## On the mechanism of action of electro-convulsive therapy: some behavioural and biochemical consequences of repeated electrically induced seizures in rats

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It is established that electro-convulsive therapy is an effective treatment for depression (M.R.C. 1965) although the role of the convulsion in the therapeutic effect is less clear and the mechanism of action remains obscure. However, recent studies have shown that repeated electrically induced convulsions in rats and mice potentiate behavioural responses mediated by brain monoaminergic systems (reviewed by Grahame-Smith, Green & Costain, 1978).

In the present experiments groups of rats were given 10 daily electroconvulsive shocks (150V; 50$^c$/s; 3 s) through crocodile clips applied to the ears and under halothane anaesthesia (ECS group). Control rats received anaesthetic only (Sham ECS group). Behavioural and biochemical measurements were carried out 24 h after the last shock. We confirmed the report of Evans, Grahame-Smith, Green & Tordoff (1976) that ECS rats ($n = 11$) show a slight but significant enhancement of the behavioural response (assessed by ratings of components of the behaviour) to increased dopamine synthesis following treatment with a monoamine oxidase inhibitor (tranylcypromine 10 mg/kg) and L-DOPA (50 mg/kg) compared to sham ECS rats ($n = 10$). In addition ECS rats ($n = 8$) were hyperactive in an open-field test compared to controls ($n = 8$).

Since repeated ECS has been reported to enhance behavioural responses to directly acting 5-HT and dopamine receptor agonists and does not affect 5-HT or dopamine synthesis, it has been suggested that the treatments either increase monoamine receptor sensitivity or change activity in a system modulating monoaminergic neurotransmission. The former possibility was evaluated by measuring [$^3$H]-LSD binding in membrane preparations of cortex and [$^3$H]-spiperone binding in striatum in ECS ($n = 11$) and Sham ECS ($n = 10$) treated rats. No differences emerged on these measures of 5-HT and dopamine receptor sensitivity. In addition possible ECS effects on monoamine modulating acetyl choline GABA and benzodiazepine receptor systems were investigated. However, no differences between groups were found in [$^3$H]-QNB, [$^3$H]-GABA or [$^3$H]-diazepam binding in the cerebral cortex. GABA concentrations in cerebral cortex were also unaffected by the ECS treatments.

The results confirm that repeated convulsions in rats increase functional dopaminergic neurotransmission. However, the results also rule out the possibility that ECS potentiated behavioural responses to monoamine agonists are due to generalized ECS effects on dopamine or 5-HT receptor sensitivity. Furthermore, acetyl choline, GABA or benzodiazepine receptors which may interact with monoaminergic neurotransmission are unaffected by repeated ECS.

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## An iontophoretic study of the cholinoceptive properties of respiratory neurones in the rat medulla

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Units whose discharge pattern can be related to some phase of the respiratory cycle have been located in the cat medulla (Cohen & Wang, 1959, Merrill, 1970). Investigations of the pharmacological properties of these neurones by microiontophoresis include the effects of acetylcholine GABA and glutamate (Denavit-Saubie and Champagnat, 1978 and Kirsten, Satayavivad, St. John & Wang, 1978). The present study was undertaken to investigate the cholinergic properties of medullary respiratory units in the rat.

Experiments were performed on urethane anaesthetized male Wistar rats (200–400 grams). A diaphragm electromyogram was used as a record of central respiratory rhythm and was displayed on one channel of a dual beam oscilloscope. In this way the neuronal pattern of discharge could be linked to some phase of the respiratory cycle and be recorded on film.

Single units were recorded in the medullary reticular formation using conventional microiontophoretic techniques (Bradley & Dray, 1974). Drugs were applied from five-barrel micropipettes. The recording barrel contained 4M NaCl while the other barrels contained a selection of the following: acetylcholine

chloride (ACh) 0.3 M, pH 4.0–5.0, monosodium glutamate 0.25 M, pH 8.0–9.0, nicotine 0.2 M, pH 3.0–4.0, dihydro-β-erythroidine (DHβE) 10 mM (in 0.165 M NaCl), pH 4.0–5.0, acetyl-β-methylcholine chloride (methacholine) 0.5 M, pH 4.0–5.0, atropine Sulphate 30–40 mM, pH 5.0–6.0 and muscarine chloride 0.3 M, pH 4.0–5.0. Pontamine sky blue was used for current control and marking neurones as previously described (Boakes, Bramwell, Briggs, Candy & Tempesta, 1974). The neurones tested were concentrated in the area of nucleus ambiguous and the lateral reticular nucleus.

Most neurones tested were excited by acetylcholine which increased both the number of spikes per burst and the number of bursts per epoch. This effect contrasts with the glutamate response at higher currents where the discharge pattern changed from phasic to tonic. Nicotine excited the majority of neurones. Sometimes the effect of nicotine was prolonged as was seen when the drug was applied to non-respiratory cells, but more often a more rapid effect was obtained similar to that seen with acetylcholine on respiratory cells.

All nicotine responses were blocked by DHβE at very low currents. Acetylcholine responses were abolished in a few cases but even when ACh was applied at low currents were more resistant to the antagonist than were nicotine responses. Atropine was applied to a few neurones and blocked the acetylcholine response in all cases. Muscarine excited most cells tested but the muscarine agonist methacholine even at high currents produced little effect.

From the data obtained so far it appears that there are not separate populations of respiratory cells displaying either muscarinic or nicotinic sensitivity. Instead the evidence points to both muscarinic and nicotinic receptors being present on the same neurone.

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## Further evidence for the possible co-existence of 5-hydroxytryptamine and substance P in medullary raphe neurones of rat brain


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Recent results have indicated that certain medullary raphe neurones that accumulate radioactive 5-hydroxytryptamine (5-HT) (Chan-Palay, Jonsson & Palay, 1978), and contain immunoreactive 5-HT (Hökfelt, Ljungdahl, Steinbusch, Verhofstad, Nilsson, Brodin, Pernow & Goldstein, 1978), also contain substance P-like immunoreactivity. In order to investigate this possibility further, we examined the effects of the neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) on descending substance P (SP) fibres in rat spinal cord.

Rats received a single injection into the lateral ventricle of 5,6-DHT (75 μg free base) dissolved in saline containing ascorbic acid 0.5 mg/ml. Examination of the SP content of spinal cord and ventromedial medulla revealed significant SP depletions (Table 1) 2 weeks after 5,6-DHT in areas previously shown to be almost completely depleted of 5-HT following 5,6-DHT treatment, (Baumgarten, Björklund, Lachenmayer, Nobin & Stenevi, 1971). The dose of 5,6-DHT used does not deplete spinal cord noradrenaline (NA) and in fact after 10 days NA levels are raised above control levels (Nobin, Baumgarten, Björklund, Lachenmayer & Stenevi, 1973). There was only a small depletion of SP from the medulla and the most rostral parts of the spinal cord (14–37%), but there was a marked reduction of SP in the ventral spinal cord, especially in lumbar segments (>90%). There was also a smaller, but significant, loss from dorsal spinal cord (26–46%). At longer times after 5,6-DHT (up to 20 months) there was no recovery of SP content in any region of spinal cord or medulla, except the region containing the cell bodies of the medullary raphe nuclei. Immunohistochemistry 2–3 days after the administration of 5,6-DHT revealed accumula-