The Biochemical Mode of Action of Neuroleptics

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ABSTRACT

The biochemical mode of action of neuroleptics on the dopaminergic pathways has been widely studied. Neurological and endocrinological side effects are perfectly explained by the impact of neuroleptics on the striatum and on the tubero-infundibular tract. Antipsychotic properties of neuroleptics are likely linked to their action on the mesolimbic and mesocortical regions.

Some differences between the various neuroleptics may be explained by their preferential action on certain types of dopaminergic receptors. Furthermore the biochemical mode of action of neuroleptics gives some consistence to the dopaminergic hypothesis in schizophrenia. The regulation of the dopaminergic activity by GABA opens up new perspectives on the antipsychotics of the future.

INTRODUCTION

If CPZ, the first neuroleptic was introduced in psychiatry in 1952 (Lôo, Zarifian, 1971), it is only in 1963 that it was demonstrated by Carlsson and Lindqvist that neuroleptics were ablte to block the DA transmission in the CNS (Carlsson, 1978). The mode of action at the synaptic cleft level involves both post-synaptic and pre-synaptic receptors (Walters, 1976; Bartholini, 1977a). But we have new evidences to believe that the consequences of this blockade are different in the different DA pathways (Bartholini, 1977b).

We shall now consider separately the effects on the three main dopaminergic systems, the modifications of these effects with time, the relative affinity of the neuroleptics for the different DA pathways and some other recent findings on the mode of action of the neuroleptic drugs.

The effects of neuroleptics on the striatum

We can consider that there are three main dopaminergic pathways in the CNS ; the nigro-strial system, the meso-limbic and meso-cortical systems and the tubero-infundibular system.

The effects of neuroleptics on the striatum were extensively studied in the recent years. In acute conditions, with a single dose of neuroleptics the blockade of post-synaptic DA receptors is followed by an activation of the DA pre-synaptic neurons (Seeman, 1977a; Creese, 1976; Iversen, 1975). The turn-over of DA is increased as it is proved by the increase of HVA and DOPAC which are the two main catabolites of DA (Glowinski, 1974). The blockade of the pre-synaptic receptors that are inhibitors on the DA synthesis in normal conditions also plays a role in the activation of the neurons (Seeman, 1977b; Burt, 1977; Nowycky, 1977). As DA is an inhibitory neurotransmitter, the blockade of the post-synaptic receptors enhances the activity of the cholinergic post-synaptic neurons (Bartholini, 1977c). We know also that the post-synaptic receptor is linked to an adenylcyclase system that is activated normally by the DA (Kebabian, 1978). As a consequence of the blockade, the increase of the acetylcholine activity stimulates the DA synthesis in the pre-synaptic neuron by a feedback mechanism (Scatton et al., 1976). This cholinergic hyperactivity is responsible for the well known extra-pyramidal symptoms so often present after the administration of neuroleptics. Also we know that anticholinergic drugs like trihexyphenydile can reduce the intensity of the EPS. It seems possible that low doses of neuroleptics block only the pre-synaptic receptors (Nowycky, 1977), enhancing the DA activity, whereas high doses block the post-synaptic receptors reducing the DA transmission.

The effects of neuroleptics on the meso-limbic and meso-cortical systems

Neuroleptic drugs enhance also the activity of DA neurons in the limbic systems (Anden, 1976; Carlsson, 1976). However the nature of the post-synaptic neurons is not known at the present momen. There are

also cholinergic neurons in the limbic system but they show no modification of their activity after the administration of neuroleptics and there is no evidence to think that cholinergic neurons are in connection with DA neurons. So, there is a fundamental difference between the striatum and the limbic system with respect to the action of neuroleptics: in the striatum, cholinergic neurons are under the control of DA pathways whereas in the limbic system there is an independence between the two categories of neurons. It is supposed that the antipsychotic action of the neuroleptics is linked to their activity in the limbic system (Van Praag, 1977; Crow, 1977) and we can notice that in agreement with the indepedence of the cholinergic neurons the anticholinergic drugs do not modify the antipsychotic activity of neuroleptics. These data seem to be true in the mesolimbic system as well as in the meso-cortical system made of DA fibers going to the pre-frontal cortex. An hypothesis has been raised that in these two regions the cholinergic inhibition was under NA control but this point is not confirmed.

The effects of neuroleptics on the tubero-infundibular system

The release of prolactin by the pituitary cells is under dopaminergic control (Brown, 1976; Creese **et al.**, 1977) and DA is the main or may be the only inhibitory substance controlling prolactin secretion. The blockade of the DA tubero-infundibular system by neuroleptics produces as a consequence an increase of PRL secretion and PRL plasma level. This effect is at the origin of the endocrinological side effects of the neuroleptics such as galactorrhea, amenorrhea. Finally we must underline that the tubero-infundibular system is poorly protected by the blood brain barrier and that the action of a neuroleptic drug at this level is not a proof of its action into the CNS.

Differential affinity of neuroleptics on the different DA systems

The different neuroptics belong to different chemical families such as phenothiazines, butyrophenones, benzamides and thioxanthenes. The affinity of these neuroleptics for the DA receptors is not the same ac-

cording to their localization into the brain (Laduron and Leysen, 1977). For a given neuroleptic the blockade of the DA receptors can be stronger in the striatum than in the limbic system or vice versa. We know for instance that thioproperazine has a higher affinity for the striatum than for the limbic system, this is true also for haloperidol and pipothiazine but it is the opposite for sulpiride. We can notice also that this preferential affinity for the striatal DA receptors is in agreement with the existence of EPS which are very frequent with haloperidol and very rare with sulpiride.

Differential effects of neuroleptics on the DA systems as a function of time.

Up to very recently biochemical data on the mode of action of neuroleptics were based on single dose in acute conditions of observation. A pre-treatment of 11 days of the animals with neuroleptics demonstrated that the data were different in chronic conditions (Lerner, 1977; Scatton et al., 1975). One of the first observation was made with a long acting depot neuroleptics : the palmitic ester of pipothiazine. It was shown that after an initial increase of HVA link to the hyperactivity of the presynaptic DA neurons there was a decrease of HVA under the baseline level indicating a phenomenon of tolerance to the blockade. This phenomenon of tolerance was found only in the striatum and not in the meso-limbic or in the meso-cortical systems (Scatton 1977). This observation is in agreement with the clinical effects of neuroleptics. As we know the EPS very often have a tendancy to decrease or to disappear after a few weeks of treatment whereas the antipsychotic activity still remains.

We demonstrated also recently that there was no phenomenon of tolerance for the tubero-infundibular system in man and that the plasma level of prolactine remains high all over the period of neuroleptic treatment. This observation is also in agreement with the persistance of the neuroendocrinological side effects over the time under neuroleptic drugs.

Some recent findings seem to demonstrate that the biochemical mode of action of neuroleptics is more complex than we thought (Lloyd et al., 1977; Mao et al., 1977). The specificity of neuroleptics for the DA receptors is relative and CPZ for instance blocks also the NA and 5HT receptors. Pimozide is the neuroleptic which seems to have the better specificity for DA receptors. Almost all neuroleptics show evidence of direct or indirect blockade of 5HT neuron function (Lloyd et al., 1977). If 5HT receptor blockade alone by neuroleptics is not sufficient to give antipsychotic activity to a compound it seems that the combination with DA receptor blockade is a property of the major part of antipsychotic drugs (Lloyd et al., 1977).

Different substances like GABA (Bartholini et al., 1978; Pycock and Horton, 1976), acetylcholine, histamine, opiates (Muller and Seeman, 1977) and prostaglandins may play a role in the antipsychotic action of neuroleptics.

All antipsychotic drugs block DA receptors but clinically ineffective drugs in schizophrenia can also block DA receptors like metochlopramide. This point suggests that besides their ability in blocking DA transmission, antipsychotics could possess other pharmacological properties not yet discovered. Futhermore there are now evidences to show that the blockade of only a subpopulation of DA receptors will result with antipsychotic effects (Schwarez et al., 1978).

In conclusion, these new data could lead to a better knowledge of the biochemical disorders involved in schizophrenia and also to the discovery of new antipsychotic agents (Henn et al., 1977).

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الملـــوجز

كيفية العمل البيوكيميائية للمهدئات العظيمة (نيوروليبتكس)

ان كيفية العمل البيوكيميائية للمهدئات العظيمة على المسارات العصبية التى تعمل بواسطة أنزيم الدوبامين قد درست دراسة واسعة ، ولقد فسرت باتقان الأعراض الجانبية لهذه المهدئات على الجهاز العصبى وجهاز الغـدد الصماء وذلك من خـــلال تأثيرها على الجزء المخطط من المخ (ستریاتم) والجهاز الحدبى القمعى · ويمكن القول بأن الخواص المضادة للذهان لهذه العقاقير متعلقة بفعلها على المنطقة الطريفية الوســـطى والمنطقـــة القشرية الوسطى ، كذلك بين البحث أن بعض الفروق بين المهدئات العظيمة المختلفة قد تفسر على أساس ما تفضله من نوع المستقبلات الدوباميزيرجية بالاضافة الى ذلك فان طريقة العمل البيوكيميائية للمهدئات العظيمة تعطى بعض الاتساق للنظرية الدوباميزيرجية للفصام ، ان تنظيم النشاط الدوباميزيرجى بواســطة (جابا) · يفتح أفاقا جديدة أمام مضادات الذهان المستقبلية) ·

ABSTRAIT

Le mode d'action biochimique des neuroleptiques.

Le mode d'action biochimique des neuroleptiques sur les passages dopaminergiques a été largement étudié. Les contre effects neurologique et endocrinologique sont parfaitement expliqués par l'impact des neuroleptiques sur le strié et sur le trajet tubero-infantibulaire.

Les Propriétés antipsychotique des neuroléptiques sont vraisemblablement liées à leur action sur les régions mesolimbic et mesocorticale.

Quelques differences entre les diverses neuroleptiques pourrait être expliquée par leur action préférentielle sur certain types de recepteurs dopaminergique.

En plus, le mode d'action biochimique des neuroleptiques donne quelques consistence à l'hypothèse dopaminergique dans la schizophrénie.

La regulation de l'activité dopaminergique par GABA ouvre de nouvelles perspectives pour les antipsychotiques du futur.