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# DIFFERENTIAL EFFECTS ON BRAIN CATECHOLAMINES BY DEBRISOQUIN

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Our group has recently developed a direct method for determining the rates of production of 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA), the major metabolites of brain norepinephrine (NE) and dopamine (DA), respectively, by the awake primate brain (1,2). Since the quantities of HVA and MHPG in brain vary as a function of the activity of NE and DA neurons (3,4), it is likely that these measures of the rate of production of neurotransmitter metabolites by brain provide indices of the functional state of central nervous system (CNS) NE and DA systems. As part of a series of experiments aimed at determining relationships between brain production of HVA and MHPG and plasma and/or urinary HVA and MHPG concentrations, we measured brain metabolite output before and after treatment of monkeys with debrisoquin.

Debrisoquin (Declinax) is an antihypertensive agent which does not penetrate brain but which inhibits monoamine oxidase (MAO) outside the CNS (5). Because of this selective peripheral MAO inhibition it has been suggested that this drug may be of use in determining the contribution of the CNS to total body production of MHPG (6). It has been found that there is a differential effect of debrisoquin on brain DA and NE systems and these results are reported here. The implications of these findings for both basic and clinical investigations are also noted.

The technique for determining the rate of production of neurotransmitter metabolites by the awake primate brain has been described in detail elsewhere (1,2) but may be briefly outlined as follows. Monkeys (Macaca arctoides) are anesthetized with ketamine (10 mg/kg body weight initially and then as needed), a catheter is percutaneously placed in the femoral vein, and under fluoroscopic control the catheter is then guided up into the sigmoid sinus allowing for a direct sampling of venous blood as it leaves brain. A second catheter is percutaneously placed in the femoral artery and advanced to the thoracic aorta. Eighteen to twenty hours later, by which time the animal is fully alert, specimens of blood are obtained from the venous and arterial catheters and cerebral blood flow (CBF) is determined using the $N_2O$ method of Kety and Schmidt (7). Concentrations of neurotransmitter

metabolite in the plasma of the venous (V) and arterial (A) specimens are determined and when this V-A difference is multiplied by the CBF one obtains a measure of the rate of neurotransmitter metabolite production/100 g brain $min.^{-1}$. In the specific studies reported here HVA and MHPG in plasma were quantitated by the mass spectrometric technique of selected ion monitoring using previously described methods (1,2). Five monkeys (Macaca arctoides) were tested both before and during treatment with debrisoquin which was given according to the following schedules: 0.3 mg/kg body wt b.i.d. on days 1 and 2, 0.6 mg/kg body wt b.i.d. on days 3 and 4, and 1.5 mg/kg body wt b.i.d. on days 5, 6, and 7. On the seventh day of drug treatment the rate of production of MHPG and HVA by brain was determined. The amount of time elapsing between the before and during treatment periods varied from one to three months. Previous work indicated that when animals were retested after a period of several months there were no significant differences in the mean rates of production of MHPG or HVA between the two times.*

The effects of one week's treatment with debrisoquin on the production by the awake brain of HVA and MHPG are shown in Table 1. As may be seen, there was no effect upon HVA

Table 1. Effects of treatment with debrisoquin upon the production of HVA and MHPG by the awake monkey brain

| | ng ± SEM HVA/100 g brain $min.^{-1}$ | ng ± SEM MHPG/100 g brain $min.^{-1}$ |
|---|---|---|
| Pretreatment | 127.9 ± 68.6 (N = 4) | 58.6 ± 10.7 (N = 5) |
| During treatment with debrisoquin | 131.5 ± 72.7 (N = 4) | 19.9 ± 8.0 (N = 5) |

The difference between pre and during treatment for HVA is statistically nonsignificant whereas for MHPG the difference is significant (paired "t" test, $p < 0.01$).

*Unpublished observations, J. W. Maas, S. E. Hattox & D. H. Landis.

production whereas there was a marked decrement in MHPG output which was statistically significant ($p < 0.01$). Debrisoquin treatment was without effect upon CBF *per se*.

The finding that debrisoquin decreases the brain production of MHPG but has no action on HVA output suggests that the drug is not acting directly via inhibition of MAO in CNS neurons for if this were the case it would be expected that both HVA and MHPG production would be diminished. This interpretation is also compatible with other results indicating that the drug does not penetrate into brain *per se* (5). It would thus appear that the drug is exerting its selective action on brain NE systems by some other mechanism, viz. by inducing changes in the afferent input to the CNS or by the production of an active metabolite. Whatever the mechanism of action, the finding that debrisoquin produces changes in the functioning of brain NE systems without altering DA systems suggests that this drug may be of use in both animal and human studies where a differentiation between the roles which DA and NE systems have in producing given physiological or behavioral states is desired. Debrisoquin may be of particular value in clinical studies since it would appear that the drug can be given to human subjects with a minimum of risk.

It should be noted that, although its mode of action is apparently different, debrisoquin is similar to clonidine in that both are antihypertensives and both produce decrements in the functioning of CNS noradrenergic systems without affecting CNS DA (2,8). Given these similarities it is possible that debrisoquin, like clonidine, might be of use in the treatment of opiate withdrawal (9) or Gilles de la Tourette's syndrome (10). Finally, other illnesses which are postulated to be mediated, in part at least, by hyperactivity of noradrenergic systems, viz. mania or acute psychoses, might respond to treatment with debrisoquin.

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