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In vivo effects of GABA uptake inhibitors on the response of cat spinal neurones to GABA analogues

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The 'high' affinity uptake of GABA by slices of cat spinal cord is inhibited by relatively low concentrations of (+)-2,4-diaminobutyric acid (DABA), (−)-nipecotic acid, guvacine and arecaidine. The importance of such carrier-mediated uptake into neurones and glia in terminating the action of GABA *in vivo* has been suggested by the finding that these inhibitors enhance the inhibition of neurones by electrophoretic GABA in the cat central nervous system (Lodge, Johnston, Curtis & Brand, 1977). The possibility was not excluded, however, that the inhibitors enhanced the action of GABA by interactions at postsynaptic GABA receptors and/or ionophores.

Muscimol and isoguvacine are potent bicuculline-sensitive depressants of the firing of cat spinal neurones. In cat spinal tissue muscimol is a weak inhibitor of GABA uptake (33% inhibition at 2×10^{-4} M; GABA 10^{-8} M) whereas isoguvacine does not influence uptake significantly at 2×10^{-4} M. Thus high affinity GABA uptake processes seem unlikely to be involved in terminating the action of these two compounds *in vivo*, particularly that of isoguvacine.

Experiments were performed on 6 cats anaesthetized with pentobarbitone to compare the effects of the inhibitors of GABA uptake on the inhibition of spinal neurones by electrophoretic GABA, muscimol and isoguvacine. The action of muscimol was enhanced to a similar extent to that of GABA on all 10 cells tested by concentrations of (−)-nipecotic acid (7 cells), DABA (3 cells) and arecaidine (3 cells) which did not enhance the action of glycine.

The action of isoguvacine on 16 of 21 cells was not increased by the uptake inhibitors ejected in amounts which enhanced the inhibitory action of GABA: (−)-nipecotic acid (10 cells), DABA (5 cells), guvacine (15 cells). When the currents ejecting the inhibitors were increased 3–4 fold the action of isoguvacine was also increased. On the other 5 cells the inhibitors increased the effect of isoguvacine, but to a lesser extent than that of GABA, even when ejected with relatively low currents.

The results with muscimol indicate that the uptake inhibitors may interact cooperatively at GABA postsynaptic receptors/ionophores, so enhancing the effectiveness of GABA agonists, and/or interfere with transport processes which inactivate muscimol. The selectivity demonstrated using GABA and isoguvacine might indicate that low concentrations of the uptake inhibitors enhance the action of GABA by a relatively specific effect on cellular uptake. On the other hand this selectivity may have arisen from differences in the tissue distribution of electrophoretically administered GABA and isoguvacine. More direct evidence is required of the nature of possible transport processes for muscimol and isoguvacine in spinal tissue.

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