Using previously described techniques (Waddington & Cross, 1978a, b; Waddington & Crow, 1978), male Sprague-Dawley rats of 150–200 g were given unilateral intrastriatal injections of kainic acid (KA, 2.5 μg/1 μl saline) to destroy striatal perikarya. After 17 days rats were tested for rotational responses to challenge with the DA agonist apomorphine (0.25 mg/kg s.c.). At 21 days after the lesion animals were given unilateral intranigral injections of the GABA agonist muscimol (2 ng/1 μl saline) ipsilateral to the striatal KA lesion and rotational responses recorded. After a further 7 days (i.e. 28 days post-lesion) rats were killed and striatal and nigral tissue dissected out from frozen sections for assay of glutamic acid decarboxylase (GAD) activity and GABA concentration.

Rats with unilateral striatal KA lesions showed ipsilateral rotational responses to apomorphine, and these responses were correlated with depletions of nigral GABA in the lesioned hemispheres ($r = 0.796$, $P < 0.01$). This supports the suggestion (Garcia-Munoz, Nicolaov, Tulloch, Wright & Arbuthnott, 1977) that the striatonigral GABA pathway constitutes the striatal output system and indicates that the rotational response to apomorphine is a good index of the integrity of this system. These ipsilateral rotational responses to apomorphine were also significantly correlated with the contralateral rotational responses to intranigral muscimol ($r = 0.774$, $P < 0.05$). Similarly, contralateral rotational responses to intranigral muscimol were correlated with depletions of nigral GABA ($r = 0.665$, $P < 0.05$).

Depletions of nigral GABA were not related to decreases in striatal GAD activity ($r = 0.180$, N/S). Striatal GAD activity presumably reflects not only the integrity of the cell bodies of origin of the striatonigral GABA pathway but also that of striatal GABAergic interneurons, and therefore seems to be a poor index of striatonigral function.

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References

GARCIA-MUNOZ, M., NICOLAOV, N.M., TULLOCH, I.F., WRIGHT, A.K. & ARBUTHNOTT, G.W. (1977). Feedback loop or output pathway in striatonigral fibres? *Nature, Lond.*, **265**, 363–365.

WADDINGTON, J.L. & CROSS, A.J. (1978a). Denervation supersensitivity in the striatonigral pathway. *Nature, Lond.*, **276**, 618–620.

WADDINGTON, J.L. & CROSS, A.J. (1978b). Neurochemical changes following kainic acid lesions of the nucleus accumbens. *Life Sci.*, **22**, 1011–1014.

WADDINGTON, J.L. & CROW, T.J. (1978). Methodological problems in the measurement of drug-induced rotational behaviour. *Psychopharmac.*, **58**, 153–155.

Central properties of α-allophanyl-α-allyl-γ-valerolactone (valofan)

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The hydroxylated barbiturate proxibarbal (5-allyl-5(β-hydroxypropyl) barbituric acid) is used prophylactically in the treatment of migraine. Proxibarbal rearranges in solution (and perhaps also by *in vivo* metabolism) to produce the lactone, valofan (α-allophanyl-α-allyl-γ-valerolactone) (Bobranski, Konieczny & Syper, 1962). Valofan may be responsible for the pharmacological actions on the parent drug (Hano, Trabka & Sieroslawska, 1968), but its central actions are unknown. The present study investigates biochemically and behaviourally the action of valofan, following acute administration, on cerebral dopamine and 5 hydroxytryptamine (5HT) mechanisms.

Administration of valofan (in doses of 0.5 to 1.5 g/kg ip) to mice (20–25 g) produced a decrease in exploratory behaviour progressing to loss of righting reflexes and unconsciousness. Administration of valofan (in doses up to 2.0 g/kg ip) to rats had similar effects, and inhibited the stereotyped behaviour induced by administration of amphetamine sulphate (5 mg/kg ip) or apomorphine hydrochloride (0.5 mg/kg sc). (ED_{50} 1.3 g/kg in each case). However, this effect was only observed at doses causing marked sedation.

Administration of valofan (1.5 g/kg ip) to rats elevated dopamine, HVA and DOPAC levels in both mesolimbic and striatal areas ($P < 0.05$). This effect was maximal at 3 h and thereafter declined so that HVA levels were markedly reduced in both brain regions at later time intervals (8 or 16 h) when compared with control animals ($P < 0.05$). Most of these effects had disappeared by 24 hours.

These effects on cerebral dopamine were not

accompanied by changes in 5HT. Administration of valofan (500 mg/kg ip) to mice produced a transient increase in whole brain tryptophan ($P < 0.05$) 0.5 h following dosing, but otherwise did not alter whole brain levels of 5HT, 5HIAA or tryptophan in the subsequent 24 h period.

Incorporation of valofan ($10^{-8} - 10^{-4}$ M) into *in vivo* dopamine (10^{-4} M) stimulated striatal adenylate cyclase preparations failed to alter the dopamine stimulation. Similarly, valofan ($10^{-9} - 5 \times 10^{-6}$ M) failed to inhibit specific binding of [^{3}H]-spiperone (0.5 nM; 21 Ci/mmole) to striatal preparations as judged using (+)-butaclamol (5×10^{-6} M) as displacing agent.

This data suggests an effect of valofan on cerebral dopamine function not associated with a direct receptor action. The alterations in dopamine turnover are compatible with reduced transmitter release reminiscent of that caused by cessation of impulse flow following administration of γ-butyrolactone.

References

BOBRANSKI, B., KONIECZNY, M. & SYPER, L. (1962). Investigation on the mechanism of the degradation of 5-allyl-5(β-hydroxypropyl)-barbituric acid in the organism. *Arch. Immun. Ther. Exp.*, **10**, 895–904.

HANO, J., TRABKA, J. & SIEROSLAWSKA, J. (1968) Neuropharmacological properties of some substituted γ-butyrolactones. *Arch. Immun. Ther. Exp.*, **16**, 137–154.

Superior colliculus lesions do not alter dopamine mediated circling behaviour

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The efferent pathways responsible for circling behaviour produced by apomorphine in rats with unilateral 6-hydroxydopamine lesions of the nigro-striatal pathway are unknown. Recent data has indicated that the zona reticulata of the substantia nigra gives rise to a major nondopaminergic outflow pathway from the basal ganglia (Olianas, De Montis, Concu, Tagliamonte & Di Chara, 1978). This pathway appears to mediate behavioural responses induced by changes in striatal dopamine function. A major target area for substantia nigra efferents is the superior colliculus (Graybiel & Sciascia, 1975) and it is possible that a nigro-tecto-spinal tract may be involved in the mediation of turning behaviour. Using lesioning techniques we have investigated this possibility in the rat.

Unilateral electrolytic ablation of the posterior and rostral superior colliculus (A 1.0; L 0.9; V + 0.4: A 1.8; L 0.9; V + 0.3) according to De Groot (1959) induced transient spontaneous slow ipsiversive rotation in wide circles (rate of circling 2.1 ± 0.3 rotations per min on day 8 following surgery). The rotation was not enhanced by the administration of amphetamine sulphate (5 mg/kg ip; 30 min previously) or apomorphine hydrochloride (0.5 mg/kg sc; 15 min previously).

Animals with unilateral 6-hydroxydopamine (8 μg/3 μl saline 0.9%) lesions of the medial forebrain bundle (MFB) at the level of the lateral hypothalamus (A 4.6; L 1.9; V − 3.0) showed tight contraversive circling to apomorphine (15.5 ± 5.3 rotations per min) and ipsiversive turning to amphetamine (8.5 ± 0.6 rotations per min) 19 days following surgery. Subsequent bilateral electrolytic lesioning of the superior colliculus did not alter the circling induced by these drugs.

6-Hydroxydopamine lesioning of the MFB at the level of the left lateral hypothalamus and right rostral hypothalamus (A 6.6; L 2.3; V 1.7) produced animals showing marked rotation towards the intact striatum in response to apomorphine (20.7 ± 4.4 rotations per min) but only slight rotation towards the denervated striatum in response to amphetamine (1.7 ± 0.8 rotations per min) 19 days following surgery. Subsequent electrolytic lesioning of the left superior colliculus failed to alter the rotational response to these drugs. Thus, confirming the lack of collicular involvement.

Other animals having a unilateral 6-hydroxydopamine lesion of the MFB at the level of the lateral hypothalamus (rotation to apomorphine and amphetamine 23.8 ± 1.8 and 14.0 ± 2.8 rotations per min respectively, 27 days following surgery) subsequently received an electrolytic lesion of the dorsal tegmental decussation (A 1.4; L 0.0; V − 3.3). This lesion failed to attenuate amphetamine-induced circling although it did cause a 45% reduced apomorphine-induced rotation ($P < 0.025$).

It is concluded that the nigro-tectal tract does not play a role in circling induced by striatal dopamine receptor imbalance but that fibres passing close to