Muscimol and the Uptake of \( \gamma \)-Aminobutyric Acid by Rat Brain Slices

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Abstract. Muscimol is a weak, non-competitive inhibitor \((K_i \approx 1.2 \times 10^{-8} \text{M})\) of the uptake of \( \gamma \)-aminobutyric acid by slices of rat cerebral cortex.

Key-Words: Muscimol — Amanita Muscaria — \( \gamma \)-Aminobutyric Acid.

Muscimol (Fig. 1), a psychotomimetic isolated from the mushroom *Amanita muscaria* (Engster, 1967; Waser, 1967), is a structural analogue of \( \gamma \)-aminobutyric acid (GABA), an inhibitory synaptic transmitter of major significance in the mammalian central nervous system (Curtis and Johnston, 1970). Both muscimol and GABA are powerful inhibitors of the firing of central neurones when administered by microelectrophoresis (Johnston *et al.*, 1968) and the inhibition induced by these compounds can be antagonised by the convulsant alkaloid bicculline (Curtis *et al.*, 1970). Unlike GABA, however, muscimol exerts pronounced central effects when administered systemically to healthy adult mammals (Waser, 1967; Theobald *et al.*, 1968; Scotti de Carolis *et al.*, 1969). A high affinity uptake system for GABA has been described in CNS tissue slices (Iversen and Neal, 1968), which concentrates GABA predominantly into nerve terminals (Neal and Iversen, 1969; Bloom and Iversen, 1971), and which may be important for the removal of GABA from the extracellular synaptic environment (Curtis *et al.*, 1970). The present investigation is concerned with the influence of muscimol and some related compounds on this GABA uptake system.

The uptake of \( ^3 \text{H}-\text{GABA} \) (specific activity 2.0 Ci/mmol, New England Nuclear Chemicals GmbH, Germany) by slices of rat cerebral cortex during 10 min at 25°C was studied using the method of Iversen and Neal (1968). Muscimol and derivatives were kindly provided by Dr. P. Hackett of the Woodstock Agricultural Research Centre, Sittingbourne, Kent.

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Fig. 1. Structural formulae for GABA, muscimol and derivatives

Fig. 2. Kinetic analysis of muscimol-induced inhibition of GABA uptake in slices of rat cortex. Uptake of $^{3}$H-GABA ($V$, µmoles/g/min) was determined after incubation of cortical slices for 10 min in media containing various concentrations of GABA ($S$, 10^{-4} M) in the presence and absence of 5 x 10^{-4} M muscimol. Each point is the mean ± S.E. of 4 determinations

Muscimol proved to be a relatively weak, but specific, inhibitor of GABA uptake. Kinetic analysis of this inhibition using a Lineweaver-Burk plot (Fig. 2) indicated that muscimol-induced inhibition was non-competitive in nature with a $K_t$ of 1.2 x 10^{-3} M, compared to a $K_M$ for GABA of 2.3 x 10^{-5} M. Muscimol (5 x 10^{-4} M) did not significantly