Effects of Certain Psychopharmaca on Intraneuronal Levels of 5-HT and Catecholamines in the Specific Monoamine Neurons of the Rat Brain

Monoamine oxidase (MAO) inhibitors increase the levels of 5-hydroxytryptamine (5-HT) in the brain, but the effects differ greatly with the particular inhibitor used and with the species of animal[1–4]. It has recently become possible to study their action also at the cellular level[5]. In untreated animals, 5-HT accumulated almost exclusively within nerve terminals belonging to specific 5-HT neurons; the cell bodies, on the other hand, have very small concentrations, those in their axons being so low that it is impossible to visualize them even with the highly sensitive fluorescence method of FALCK and HILLARP[6,7]. It was found, however, that in mice and rats a very marked increase occurs not only in the terminals but also in the cell bodies and axons following treatment with either one of the two chemically different MAO inhibitors nialamide (isonicotinyl-benzylcarbamylethylhydrazine) and MO-911 (N-benzyl-N-methylpropynylamine). Iproniazide (N-isopropyl-N-isonicotinylhydrazine) gave a similar but less marked increase.

Noradrenaline in the specific catecholamine neurons showed no clear increase, but the terminals normally have such high concentrations of stored amines that even a fairly large increase could remain undetected.

The effects of certain other MAO inhibitors of different chemical structure have now been studied by means of the fluorescence method. The results are reported in the present paper.

The effects of imipramine and tetrabenazine on the intraneuronal amine levels were also examined. Imipramine has previously been reported to induce an increase in the brain 5-HT[8]. Tetrabenazine, like reserpine, is known to deplete the stores of monoamines[9,10]. Its chemical structure is quite different from that of reserpine and its effects are short-lasting instead of long-lasting.

Male albino rats (b. wt. 150–250 g) were divided into groups of eight animals, which were given a single intraperitoneal dose of 2-phenylcyclopropylamine (Tranylcypromine; 5 and 10 mg/kg), β-phenylisopropylhydrazine (JB 516, Catron®; 5 and 15 mg/kg), isocarboxazide (Marplan®; 5 and 15 mg/kg), imipramine (Tofranil®; 50 and 150 mg/kg), or tetrabenazine (Nitoman®; 50 and 150 mg/kg). Other animals were used as controls. Half of the animals were killed 4 h and the other half 20 h after administration of the drugs. The animals were kept at a temperature of about + 29°C for $1\frac{1}{2}$ h before killing, since the monoamine metabolism will be considerably decreased if hypothermia develops[11].

The animals were killed by decapitation under light ether anesthesia. The medulla oblongata, pons and mesencephalon were removed, freeze-dried, treated with formaldehyde gas, embedded in paraffin, and sectioned as described by DAHLSTRÖM and FUXE[5]. The formaldehyde treatment results in a conversion of primary catecholamines and 5-HT to intensely fluorescent products.

Both doses of 2-phenylcyclopropylamine and β-phenylisopropylhydrazine produced a strong yellow fluorescence in the cell bodies, axons, and terminals of the 5-HT neurons 4 h after administration. The fluorescence microscopical picture was about the same as that observed 4–6 h after nialamide (100–500 mg/kg) or MO-911 (300–400 mg/kg)[5]. After 20 h of treatment, a medium increase was observed – especially within the cell bodies. In a biochemical study, Tranylcypromine was found to induce a rapid and high increase in the 5-HT content of the rat brain stem, showing a peak at about 4 h[12]. Levels of noradrenaline were far less affected.

Isocarboxazide, on the other hand, caused a far less marked increase in the yellow fluorescence of the 5-HT neurons 4 h after administration, even at the higher dose level. A small and sometimes medium increase was observed in the cell bodies and axons of the neurons, while the terminals were unaffected. The doses used, however, were probably too low[4]. After 20 h the effect was still weaker and the axons could often not be observed. None of the MAO inhibitors caused any certain increase in the green fluorescence of the catecholamine neurons.

All six of the MAO inhibitors so far examined – although they belong to quite different chemical categories – give the same qualitative changes, namely an increase in the 5-HT levels in the cell bodies and axons of the specific 5-HT neurons and also in their terminals, where 5-HT is normally stored in high concentrations. When the drugs are administered in doses known from many biochemical studies to produce an efficient inhibition of brain MAO and a 5-HT content which is two to several times higher than that normally present, the increase in intraneuronal 5-HT is marked to very marked. No other structures in the brain have been found to contain 5-HT in amounts significant from a quantitative point of view. The findings of this and previous studies[5,13] thus strongly support the view that the increase in 5-HT biochemically demonstrated to occur in the brain and spinal cord on MAO inhibition is due to the raised levels of the amine in the specific 5-HT neurons. The catecholamines in the rat brain are usually affected to a much lesser degree[12,14,15]. This, and the fact that even a fairly large increase could remain undetected in the terminals (see above), where most of the catecholamines are localized, may explain why no or only a slight increase[5] has been observed in the noradrenaline neurons.

Following the administration of imipramine, the terminals and axons of the 5-HT neurons appeared as in normal animals while the cell bodies seemed to show a slight increase. No obvious changes were observed in the catecholamine neurons.

Tetrabenazine (4 h, 50, and 150 mg/kg) caused a complete disappearance of the fluorescence in the cell bodies,

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axons and terminals of the catecholamine and 5-HT neurons alike, with the exception that a small number of terminals were still observed with the lowest dose. An almost complete recovery occurred 20 h after the administration of the lowest dose. The terminals showed, however, somewhat reduced fluorescence intensity. With the higher dose also, the cell bodies of the catecholamine neurons had a somewhat reduced intensity.

Zusammenfassung. Die Zunahme von 5-HT, welche sich im Gehirn der Ratte nach Verabreichung von chemisch sehr verschiedenen Ganglienblockern vollzieht, konnte mit Hilfe einer hochempfindlichen histochemischen Methode auf spezifische 5-HT-Neuronen lokalisiert werden, deren Zellkörper, Axonen und Terminalen schnell ihren Amingehalt vermehren können. Bei den Katecholamin-Neuronen konnten keine deutlichen Veränderungen beobachtet werden. Tetrabenazine verursachen eine schnelle, totale Entleerung der Monoamindepots aller Teile der monoaminhaltigen Neuronen, gefolgt von einer schnellen Neubildung von Monoaminen[16].

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EMG Responses to Capsular Stimulation in the Human

Capsular stimulation is commonly used during stereotactic operations to help in identifying some deep structures and to avoid damage to the cortico-spinal tract[1]. In this paper some observations concerning the latency and the electromiographic (EMG) characteristics of motor responses obtained in man, by stimulating the cortico-spinal tract at capsular level, are reported. The available literature on this subject is very poor[2].

Our data have been obtained during stereotactic operations performed under local anaesthesia in patients affected by Parkinson's disease, using the stereotactic equipment of Talairach[3]. Capsular stimulations have been performed using the Wyss mono- or bipolar electrode. Stimulation parameters: monophasic square waves; single pulses or with a frequency from 1 to 10 c/s; pulse duration 1 to 5 msec; 1 to 4 V. The muscular responses were recorded by macro-electrodes (needle or surface electrodes) on a two-channel oscilloscope (Polyscop-Horstfehr): one channel was used to record the stimulus artifact, the other one to record the muscular response.

Stimulation of the internal capsula with single shocks (1–5 msec, 1–4 V) evoked responses localized to the musculature of the contralateral side of the body in the form of violent muscular jerks; responses on the homolateral side of the body have never been obtained. The evoked motor response consisted of contraction of a single muscle or, more often, of many muscles. With stimuli of greater strength, the responses always appeared in complex muscle systems of the two limbs. Because the response generally involved agonist and antagonist muscles, the amplitude of limb movements was generally small and it was very difficult sometimes to identify by clinical observation all the muscles involved. The jerks obtained in a muscle in a state of complete relaxation, using rhythmical stimuli (1 to 4 c/s), seemed, on clinical observation, to be of the same amplitude; the EMG records, on the contrary, demonstrated small continuous variations of amplitude.

The latency between the beginning of the stimulus and that of the EMG responses was different for the various

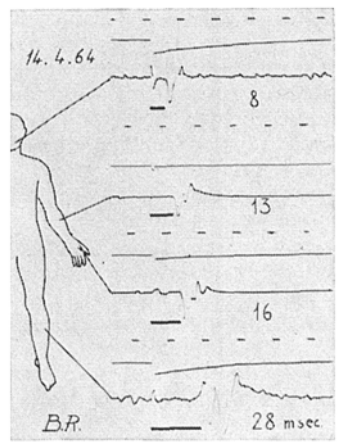

Fig. 1. Capsular stimulation. Parameters: 1 msec, 2 V. Different latency of muscular response in various districts of the body. M. orbicularis oris: 8–9 msec. M. extensor digitorum communis: 13 msec. Thenar: 16 msec. M. tibialis anterior: 27–30 msec.

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