On the Role of Rate of Brain Norepinephrine Release in the Antibenzoquinolizine Action of Desipramine*

By
F. Sulser and F. Soroko

With 3 Figures in the Text

(Received February 16, 1965)

The antagonism of the reserpine-like syndrome elicited in rodents by reserpine and particularly by tetrabenazine and other synthetic benzoquinolizines is widely used as a model to study the antidepressant action of compounds devoid of stimulatory activity, such as iminodibenzyl- or dibenzocycloheptadiene derivatives. The reserpine-like syndrome includes peripheral autonomic symptoms (ptosis, miosis, bradycardia, diarrhea) and behavior changes of central origin (sedation and lack of exploratory activity). The antagonism of peripheral autonomic symptoms such as ptosis is not specific, however, for antidepressants of the imipramine-type but is shared by diverse pharmacological agents such as peripheral sympathomimetics, antihistaminics, ganglion-blocking and postganglionic adrenergic neuron blocking drugs. The antagonism of the behaviour changes elicited by reserpine-like compounds bears more significance but seems to be more difficult to achieve.

Studies on the antibenzoquinolizine action of desipramine (DMI) and other imipramine-like drugs in the rat have shown that this type of antidepressant not only blocks certain peripheral symptoms of the reserpine-like syndrome but can cause complete "reversal" resulting in 'compulsive' motor hyperactivity (Brodie et al. 1961; Sulser et al. 1962; Besendorf et al. 1963, Watts et al. 1964). Scheckel and Boff (1964) demonstrated that DMI-like compounds caused consistent stimulation when combined with tetrabenazine in rats conditioned to respond in the Sidman continuous avoidance procedure. More recently, Pöldinger (1963) described this paradoxical reaction in man. Depressed patients given DMI followed by tetrabenazine developed distinct motor excitation and remained in a hypomanic mood. Other investigators reported only slight and partial antagonistic behavior effects in rats pretreated with DMI and

* Presented in part before the American Society for Pharmacology and Experimental Therapeutics at Lawrence, Kansas, August, 1964.
did not obtain "reversal" of the reserpine-like syndrome (Theobald et al. 1964; Metyšová et al. 1964).

Our previous studies on the antagonism of the sedative properties of synthetic benzoquinolizines by DMI have shown that this action requires the release of stored catecholamines, for DMI failed to 'reverse' the sedative action of reserpine-like compounds in rats whose brains had been selectively depleted of catecholamines (Sülsér et al. 1964). It was further suggested that an important factor in this antagonistic action of DMI on reserpine-like drugs might be the rate at which catecholamines are released.

Evidence presented in this paper shows that the degree of antagonism elicited by DMI on the reserpine-like syndrome (ptosis, muscle rigidity, lack of exploratory behavior), is indeed related to the rate of brain norepinephrine release.

Methods

Desipramine (DMI) was administered as the hydrochloride to male Sprague-Dawley rats (200–250 g) 45 min before the reserpine-like drugs. The free bases of tetrabenazine and P-2565 (parent alcohol of benzquinamide) were dissolved by adding a drop of IN HCl and injected intraperitoneally as the hydrochlorides; reserpine was used in the form of the lyophilized phosphate salt or as 'Serpasil' Ciba.

Rats were killed by decapitation, the brains removed and analyzed for norepinephrine and serotonin according to the method of Mead and Finger (1961). Since the benzoquinolizines interfered with the fluorometric assay of norepinephrine the drugs were removed by shaking the acidic solution twice with chloroform before oxidation of norepinephrine to the fluorophor. The fluorescence spectra were recorded in every experiment and checked for interference. If interference occurred with high doses despite washing, a drug blank was subtracted. The drug blank was calculated as the difference between the brain norepinephrine reading of reserpinized animals and the norepinephrine reading of reserpinized animals given the benzoquinolizines.

Results

1. The Effect of Desipramine (DMI) on the Reserpine-like Syndrome Elicited by Various Drugs which Release Brain-norepinephrine

Rats were given DMI (20 mg/kg i.p.) followed in 45 min by various drugs which release brain monoamines, in doses which deplete brain-norepinephrine to about 25% of normal within 2–4 hours: Reserpine ('Serpasil') 5 mg/kg i.p., α-methyl-m-tyrosine 250 mg/kg i.p., the syn-