DYNAMICS OF CHANGES IN BRAIN GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY UNDER THE INFLUENCE OF TRIFLUOPERAZINE AND FLUACIZINE

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The dynamics and localization of glucose-6-phosphate dehydrogenase activity in the various structures of the brain was studied histochemically in experiments on rats after a single or repeated injection of the neuroleptic trifluoperazine and the antidepressant fluacizine. Both preparations were shown to modify the enzyme activity in many brain formations.

KEY WORDS: glucose-6-phosphate dehydrogenase; brain; trifluoperazine; fluacizine.

Glucose-6-phosphate dehydrogenase (G-6-PDH) is the key enzyme of the pentose cycle [5, 8]. Phenothiazine derivatives have a significant effect on G-6-PDH activity and the pentose cycle in brain homogenates [7, 9, 11, 12]. However, the histotopography and dynamics of these changes in the various brain structures in relation to the dose and times of administration of the psychotropic drugs await explanation.

This paper describes the results of a histochemical study of the effect of the neuroleptic trifluoperazine and the new Soviet antidepressant fluacizine on G-6-PDH activity in various structures of the rat brain.

EXPERIMENTAL METHOD

Male albino rats (200 experimental and 100 control) were used. The brain was removed 1, 3, and 24 h after a single subcutaneous injection of trifluoperazine and fluacizine in doses of 1, 5, 20, and 50 mg/kg. In the experiments involving prolonged subcutaneous injections (7, 15, and 30 days) effective doses of trifluoperazine (1 mg/kg) and of fluacizine (10 mg/kg) were used. The brain was removed 3 and 24 h after the last injection of the preparations. G-6-PDH activity was determined in brain sections 20 μ in thickness obtained from adjacent blocks in a cryostat at −10°C.

EXPERIMENTAL RESULTS AND DISCUSSION

Very slight changes in G-6-PDH activity were observed in the brain 1 and 3 h after a single injection of trifluoperazine and fluacizine in a dose of 1 mg/kg into the rats. Trifluoperazine in a dose of 5 mg/kg gave a weak or moderate decrease respectively in the activity of the enzyme after 1 and 3 h in the rostral portions of the limbic and frontal cortex, the lateral nuclei of the septum, the midline nuclei of the thalamus (nuc. reuniens, nuc. rhomboidalis, centrum medianum, parvocellular part of the medio-dorsal nucleus), the medial zone of the posterior hypothalamus (except the mammillary bodies), layer II of the superior colliculi, the central gray matter, the interpeduncular nucleus, and the medial zone of the medullary reticular formation including the region of the raphe (1st group of structures). Fluacizine in doses of 5 and 20 mg/kg produced a less marked decrease of enzyme activity in these formations after 1 and 3 h respectively. In addition, unlike trifluoperazine, fluacizine had a weak stimulant action of G-6-PDH in the parietal,

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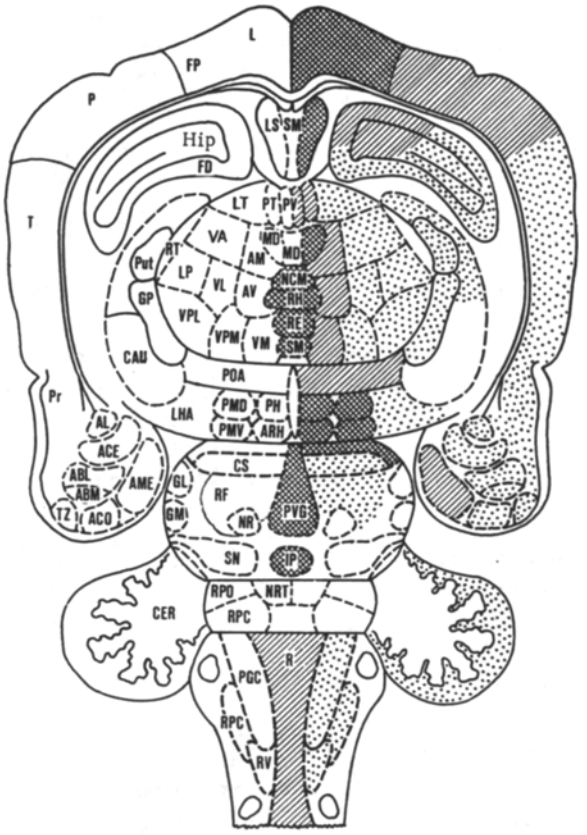

Fig. 1. Scheme of changes in glucose-6-phosphate dehydrogenase activity in brain structures after prolonged (15 days) administration of trifluoperazine in a dose of 1 mg/kg. Cross-hatched area represents sharp increase, obliquely shaded area moderately increased, dotted area slightly increased enzyme activity; AL) lateral amygdalar nucleus; AM) antero-medial thalamic nucleus; AV) antero-ventral thalamic nucleus; ABL) lateral part of basal amygdalar nucleus; ABM) medial part of basal amygdalar nucleus; ACE) central amygdalar nucleus; ACO) cortical amygdalar nucleus; AME) medial amygdalar nucleus; CAU) caudate nucleus; CER) cerbellum; CS) superior colliculi; FD) fascia dentata; FP) posterior region of frontal cortex; GL) lateral geniculate body; GM) medial geniculate body; GP) globus pallidus; Hip) hippocampus; IP) interpeduncular nucleus; L) limbic cortex; LP) postero-lateral thalamic nucleus; LS) lateral septal region; LT) lateral thalamic nucleus; LHA) lateral region of hypothalamus; MD) medio-dorsal thalamic nucleus; NR) red nucleus; NCM) central medial thalamic nucleus; NRT) reticular tegmental nucleus; P) parietal cortex; PH) posterior hypothalamic nucleus; Pr) piriform cortex; PT) parataenial nucleus; PV) paraventricular thalamic nucleus; PMD) premammillary dorsal nucleus; PMV) premammillary ventral nucleus; POA) preoptic area; Put) putamen; PVG) paraventricular gray matter; R) nucleus raphe; RE) nucleus reuniens; RH) nucleus rhomboidalis; RF) mesencephalic reticular formation; RGC) gigantocellular reticular nucleus; RT) reticular thalamic nucleus; RN) ventral reticular nucleus; RPC) parvocellular reticular nucleus; RPO) oral reticular nucleus of the pons; SM) medial septal region; SN) substantia nigra; T) temporal cortex; TZ) transitional zone of amygdala; VA) anterior part of ventral nucleus; VL) ventro-lateral nucleus; VM) ventro-medial nucleus; VPL) postero-lateral ventral nucleus; VPM) postero-medial ventral nucleus.

temporal, and piriform cortex, hippocampus, gyrus dentatus, amygdala, striopallidum, and cerebellar cortex (2nd group of structures). The G-6-PDH activity in all the structures listed above returned to its initial level 24 h after the injection of trifluoperazine and fluacizine in the above doses.

Under the influence of higher doses of trifluoperazine (20 and 50 mg/kg) and fluacizine (50 mg/kg) dissimilar histochemical changes (an increase or decrease in enzyme activity in the structures of group 1) were observed in the rat brain. After 24 h the preparations exhibited no inhibitory action whereas a weak (fluacizine) or moderate degree (trifluoperazine) of stimulation was found in all the structures of this group. In the structures of group 2 histochemical changes were absent after 1, 3, and 24 h.

Prolonged administration (7, 15, and 30 days) of fluacizine (10 mg/kg) and trifluoperazine (1 mg/kg) increased (respectively moderately and sharply) G-6-PDH activity in those parts of the brain (the 1st group of structures) in which a decrease in enzyme activity was observed after administration of a single dose (Fig. 1). In the 2nd group of structures the effect of the drugs consisted of a slight increase in G-6-PDH activity. Histochemical changes in the brain 3 and 24 h after the last injection of the drugs were identical: the maximal effect of the drugs was observed after their administration for 15 days. After single and repeated injections of trifluoperazine and fluacizine, histochemical changes were found chiefly in the glial cells and the small neurons.

A single injection of trifluoperazine and fluacizine thus gave rise to phasic changes in G-6-PDH activity in the 1st group of brain structures: in relatively small doses the preparations depressed, but in larger doses they stimulated the activity of the enzyme. In the course of prolonged administration the stimulant effect of fluacizine and, in particular, of trifluoperazine increased. In the 2nd group of structures the phase of enzyme activation occurred without a preceding phase of inhibition.

Previous investigations [1-3] showed that fluacizine and, in particular, trifluoperazine cause a marked decrease in the activity of many flavin and NAD-dependent dehydrogenases (succinate, isocitrate, malate, glutamate, lactate, $NAD \cdot H_2$, and $NADP \cdot H_2$ dehydrogenases, cytoplasmic and mitochondrial α-glycerophosphate dehydrogenases) in the 1st group of structures. These changes are evidence of considerable disturbances in oxidative metabolism (the Krebs' cycle, the mitochondrial respiratory chain, glycolysis, and other mechanisms), which probably lead to the development of hypoxia in the structures mentioned above. Biochemical investigations showed that when the principal pathways of oxidative metabolism are inhibited, the functional activity of the pentose shunt and G-6-PDH increases [4-6, 8]; this may lead to replenishment of the energy reserves and to the supply of $NADP \cdot H_2$ and pentoses for building processes. Activation of G-6-PDH in the 1st group of brain structures can therefore be regarded as a compensatory process. The fact that the main increase in G-6-PDH activity is in the glial cells points to an increase in the trophic function of the latter. Inhibition of activity of the flavin and NAD-dependent dehydrogenases and the secondary activation of G-6-PDH thus reflect the depriming effect of trifluoperazine and, to a lesser degree, of fluacizine on the 1st group of structures.

In the 2nd group of structures the activity of the flavine and NAD-dependent dehydrogenases was unchanged after a single does of fluacizine, but their activity was increased after repeated injections [1-3]. A single dose of trifluoperazine led to a slight decrease in activity of the flavine and NAD-dependent dehydrogenases in most of the 2nd group of structures. After repeated injections of trifluoperazine this effect disappeared and, in a few cases, it was replaced by a stimulant effect, i.e., adaptation phenomena developed. Consequently, the changes in G-6-PDH activity in the above structures was unconnected with disturbances of oxidative metabolism. According to the biochemical data [4, 5], during excitation of the brain there is an increase in G-6-PDH activity unaccompanied by disturbances of energy metabolism. It can therefore be concluded that the character of G-6-PDH activation in the 1st and 2nd groups of brain structures is caused by different mechanisms.

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