gated the effects of several 'inhibitory' amino acids on stimulus-induced DA release as distinct from basal efflux.

Methods were as described previously (Martin & Mitchell, 1979). Briefly, small prisms of striatal tissue were suspended in physiological medium and incubated with [^{3}H]-dopamine to allow high affinity uptake. Tissue was then loaded onto filters in chambers kept at 37°C and continuously superfused with medium. Fractions of the effluent were collected and counted for radioactivity. After several minutes, when a steady rate of basal efflux was reached, more medium was added. This was either normal or with 15 mM K^+ (a submaximal pulse) and with the compounds under study added.

Under these conditions, we were unable to show any effect of GABA (10^{-5} M to 10^{-3} M) on either basal or K^+-induced release. Furthermore, bicuculline methiodide (10^{-5} M to 10^{-4} M) showed no effect on K^+-induced release, suggesting that the control K^+ pulse did not represent an already maximal facilitation of DA release by endogenous GABA. However, glycine did show a marked (concentration-dependent) facilitation of K^+-induced DA release without effect on basal efflux. The threshold for the effect was between 10^{-5} M and 10^{-4} M with a 4-fold facilitation at 10^{-3} M. Taurine and β-alanine (which often show properties intermediate between GABA and glycine) gave a small but significant facilitation of K^+-induced release only at 10^{-3} M. The facilitation of K^+-induced DA release by glycine (3.10^{-4} M) could not be blocked by strychnine (10^{-4} to 10^{-3} M). (Strychnine-resistant effects, thought to be mediated by glycine have been described in spinal cord (Ryall, Piercey & Polosa, 1972).) The glycine effect of DA release was however completely blocked by picrotoxinin (10^{-4} M) or by replacement of 87% of the Cl^- in the medium with the impermeant anion isethionate, and also by 10^{-4} M bicuculline methiodide. These results suggest the existence of a strychnine-insensitive receptor for glycine on DA terminals, capable of modulating DA release, and further that this effect of glycine on DA release is dependent on Cl^- and can be modified by a bicuculline-sensitive mechanism.

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Regional changes in brain dopamine receptor function during six months trifluoperazine administration to rats

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During 12 months continuous administration of neuroleptic drugs to rats striatal dopamine (DA) receptors become supersensitive (Clow, Jenner, Theodorou & Marsden, 1979; Clow, Jenner & Marsden, 1979). We now report changes in DA receptor activity in striatal, mesolimbic and mesocortical DA containing areas of brain during 6 months administration of trifluoperazine hydrochloride (TFP; 2.8–4.0 mg kg^{-1} day^{-1} p.o.) to male Wistar rats.

TFP administration for 1 month caused inhibition of apomorphine (0.5 mg/kg sc)—induced stereotyped behaviour, which disappeared by 3 months to be replaced by an exaggerated response to apomorphine after 6 months drug intake (stereotypy scores: TFP group 3.38 ± 0.22; control group 2.50 ± 0.14; $P < 0.05$).

Dopamine (1–150 μM) stimulation of striatal adenylate cyclase activity was inhibited 1 and 3 months after beginning TFP administration (stimulation caused by 50 μM DA being 39% and 60% respectively) of control values at these times; $P < 0.05$). After 6 months drug administration DA stimulation of striatal adenylate cyclase was enhanced (stimulation caused by 50 μM DA being 144% of control values; $P < 0.05$).

Specific binding of [^{3}H]-spiperone (0.125–4.0 nM) (defined in the presence and absence of 10^{-4} M DA) to striatal tissue after 2 weeks drug administration indicated increased receptor numbers (TFP group 26.0 ± 1.7, control group 19.4 ± 1.3 pmole/g wet weight of tissue; $P < 0.05$) but by 1 month receptor numbers were reduced (TFP group 15.1 ± 1.2, control group 19.3 ± 1.6 pmole/g wet weight of tissue; $P < 0.05$). After 3 months drug administration receptor number had returned to control values (TFP group 26.3 ± 1.5, control group 25.3 ± 3.1 pmoles/g wet weight of tissue; $P > 0.05$) and by 6 months binding sites again were increased (TFP group 20.4 ± 1.3, control group 16.6 ± 1.0 pmole/g wet weight of tissue; $P < 0.05$).

Dopamine (1–150 μM) stimulation of mesolimbic adenylate cyclase activity was inhibited 24 h after commencing drug administration (stimulation caused by 50 μM DA being 57% of control values; $P < 0.05$). Thereafter during the 6 month period of drug administration the stimulation obtained was not different from that seen in control animals. Specific binding of [^{3}H]-spiperone was increased in this region 2 weeks after commencing drug administration (TFP group 11.8 ± 0.6, control group 8.1 ± 0.7 pmole/g wet weight of tissue; $P < 0.05$) and even more so after 1 month of drug administration (TFP group 23.8 ± 9.0, control group 10.3 ± 1.2 pmole/g wet weight of tissue, $P < 0.05$). After 3 and 6 months of drug intake, however, the number of binding sites in the mesolimbic area were not different from control values (6 months: TFP group 10.0 ± 1.1, control group 8.5 ± 0.6 pmole/g wet weight of tissue, $P > 0.05$).

No changes in specific [^{3}H]-spiperone binding (as judged using DA 10^{-4} M) in the mesocortical region were observed at any time during the 6 month period of drug administration.

Trifluoperazine administration to rats for 6 months appears to differentially alter dopamine sensitive adenylate cyclase activity and specific [^{3}H]-spiperone binding in striatal, mesolimbic and mesocortical areas of brain. The changes observed may reflect alterations in dopamine and 5-hydroxytryptamine receptors since [^{3}H]-spiperone labels both sites (Leysen, Niemegeers, Tollenaere & Laduron, 1978).

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