INTRODUCTION

Drugs which block central dopamine (DA)-receptors (neuroleptics) are known to stimulate the synthesis and the metabolism of DA (Carlsson and Lindquist, 1963; Javoy et al., 1970; Andén et al., 1971) and the firing activity of DA-neurons (Bunney et al., 1973). Such effects have been taken as evidence for the existence of feedback or autoregulatory mechanism in the dopaminergic system (Carlsson and Lindquist, 1963; Carlsson, 1975; Bunney and Aghajanian, 1976). According to this hypothesis the functional activity of the DA-neurons is negatively regulated by the amount of DA released from DA-terminals or dendrites (Bjorklund and Lindvall, 1975; Geffen et al., 1976; Korf et al., 1976; Nieoullon et al., 1977) onto DA-receptors located either post-synaptically in the caudate (Carlsson and Lindquist, 1963; Bunney and Aghajanian, 1976) or on non-dopaminergic terminals of the substantia nigra (Phillipson and Horn, 1976; Spano et al., 1976; Spano et al., 1977) or on the DA-neurons themselves, either in the caudate (terminal auto-receptors) (Carlsson, 1975), or in the nigra (nigral auto-receptors) (Aghajanian and Bunney, 1977). In spite of the large number of studies performed, the evidence for such mechanisms is derived from rather indirect indices of dopaminergic functional activity such as the synthesis and metabolism of DA in vivo (Carlsson and Lindquist, 1963; Kehr et al., 1972; Di Chiara et al., 1977), the in vivo activation of tyrosine hydroxylase (Zivkovic et al., 1974, 1975), the firing of DA-neurons (Bunney and Aghajanian, 1976) and the behaviour (Carlsson, 1975; Di Chiara et al., 1976). Indeed, the critical and essential step in this autoregulatory process, i.e. the release of DA, has been the subject of a rather limited number of studies and often the results obtained are not unequivocal. In vitro studies, measuring DA-release from synaptosomes or brain slices (Farnebo and Hamberger, 1971; Westfall et al., 1976; Starke et al., 1978; Raiteri et al., 1979; Reimann et al., 1979; Arbilla and Langer, 1981; Kamal et al., 1981) have provided conflicting evidence and are inadequate to study those regulatory effects which require the integrity of the DA-neurons or
of the neuronal circuits involving the caudate and the substantia nigra. On the other hand, published in vivo studies all suffer from the drawback of having been performed in anaesthetized or encephale isolé preparations (Stadler et al., 1975; Nieoullon et al., 1977, 1979). It is well known that anaesthesia drastically affects the effect of neuroleptics on the synthesis and metabolism of DA as well as on the firing of DA-neurons (Mereu et al., 1983). Moreover, in most studies performed in vivo on neuroleptics the drugs have been administered locally in the brain rather than systemically (Nieoullon et al., 1977, 1979). Finally most studies performed in vivo have measured the release of newly synthesized DA from precursor precursor-labelling rather than the release of endogenous DA (Nieoullon et al., 1977, 1979).

Recently we have described and validated the technique of transtriatal dialysis coupled to HPLC as a method to study the in vivo release and metabolism of endogenous dopamine (DA) in the rat striatum (Imperato and Di Chiara, 1984). The in vivo DA-release thus studied has the characteristics of an exocytotic release dependent upon depolarization of the terminals as it is strongly calcium-dependent, is stimulated by 30 mM KCl and by electrical stimulation of the medial forebrain bundle (MFB) and is drastically reduced by administration of -butyro lactone an agent known to block the firing of DA-neurons; drugs known to interfere with the synthesis, release, metabolism or compartmentation of dopamine produce the expected changes in the release of DA and in the output of its metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (Imperato and Di Chiara, 1984).

In order to avoid the artifacts of anaesthesia and in order to correlate the in vivo DA-release with behaviour we have modified the trans-striatal dialysis technique in order to apply it to awake rats.

Here we describe the technique used and we report the changes in the in vivo release and metabolism of DA produced by various neuroleptics.

MATERIALS AND METHODS

Male Sprague-Dawley rats were anaesthetized with a 1.5-2.0% halothane-oxygen mixture, placed on a stereotaxic apparatus (David Kopf) and two trephine holes were made in the cranium at the level of the head of the caudate nucleus (coordinates A 7.4, V 5.5 from temporal bone) according to Konig and Klippel (1970).

Through these holes a thin dialysis tube (0.2 mm o.d.) (Amicon Vitafiber, type X acrylic copolymer with a 50,000 MW cut off) was inserted transversally through both caudates. The tube was mounted on a stainless steel wire and covered with Super-Epoxy glue through its whole extent except for two zones, one on each side, 1 mm wide, correspondent to the caudate of each side. The procedure used to insert the dialysis tube was essentially the same already described except that in the present case the entire length of the dialysis tube (5.7 cm) was used. In this way, after the stainless steel was extracted from the dialysis tube, its extra-cranial portions were fastened by dental cement (Sevriton) to the parietal bone. Each end