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TESTS OF AUTONOMIC FUNCTION IN ASSESSING CENTRALLY-ACTING DRUGS

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The major classes of centrally-acting drugs in psychotherapeutic use have marked peripheral autonomic actions in man, which may appear at therapeutic doses and not be related only to overdosage. Studies on the central nervous pharmacological effects of these drugs in man are severely limited methodologically, and it has been tempting, therefore, to extrapolate from their peripheral autonomic effects to possible central actions. It has to be admitted with disappointment, however, that no consistent spectra of such actions have been described which provide convincing bases for hypothetical central mechanisms of action. Nevertheless, studies of the peripheral autonomic actions of drugs of any therapeutic class are an important part of their early screening because they may be predictive of important adverse effects and drug interactions that may be encountered during their long-term therapeutic use.

The neurochemical basis of transmission in the autonomic nervous system continues to attract attention (Burnstock, 1979) and in recent years evidence has been produced for purinergic and peptidergic mechanisms. It is probable that many psychotropic drugs will be found to influence these systems, but this review will be limited to some of the methods available for studying their actions on the better known human cholinergic (ACh), noradrenergic (NA), dopaminergic (DA) and serotoninergic (5HT) systems.

Human isolated tissue

a) *Smooth muscle* The autonomic receptor population of different types of human smooth muscle have been characterized and used to study the postsynaptic agonist and antagonist actions of many drugs. The value of such studies was illustrated by the demonstration that the so-called 'false transmitter' α-methylnoradrenaline had α-adrenoceptor agonist activity similar to that of noradrenaline on human isolated smooth muscle (Coupar & Turner, 1970). The facilitatory effect of methysergide on cholinergic transmission (Katsuragi & Furukawa, 1979) was first demonstrated on human isolated intestinal muscle (Metcalfe & Turner, 1970). Human tissue, including vascular tissue, may also be used to study presynaptic effects of drugs (Moulds, Rittinghausen & Shaw, 1979). Many psychotropic drugs have cardiotoxic properties, and the measurement of human intracellular action potentials, and their modification by drugs (Coltart & Meldrum, 1971) may prove of value in elucidating their action and predicting their effects.

b) *Platelets* The human platelet has two properties which have been used in the study of psychotropic drug action; 1) DA and 5-HT uptake, storage and release; 2) aggregation. These will be discussed in greater detail in later articles in this series.

Cardiovascular system

a) *Superficial hand vein* Sicuteri (1973) described a method for recording pressure changes in a human peripheral vein *in vivo* in which a small gauge needle inserted in the vein was used both to perfuse it with pharmacologically active agents and also to measure intraluminal pressure changes by means of a pressure transducer. Although sensitive enough to record the vascular effects of agonists such as 5-HT, it suffered from practical problems such as blockage of the needle which interfered with pressure recordings. Nachev, Collier & Robinson (1971) described a simple but elegant method for estimating changes in hand vein diameter in which a dissecting stereomicroscope was focussed on a cross drawn over the chosen vein after inflation of a sphygmomanometer cuff on the upper arm to 45 mmHg and refocussed as the vein dilated or constricted in response to pharmacological agents infused distal to the site under study. The distance through which the microscope moved to refocus the cross was a measure of the change in vein diameter. Limitations to this method are that continuous recording of vessel diameter is not possible, and observer bias is difficult to eliminate. These have been overcome by means of a light lever resting on the dorsal surface of the hand over the vein and connected to a displacement transducer with an appropriate amplifier and recorder (White & Udwadia, 1975). Aellig (1979) has recently devised a further modification of the method in which a light core mounted in a small tripod is placed over the summit of the vein under study. This core alters the voltage generated in surrounding coils, the changes being proportional to its displacement. This method

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has the advantage that the device can be exactly calibrated and therefore allows direct measurement of venous diameter at a chosen congestion pressure.

This *in vivo* preparation is sensitive to the effects of many agonists including NA, 5-HT, histamine and prostaglandins, and to the actions of specific and non-specific antagonists (Robinson & Collier, 1979). A limitation, however, is that the tone of a venous segment under study depends not only on local pharmacological treatments but also on reflex changes in vascular tone due to other events, both physiological and environmental. The success of the method therefore depends on strict control of experimental conditions and frequent repetition of control dose response curves to the agonist under investigation in order to confirm the stability and sensitivity of the preparation.

Other methods of studying the effects of drugs on the venous system in man have been reviewed by Robinson (1978).

b) *Skin temperature* Skin temperature depends primarily on arterial blood flow and acute changes following drug administration may reflect changes in flow. However, psychological changes such as anxiety can influence skin temperature as do metabolic events in underlying tissues. It is essential to control strictly experimental conditions, to record accurately ambient temperature with thermocouples and to allow adequate time for temperature equilibration. It is also necessary to ensure mental relaxation as far as possible, although in studies involving psychiatric patients this may be impossible and make difficult a true assessment of experimental results. Pharmacological responses of cutaneous vessels vary in different areas, vasoconstrictor α-adrenoceptors being present in hand and forearm but absent from the chest. Vasodilatation of the skin of the neck and upper chest is generally due to active dilatation, while in the hand it depends mainly on decreased vasoconstrictor tone. Despite the limitations of this procedure, the influence of adrenergic receptor agonists and antagonists have been investigated (for example Royds & Lockhart, 1974).

c) *Plethysmography* Arterial flow into a limb or part of a limb may be measured by a variety of methods (Roddie & Wallace, 1979) of which venous occlusion plethysmography appears to be the best. Reflex vascular changes following intravenous or oral drug administration may be avoided by infusing the drug into the brachial artery of one arm and using the other arm as a control (Collier, Large & Robinson, 1978). Although this method is only suitable for short-term studies of drug action, and the effects of long-term treatment may differ from those of acute administration, it has permitted assessment of the relative effects of drugs on the venous and arterial systems (Robinson & Collier, 1979).

d) *Heart rate* Resting heart rate is largely determined by the balance of cardiac parasympathetic and sympathetic tone. A modest increase in heart rate is usually due to withdrawal of parasympathetic tone due either to an anticholinergic action of a drug, or to an α-adrenoceptor blocking or direct vasodilator action producing reflex withdrawal of cholinergic tone. Many psychotropic drugs have one or more of these actions, but the possession of anticholinergic properties is usually shown more easily by other more prominent atropine-like effects such as reduction in salivary volume. Some psychiatric conditions such as anxiety are associated with resting heart rates which differ significantly from normal controls, and this has to be considered in any study of drug action. This subject has been discussed in detail by Tyrer (1976).

Inhibition of exercise-induced tachycardia is used routinely for the assessment of a drug's β-adrenoceptor blocking properties (McDevitt, 1977). A control tachycardia of greater than 150 beats/min is desirable if adequate dose response curves are to be obtained.

e) *Baroreflex activity* Uncertainty often exists as to whether drug-induced changes in heart rate and blood pressure are direct effects or mediated through an influence on baroreflex activity. A variety of methods have been described for assessing baroreflex function in man, but few unequivocal effects of drugs upon it have been demonstrated.

i) Increases in blood pressure are produced by intravenous injections of small boluses of phenylephrine. A stimulus response line is obtained from the regression of pulse interval on systolic arterial pressure during the rise in pressure produced by phenylephrine. The slope of the regression line is used as an index of baroreflex sensitivity, and is expressed as milliseconds of increase in pulse interval per mmHg rise in arterial pressure (Smyth, Sleight & Pickering, 1969). Clonidine appears to increase the gain of the baroreflex arc (Sleight & West, 1975). In one study short and long-term antihypertensive treatment with β-adrenoceptor antagonists did not appear to influence it, but no positive control drug was included in the study (Simon, Kiowski & Julius, 1977). In another study, however, baroreflex activity increased significantly in young hypertensive patients after treatment with β-adrenoceptor antagonists (Watson, Stallard & Littler, 1979). The sensitivity of this method to assess drug action on baroreflex activity must, therefore, be considered uncertain.

ii) Circulatory changes following a standard Valsalva manoeuvre in which subjects support a column of water for a given period of time by a forced expiration have been used to assess baroreflex activity (Korner, Tonkin & Uther, 1979). No unequivocal drug-induced changes appear to have been demonstrated by this method.

iii) A techique has been developed which involves the application to the neck of variable pressure by means of a sealed chamber applied around the neck, thus changing carotid sinus transmural pressure. This selectively tests carotid baroceptors and permits study of reflex responses of both heart and peripheral circulation (Ludbrook, Marcia, Ferrari & Zanchetti, 1977). Results of its use in the study of drug action are awaited with interest.

f) *Blood pressure* Methods available for measurement of blood pressure in clinical pharmacological studies have been reviewed by Raftery (1978).

i) Autonomic neuropathy, such as that found in some patients with diabetes mellitus, may be associated with changes in cardiovascular responses. For example, the increases in blood pressure and heart rate produced by static muscular exercise such as sustained hand grip are reduced in the presence of such a neuropathy (Ewing, Irving, Kerr, Wildsmith & Clarke, 1974). This autonomic response, which is reflex in nature, is thought to be initiated by stimuli from the exercising muscle. The pressor response is thought to be mediated partly by an increase in cardiac output and partly by peripheral α-adrenoceptor mediated vasoconstriction. In essence, therefore, it resembles other reflex responses such as the Valsalva manoeuvre. It has been argued (Harrison, 1964) that a similar test involving the maintenance of an outstretched leg against gravity for as long as possible is in reality a form of stress with important physiological effects, as it is accompanied by increased levels of plasma catecholamines and cortisol, and pupillary dilatation, as well as raised heart rate and blood pressure. There is no doubt that this task is unpleasant and painful, but the relative contribution of somatic and psychic distress to the physiological changes is open to question, as are the effects of anxiolytic agents upon these physiological variables (Farhoumand, Harrison, Pare, Turner & Wynn, 1979).

ii) Tyramine is an indirectly-acting sympathomimetic amine which releases NA from storage sites in adrenergic nerve endings. The released NA stimulates postsynaptic receptors leading to a rise in systolic blood pressure. Monoamine reuptake inhibiting antidepressives such as imipramine inhibit reuptake of NA released into the synaptic cleft, and also inhibit the uptake of tyramine, so reducing the pressor response to injected tyramine (Ghose, Gifford, Turner & Leighton, 1976). The pressor effect of noradrenaline, on the other hand, is potentiated (Ghose, 1977). Essentially, the tyramine pressor response test consists of administration of incremental doses of intravenous tyramine, beginning with 0.5 mg, in a relaxed supine subject. Following injection of each dose, the blood pressure rises rapidly after a latent period of 1 min to reach a maximum within 3 min. The baseline is reached again within about five minutes. The dose is increased until the systolic pressure rises to 30 mmHg or more above baseline. From the dose response curve obtained, the tyramine dose required to elevate the systolic pressure by 30 mmHg after treatment with a drug is compared with that after placebo, to give a dose-ratio. Tyramine sensitivity is influenced by age, sex, hormonal status and psychiatric condition (Ghose, Turner & Coppen, 1975; Ghose & Turner, 1977), all of which must be considered when using it in clinical pharmacological studies. Nevertheless, when carried out under carefully controlled conditions, changes in tyramine sensitivity have been shown to correlate closely with plasma levels of monoamine uptake inhibiting drugs (Ghose *et al.*, 1976).

g) *Systolic time intervals and high speed surface ECG* Many psychotropic drugs, particularly the monoamine reuptake inhibitors, possess cardiotoxic actions, the mechanism of which is not yet clear. Several experimental techniques have been used to study the cardiac effects of these drugs, including His bundle ECG (Burrows, Vohra, Hunt, Sloman, Scoggins & Davies, 1976), but noninvasive techniques such as systolic time intervals and high speed surface ECG (Burgess, Turner & Wadsworth, 1978) are more appropriate for routine screening procedures in patients and normal volunteers. The use of systolic time intervals in clinical pharmacology has been reviewed elsewhere (Gibson, 1979).

Salivary volume

The most sensitive and easily measurable anticholinergic effect of psychotropic drugs is a reduction in salivary flow rate and a variety of methods have been described for this purpose. Basal or stimulated flow rates may be measured, stimulation usually taking the form of chewing on a neutral insoluble material such as wax or parafilm, or sucking an acid-flavoured sweet. In all types of test, saliva flow per unit time is measured. The volume can be measured by (i) spitting all saliva secreted into a measuring cylinder through a funnel (Kingsley & Turner, 1974); (ii) a suction mechanism ensures that a saliva ejector applied orally collects all saliva on the floor of the mouth (Bertram, Kragh-Sorensen, Rafaelsen & Larsen, 1979); (iii) a suction cup applied over the orifice of the parotid duct collects all saliva produced from that gland during a given time (Speirs, 1977). The last method is particularly useful for studies of salivary drug concentration, but is difficult to apply to all subjects for most purposes.

Another approach is to measure salivary production by increase in weight of dental wool

cylinders inserted into the cheeks and floor of the mouth for a given time period (Dollery, Davies, Draffan, Dargie, Dean, Reid, Clare & Murray, 1976). Although no formal comparison of these methods appears to have been carried out, personal experience suggests that the first method described is the most simple and convenient, and is adequate for screening psychotropic drugs for clinically significant anticholinergic activity.

Gastrointestinal function

The most important and frequent effect of psychotropic drugs on gastrointestinal function is to inhibit motility, generally through an anticholinergic action. This may result in clinical constipation, but may also produce important effects on gastric emptying and the absorption of other drugs.

a) *Gastric emptying* Although a variety of methods to measure gastric emptying rate have been described (Prescott, 1974; Bateman, Kahn, Mashiter & Davies, 1978), none are free from problems of interpretation, methodology or safety. The best available appears to be the comparison of the rate of absorption of an orally administered marker such as paracetamol or alcohol after treatment with the test drug compared with that after a standard anticholinergic drug and after a placebo.

b) *Colonic motility* A variety of psychotropic drugs with ACh, NA, DA and 5-HT agonist or antagonist activity may influence colonic motility. Changes in intraluminal pressure in the sigmoid colon and rectum may be measured through catheters introduced through a proctosigmoidoscope, connected to differential air pressure transducers and recorded on an appropriate polygraph (Lechin & Van der Dijs, 1979).

The eye

a) *Pupil diameter* Pupil diameter is determined by cholinergic tone on the constrictor pupillae and α-adrenoceptor tone on the dilator pupillae muscles, and a variety of psychotropic drugs influence it (Turner, 1975). The interpretation of many past studies is now recognized to be complicated by recent increased understanding of the importance of central mechanisms controlling parasympathetic outflow and it is often difficult to be certain that the pupillary actions of a drug are due to peripheral rather than central influences, even if the drug has been administered by local topical application to the eye. A variety of methods for recording pupil diameter are available ranging from simple subjective matching of the pupil with a series of holes of different known diameters, through photographic methods using ordinary light sources or infrared illumination, to sophisticated infrared and television pupillometers. The method used should depend on the information required. Changes in resting pupil diameter can probably adequately be recorded by photographic methods; for example comparison of the effects of desipramine and amitriptyline on pupillary responses to NA and methoxamine using a simple photographic method yielded results consistent with their known pre- and postsynaptic effects (Gaszner, Szabadi & Bradshaw, 1980). Changes in pupil reactivity to light and accommodation, however, require the ability to record rapid changes in pupil size in darkness and this is now best achieved by a television pupillometer (Bye, Clubley, Henson, Peck, Smith & Smith, 1979), although its cost puts this piece of equipment beyond the budget of most research departments.

b) *Accommodation* Although large changes in pupil diameter can be produced by both cholinergic and adrenergic influences, marked changes in accommodation are usually cholinergic in origin, as α-adrenoceptor agonism and antagonism produce only small albeit significant changes (Mayer, Stewart-Jones & Turner, 1977). For most purposes, determination of the near point by Scheiner's method (Taylor, 1950) is adequate, mean values of at least three recordings per eye being recorded at each time period.

c) *Intraocular pressure* Many psychotropic drugs possess atropine like effects which have the potential to raise intraocular pressure and precipitate glaucoma in patients at risk. Drug-induced changes in intraocular pressure may be measured by means of a contact tonometer which requires the production of local corneal anaesthesia before its application. This has been criticized as possibly leading to changes in corneal permeability to other drugs and more recently a non-contact tonometer has been described which was sensitive enough to demonstrate an ocular hypotensive action of a β-adrenoceptor antagonist in normal volunteers (Hill, Lewis, Stewart-Jones, Wadsworth & Turner, 1979). It depends upon the scattering of a collimated beam of light directed at the cornea when the corneal surface is indented by a pulsed column of compressed air. Its potential to detect intraocular pressure changes induced by psychotropic drugs is worthy of assessment in view of its non-invasive nature.

Critical flicker frequency

Although not a test of autonomic activity but of central nervous arousal, it is appropriate to consider critical flicker frequency (CFF) here, as it is markedly influenced by autonomic activity, particularly on

pupil diameter. The CFF may be defined as the rate at which an intermittent light source appears to a subject to be flickering as opposed to steady. The threshold frequency is determined by a large number of factors such as the wavelength, waveform and light-dark ratio of the light source, and age, pupil size and states of light adaptation and accommodation to intermittency of the subject. When these variables are controlled, however, the CFF is a remarkably stable phenomenon which is sensitive to influence by central depressant and stimulant drugs in therapeutic doses and under different physiological conditions (Turner, 1968). It is particularly useful in studying the duration of action of centrally-acting drugs and in comparing their relative central effects in multidose studies.

This test of visual intermittency has its equivalent in the auditory system (Besser, 1967; Besser & Duncan, 1967), but the latter is more difficult to carry out as a routine procedure and is subject to considerable variation over long periods of time due to changes in auditory function associated, for example, with obstructions of the Eustachian tube and external auditory meatus.

Micturition

The importance of studying the effects of a drug on micturition is to predict a potential for producing urinary retention by an atropine-like action in patients at risk. A method has been described (Kopera, 1978) in which volunteers are given a measured quantity of fluid to drink, and then void their urine into a urodropspectrometer which uses the interruption of a light beam to record passage of urine drops, permitting accurate measurement of individual drop diameter, their temporal spacing and velocity.

Sweating

Sweating is increased in anxiety and emotional excitement and its measurement forms an important part of the investigation of potential anxiolytic drugs. Methods used include a variety which measure skin conductance under different conditions (Tyrer, 1976) and others which record the number of active sweat glands. A simple method recently described (Clubley, Bye, Henson, Peck & Riddington, 1978) involves painting an area of skin with a plastic impression paint. The plastic impression is then removed using 'sellotape', mounted on a 35 mm slide, projected and the glands counted. The anticholinergic activity of drugs can be studied by producing a sweat gland response by intradermal injections of increasing concentrations of ACh and determining the inhibitory effects of drugs on the ACh dose response curve, under strictly controlled conditions of ambient temperature and physical activity.

Reductions of salivary volume and of sweat gland responses to ACh appear to be the most sensitive indices of anticholinergic activity, while changes in pupil diameter, accommodation and heart rate are less sensitive.

Tremor

Many drugs produce, exacerbate or inhibit tremor by central or peripheral mechanisms and tremor is a common symptom of psychiatric and neurological conditions. Its measurement is therefore an important part of clinical pharmacology and will be discussed in detail in a later paper in this series.

Experimental design

Although studies of autonomic pharmacology are popular in clinical pharmacology, they are beset by problems of methodology and interpretation. Chief among these is the marked variation within and between subjects in autonomic function, associated with a bewildering array of physiological, psychological and environmental factors. In any study of this type, therefore, the following should be considered:—

1) Experimental conditions should be strictly controlled, including ambient temperature, humidity, noise and other distractions.

2) The sensitivity of the method in the hands of the investigator should be established for each study, whenever possible, by the inclusion of an active standard preparation and a placebo. For example, if a new drug is being examined for potential anticholinergic activity on the eye, salivary volume and sweat gland activity, a standard anticholinergic drug should be included as well as a placebo, in the experimental design. Only if the standard drug can be differentiated from placebo in a particular test can the absence of an effect with the new drug be interpreted as freedom from such an action. It should not be necessary to add that each treatment should be administered under strictly randomized and double-blind conditions, if necessary using a double-dummy technique.

3) The time course of an experiment must be so designed to permit adequate time for acclimatization of subjects to the environmental conditions and, for example, for equilibration of thermocouples. If too much information is sought by means of a number of tests which cannot easily be accommodated within the experimental period, the inevitable haste and harrassment that ensue can produce their own

autonomic effects and prejudice the experimental results.

4) An attempt to combine pharmacokinetic with pharmacodynamic studies of this kind may lead to failure because the trauma of venesection may produce a degree of arousal in the subject which interferes with tests of autonomic function. If a marker of drug absorption is required, it is probably better to use identification in saliva or urine at appropriate times.

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