyama et al., 1968b, 1972, 1973; Oyama and Takiguchi, 1970a; Oyama, Takiguchi and Kudo, 1969; Newsome and Rose, 1971). In contrast, the level of cortisol in the plasma increases gradually. These effects were observed during diethyl ether, halothane, gamma-hydroxybutyrate, and neurolept-anaesthesia (consisting of droperidol and pentazocine) in man. ACTH in plasma determined once during operation or after operation has also been shown to be elevated (Cooper and Nelson, 1962; Yalow et al., 1969). No rise in plasma ACTH was observed in patients during surgery using spinal anaesthesia (Oyama et al., 1973b).

**Cortisol.**

In the discussion that follows, unless otherwise specified, the term cortisol and 17-OHCS will be used to mean non-conjugated steroid, both protein-bound and unbound. Bound steroids appear to be physiologically inactive, and act as a reservoir for the free forms. The peripheral blood contains free, bound, and conjugated cortisol. If there is a marked increase in cortisol secretion, the transcortin-binding sites become saturated, and the amount of free cortisol increases greatly. The concentration of plasma cortisol at any moment is determined primarily by its secretion, distribution, utilization and degradation. It is generally agreed that the response of plasma cortisol to surgical trauma is due mainly to stimulation of the pituitary-adrenal system resulting in an increased secretion.

Preoperative emotional reactions such as fear and apprehension cause adrenocortical stimulation (Franksson and Gemzell, 1955; Persky, Smith and Basu, 1971; Brunt and Ganong, 1963; Bursten and Russ, 1965). It has also been reported that sleeplessness enhances adrenocortical activity in man (Utting and Whitford, 1972).

The sedatives, which are used for preanaesthetic medication, reduce the adrenocortical stimulation caused by preoperative emotional stress in the oper-
Recently, however, it has been demonstrated that of cortisol (Hammond et al., 1958; Vandam and Moore, 1960; Brunt and Ganong, 1963). More recently, however, it has been demonstrated that there is a significant fall in plasma cortisol in man after 45 min of this technique, before surgery begins (Oyama et al., 1971).

Pentobarbitone given intravenously lowers the plasma level of cortisol to a slight degree in man (Siker, Lipschitz and Klein, 1956). Propanidid alone (5.0 mg/kg for induction) does not significantly increase plasma cortisol (Oyama et al., 1970), but ketamine (2.0 mg/kg for induction) combined with nitrous oxide does significantly stimulate adrenocortical activity (Oyama, Matsumoto and Kudo, 1970). Gamma-hydroxybutyrate (200 mg/kg of 20% solution) injected intravenously for induction also significantly elevates plasma cortisol after 30 min of anaesthesia (Oyama et al., 1968a).

Pethidine (50–250 mg for induction) combined with nitrous oxide does not stimulate adrenocortical function appreciably as indicated by the plasma cortisol level (Oyama et al., 1969c). Droperidol (0.15 mg/kg) given with nitrous oxide may be followed with subsequent doses of pethidine (20 mg), and this form of neuroleptanalgesia alone for 30 or 45 min also does not significantly influence adrenocortical function (Oyama and Takiguchi, 1970b).

Droperidol (0.15 mg/kg) plus pentazocine (1.0 mg/kg), followed with subsequent doses (30 mg) of pentazocine when needed and supplemented with nitrous oxide for 45 min, raises plasma cortisol significantly (Oyama, Takiguchi and Sato, 1971). This type of NLA also tends to elevate arterial pressure as does gamma-hydroxybutyrate. Droperidol (0.15 mg/kg) plus fentanyl (0.003 mg/kg for induction), followed by nitrous oxide and oxygen with fentanyl (0.05 mg intravenously as needed), does not increase plasma cortisol during anaesthesia, so it would seem that it is the opiate antagonist pentazocine which may be responsible for the adrenocortical stimulation.

Hydroxydione, the first successful steroid anaesthetic agent, appears to have no endocrine effect. Althesin (CT 1341) also does not change appreciably plasma cortisol levels in man (0.125 ml/kg), and the normal adrenocortical response to surgical operations is observed (Oyama and Maeda, unpublished data).

Of the muscle relaxants, the steroid-based pancuronium bromide has no effect on adrenocortical function in man, and this is true of others such as tubocurarine, suxamethonium, succinylcholine and alcuronium (Matsuki and Oyama, 1971; Matsuki, Sato and Oyama, 1971). Spinal anaesthesia has been reported to evoke no
stimulatory effect on the pituitary-adrenal system, and there is little if any increase in adrenocortical secretion during surgical procedures carried out under spinal anaesthesia (Hammond et al., 1958; Vandam and Moore, 1960; Oyama and Matsuki, 1970a). When the effect of the nerve block has dissipated, however, the adrenal cortical response to the operation becomes apparent. In those cases where a rise in circulating corticoids has been detected during spinal anaesthesia, either anaesthesia has not attained a sufficient level, or the rises in blood concentrations of cortisol were small.

No appreciable rise in plasma ACTH level has been detected during operations carried out under spinal anaesthesia, but it increased markedly when the influence of the spinal anaesthetic wore off (Oyama et al., 1973). Local anaesthetic injection per se causes no increase in cortical activity (Vandam and Moore, 1960).

Aldosterone.

Plasma aldosterone concentration is of the order of 1/2,000 that of cortisol.

The effects on plasma aldosterone levels of anaesthesia with diethyl ether, methoxyflurane, or thiopentone with nitrous oxide, were studied in 6 patients by Oyama and colleagues (1973a). Anaesthesia alone for 45 min significantly increased plasma aldosterone to 12.8 m\(\mu\)g/100 ml from a mean control level of 6.2 m\(\mu\)g/100 ml. The level was 12.9 m\(\mu\)g/100 ml 1 hour after the start of operation. Serum sodium and potassium concentrations decreased slightly.

**CATECHOLAMINES**

Intravenously administered morphine (0.2 mg/kg) or fentanyl (0.004 mg/kg) for preanaesthetic medication tended to raise plasma adrenaline, and there was a lowered noradrenaline level (Jäättelä et al., 1971). Pethidine (2 mg/kg) was not associated with elevated plasma catecholamines, but intravenous pentazocine (1.2 mg/kg) increased the levels to a maximum of 70\%, 5 min after injection (Tammisto et al., 1971).

While the phenothiazines show marked \(\alpha\)-sympatholytic effects, the protective actions of butyrophenones, including droperidol, against catecholamine-induced vasoconstriction and dysrhythmias have been demonstrated. These actions may not be related either to \(\alpha\)- or \(\beta\)-adrenergic blockade but rather to a non-specific inhibition (Edmonds-Seal and Prys-Roberts, 1970).

Reserpine may cause deleterious effects on the regulation of circulation during anaesthesia through catecholamine depletion (Pickering, 1968), and some favour the idea that responses to anaesthesia depend on whether the hypertension has been treated or not (Prys-Roberts, Meloche and Foëx, 1971). Consequently, antihypertensive therapy should not be withdrawn prior to anaesthesia (Jäättelä et al., 1972).

Diethyl ether anaesthesia increases plasma catecholamine levels in man (Price et al., 1959; Millar and Morris, 1961; Black et al., 1969), mainly due to a rise in plasma noradrenaline. Extra-adrenal sources of noradrenaline appear to contribute to the elevated plasma levels, \(P_{a,\text{CO}_2}\) probably also playing a part if raised. Ether is known as a "non-sensitizing" agent to cardiac rhythmicity (Price, 1966).

Cyclopropane elevates concentrations of noradrenaline in human arterial plasma (Price et al., 1959). This effect is greater than that caused by ether, and is roughly proportional to the concentration of cyclopropane in alveolar air. Hypercarbia also raises plasma noradrenaline to a greater extent in the presence of cyclopropane than in the conscious state (Price et al., 1960).

Halothane anaesthesia does not increase human plasma adrenaline or noradrenaline levels at normal or reduced \(P_{a,\text{CO}_2}\) or in the absence of surgery (Price et al., 1959; Millar and Morris, 1961). However, small statistically significant increases in plasma adrenaline have been detected during surgery in patients anaesthetized with halothane (Millar and Morris, 1961).

Methoxyflurane exerts no measurable influence on catecholamines in peripheral blood in man (Elliott, Black and McCullough, 1968).

Inhalation of intravenous thiopentone in man is not followed by significant changes in plasma adrenaline or noradrenaline concentrations (Price et al., 1959).

Plasma catecholamines have been found to increase during surgery with NLA (Gott and Klensch, 1970; Tammisto et al., 1971). Thalamonal (Innovar) followed with fentanyl-N\(_2\)O anaesthesia in man increased the levels of both catecholamines. Thalamonal-N\(_2\)O alone increased urinary excretion of adrenaline, but noradrenaline excretion remained unchanged (Giesecke et al., 1967). Inhibited liberation of catecholamines does not seem to explain the cardiovascular stability with NLA during surgical stimulation.

Spinal anaesthesia was not associated with any detectable change in blood adrenaline or noradrenaline levels in surgical patients (Hammond, Aronow...
and Moore, 1956; Hamelberg et al., 1960). Spinal anaesthesia probably abolishes catecholamine responses to general anaesthetic agents, as observed in the case of cyclopropane (Price et al., 1959).

GROWTH HORMONE
Anaesthesia alone for 45 min with methoxyflurane, diethyl ether, gamma-hydroxybutyrate, and NLA (droperidol and pethidine or pentazocine) increased significantly plasma growth hormone level from a preinduction level of 1.4–1.8 mUg/ml to 6–14 mUg/ml (Oyama and Takazawa, 1970, 1971; Oyama and Takiguchi, 1970c, d). Halothane, cyclopropane, thiopentone, enfurane and spinal anaesthesia, however, did not increase the level significantly (Oyama and Matsuki, 1970b; Oyama, Takiguchi and Kudo, 1971; Oyama and Takazawa, 1972). The reasons for this difference in the response of growth hormone to the various anaesthetic agents is unknown.

Surgical trauma further elevates the plasma concentration of this hormone to 17–24 mUg/ml. A peak is usually observed 1 hour after the start of an operation, after which the concentration gradually decreases (Charters, Odell and Thompson, 1969).

THYROID STIMULATING HORMONE (TSH) AND THYROXINE
TSH levels in human plasma do not change appreciably during ether, halothane, methoxyflurane, gamma-hydroxybutyrate, thiopentone, or spinal anaesthesia in man (Oyama, Matsuki and Kudo, 1972a, b, c; Matsuki and Oyama, 1972). No significant variation in plasma TSH levels has been noted even during surgical operations (Burke, 1971). Ether and halothane, however, significantly increase the serum thyroxine level, while methoxyflurane, gamma-hydroxybutyrate, thiopentone and spinal anaesthesia have caused no change (Oyama, Shibata and Matsuki, 1969). When using the latter anaesthetics, however, surgical trauma is usually associated with a rise in serum thyroxine.

Hypothermia, although recognized as a strong stress, apparently does not stimulate TSH secretion (Burke, 1971). An exceptional report was made by Wilber and Baum (1970), who found marked elevation of plasma TSH levels during surgery under hypothermia (rectal temperature 18°C) in infants.

ANTIDIURETIC HORMONE (ADH)
Premedication consisting of pethidine and barbiturate in man does not appear to stimulate ADH secretion, as judged by measurement of the plasma level. Administration of pethidine (100–185 mg) and seccobarboline (200 mg) in man have resulted in a decreased volume of urine without increase in osmolality, suggesting that these drugs do not stimulate ADH secretion.

Stress, including anaesthesia, surgery and pain, stimulates ADH secretion. The effect of anaesthesia on plasma ADH levels is believed to be due to a direct effect on the hypothalamic-pituitary system. Administration of diethyl ether, methoxyflurane, or halothane, increases human plasma ADH levels (Oyama and Kimura, 1970; Oyama and Sato, 1970; Oyama, Sato and Kimura, 1970). Blood loss is a strong stimulus to the secretion of ADH, and major surgical operations result in higher plasma ADH levels than does minor surgery (Moran et al., 1964). A transient and marked elevation in plasma ADH level is associated with peritoneal incision or visceral traction (Moran et al., 1964).

TESTOSTERONE
Testosterone concentration in human plasma during 45 min of halothane anaesthesia has been shown to decrease by 12% from control values (Oyama, Aoki and Kudo, 1972), and to fall further during surgery to 80% of the preinduction level. The lowest value (48% of control) was detected on the first postoperative day. Low concentrations of plasma testosterone persisted for 1 week postoperatively. Anaesthesia with droperidol and pentazocine combined with surgery also decreased plasma testosterone (Oyama, Aoki and Kudo, 1973). During thiopentone-nitrous oxide anaesthesia the level fell during the first 30 min of anaesthesia but it later returned to control and remained unaffected by surgery (Oyama and Kudo, 1972). However, there was a highly significant fall in plasma testosterone after the operation which persisted for 7 days. The mechanism by which the peripheral venous testosterone concentration is reduced by anaesthesia and surgery is unknown.

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