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CORTICAL ADRENERGIC AND CHOLINERGIC ACTIVITY AND EXPERIMENTAL TREMOR

It has become clearly established that typical tremorigenic drugs such as tremorine and its active metabolite oxotremorine have a cholinergic, muscarinic type of action (1, 2, 3).

Further it has been demonstrated that tremorine produces a desynchronized alert cortex in the unanesthetized restrained rabbit. The desynchronization is antagonized by atropine (4). This observation may indicate hat this EEG effect is a result of its central muscarinic action.

This cortical muscarinic effect prompted us to study the effect of topical administration of muscarinic agents and their antagonists on cortical activity in the unanesthetized restrained rabbit.

We also investigated the effect on cortical activity of several adrenergic agents as well as of their antagonists.

MATERIALS AND METHODS

Analysis of cortical activity was carried out on rabbits restrained in a leather sling.

The animals were trepaned so as to make the motor and sensorimotor cortex accessible. After removal of the dura mater, bipolar silver electrodes were placed on motor and on sensorimotor cortex.

Electrodes were used both for recording and for electrical stimulation.

Electrical stimulation of the motor cortex (usually the right motor cortex) was carried out using 2 msec pulses at a frequency of 30 Hz during 5 seconds. This intermediate frequency stimulation provokes a self-sustained response lasting beyond the stimulus. Activity of the cortex was gauged from the threshold and from the duration of the thus evoked after-discharge.

Topical application was then performed by means of drug-soaked filter paper pledgets. Pledgets measured 2 x 2 mm and weight absorbed averaged 1,5 mg. Drugs were used in a 1% solution.

RESULTS

Topical application of acetylcholine with eserine provokes an inhibition of the after-discharge. The after-discharge is shortened at the treated site and threshold level is increased.

Slide 1 shows the normal response to an electrical stimulation of the right motor cortex.

Slide 2 shows the after-discharge after topical application of acetylcholine with eserine.

This inhibitory effect may be classified as muscarinic as it is reversed by subsequent application of atropine or scopolamine.

Electrical stimulation after topical application of atropine or scopolamine is followed by a lengthening of the after-discharge duration. This is shown in slide 3.

At the site treated with atropine characteristic spikes of high amplitude appear. Similar effects are seen after systemic administration of atropine (5).

Rather surprisingly these spikes are not seen after scopolamine application.

Local anesthesia cannot be considered as a possible basis for the effect of atropine and scopolamine. Xylocaine, when applied topically was found, as can be expected, to inhibit cortical activity. These findings are in accordance with the findings of Krnjevic (6) who concludes that the local anesthetic actions of atropine and of scopolamine on cortical units are transient, lasting only a few seconds.

A further indication of the muscarinic nature of the observed inhibition of cortical after-discharge is provided by the results of topical application of nicotine.

Nicotine applied topically, in contrast with acetylcholine plus eserine, provokes an increase in after-discharge duration which may be reversed by hexamethonium (slide 4).

The effect on cortical activity of adrenergic transmitters and precursors was investigated next.

Topically applied n o r a d r e n a l i n e provokes an increase in after-discharge duration. On the average after-discharge duration is doubled.

Topically applied d o p a m i n e provokes an increase in after-discharge duration or a lowering of after-discharge threshold.

L-D O P A when topically applied provokes a lowering of after-discharge threshold or an increase of after-discharge duration. Noteworthy is the observation that the increase in after-discharge duration is of higher magnitude than the increase observed after either noradrenaline or dopamine application. In two experiments lowering of threshold and increase of after-discharge duration were observed simultaneously. This was never observed after either noradrenaline or dopamine.

The effect of topical application of adrenergic blocking agents was then investigated.

Phenoxybenzamine, phentolamine, priscoline and dihydroergotamine do not influence after-discharge threshold or duration.

Beta-blocking agents in contrast with alpha-blockers provoke an increase in after-discharge threshold. Both propranolol, a drug with marked local anesthetic properties and sotalol (MJ 1999), a beta-blocker without local anesthetic properties were used with comparable results.

Finally we should like to report on typical changes in the electroencephalographic pattern at the treated site.

When the treated site is the motor cortex these electrographic changes correspond with involuntary movements of the contralateral limbs. Such changes were observed after application of atropine (slide 5), acetyl-choline plus eserine (slide 6), phenoxybenzamine and other alpha-blockers (slide 7) and propranolol (slide 8).

To conclude, our observations may be summarized as follows (slide 9).

Acetyl-choline (applied with eserine) strongly inhibits cortical activity as gauged from the response to electrical stimulation.

This inhibitory muscarinic action may be reversed by atropine.

Cortical reactivity is also inhibited by beta-blockers.

Cortical after-discharge is facilitated by topical application of atropine and of noradrenaline, dopamine and L-DOPA.

The fact that L-DOPA is more potent than either noradrenaline or dopamine may be an indication that L-DOPA has a pharmacological action of its own. This direct cortical action of L-DOPA may be an important mode of action of this drug, which at present is being extensively investigated for its therapeutic value in the treatment of Parkinson's disease.

Involuntary movements of the limbs may be observed after topical application to the motor cortex of drugs having widely different pharmacological properties.

P. J. BERNARD I A. F. DE SCHAEPDRYVER

KORTIKALNA ADRENERGIČKA I HOLINERGIČKA AKTIVNOST I EKSPERIMENTALNI TREMOR

KRATAK SADRŽAJ

Uticaj supstancâ na osjetljivost kortikalnih ćelija može se ispitivati promatranjem njihovog efekta na kortikalni prag poslije ispražnjenja i trajanja. Acetilholin lokalno apliciran sa ezerinom snažno inhibira kortikalnu osjetljivost, kako je izmjereno iz odgovora na električnu stimulaciju. Ova inhibitorna muskarinska aktivnost može se povratiti atropinom i skopolaminom. Kortikalna osjetljivost je također inhibirana sa beta-blokerima (propranolol i sotalol). Kortikalno poslije — ispražnjenje je olakšano poslije lokalne aplikacije atropina i nor-adrenalina, dopamina i L-DOPA. L-DOPA je mnogo jači nego i noradrenalin ili dopamin u olakšavanju kortikalno poslije ispražnjenja.

Ovo zapažanje može značiti da L-DOPA ima direktnu farmakološku aktivnost. Direktna kortikalna aktivnost L-DOPA može biti jedan važan oblik aktivnosti ove supstance koji je sada u intenzivnim istraživanjima na planu terapeutske važnosti u tretmanu Parkinsonove bolesti.

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