Short communications

Sensitivity of the nictitating membrane of the cat to succinylcholine after decentralization and denervation

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Seven days after decentralization or denervation, the nictitating membrane of the cat becomes supersensitive to succinylcholine. The supersensitivity to succinylcholine is of a moderate degree (2–3 fold) and there is little difference between the supersensitivity induced by decentralization or denervation. In this respect, it is similar to the decentralization type of supersensitivity observed for other agonists which are not taken up by the adrenergic nerve endings (e.g. acetylcholine and methoxamine). Since succinylcholine causes an apparent contraction of the nictitating membrane through its action on the extraocular muscle and no effect on the nictitating membrane itself, it is concluded that both chronic decentralization and denervation produced a decentralization type supersensitivity in the extraocular muscles. The results suggest that supersensitivity in the extraocular muscles may contribute significantly to the decentralization supersensitivity of the nictitating membrane of the cat, *in vivo*, especially for those agonists which cause contractions of both the nictitating membrane and the extraocular muscle.

Experiments *in vivo* in cats led to the postulation that denervation of the nictitating membrane caused the development of two qualitatively different types of supersensitivity (Trendelenburg, 1966). One type is specific for (−)-noradrenaline and is similar to that caused by cocaine. The other type is similar to the supersensitivity produced by decentralization and is nonspecific, being equally pronounced for (−)-noradrenaline as well as other agonists such as acetylcholine and adrenaline.

Recently, it has been shown that contraction of the extraocular muscles leads to an apparent contraction of the nictitating membrane in the cat (Paton & Thompson, 1970). Since several agonists (e.g. adrenaline and acetylcholine) whose actions are enhanced by decentralization also contract the extraocular muscles (Eakin & Katz, 1967; Sanghvi, 1967; Paton & Thompson, 1970), it is possible that the extraocular muscles may play an important role in the decentralization supersensitivity observed *in vivo*. The purpose of these experiments was to determine whether the extraocular muscle can become supersensitive after chronic decentralization or denervation by assessing the sensitivity of the nictitating membrane to succinylcholine. This agent was chosen because it causes a contraction of the nictitating membrane through its action on the extraocular muscle and has no effect on the nictitating membrane itself (Paton & Thompson, 1970).

Methods.—Cats of 2–3 kg body weight and of either sex were used. After induction of anaesthesia with ether, spinal preparations were set up as described by Burn (1952). The responses of the nictitating membrane were recorded isometrically with a Grass force-displacement transducer and polygraph; the resting tension on the membrane was 10 g. Blood pressure was recorded via the left femoral artery by means of a Statham pressure transducer and Grass polygraph. Heart rate was recorded on a Grass tachograph. All injections were made into the right femoral vein.

In all experiments, 3 mg/kg (i.v.) of chlorisondamine was given 5 min after completion of the preparation. This reduced the tone of the nictitating membrane to a negligible level (Green & Fleming, 1967). Forty minutes later, a dose-response curve was determined for succinylcholine by the sequential injection of doses of succinylcholine which increased by a factor of 3. No attempt was made to obtain a full dose-response curve, since the occurrence of vigorous muscle fasciculation after doses higher than 100 μg/kg makes this impossible. The time intervals between injections were long enough (15 min) for the return of the nictitating membrane to preinjection level. At the end of the experiment, the maximal shortening of the nictitating membrane was determined by injecting 10 mg/kg (i.v.) of (−)-phenylephrine.

Denervation was accomplished by surgical removal of the right superior cervical ganglion and decentralization by the excision of approximately 2 cm of the

right cervical sympathetic nerve (preganglionic fibres). Anaesthesia for these procedures was induced with ether after premedication with atropine (0·1 mg/kg, s.c.).

Results.—Figure 1A shows the results from control experiments in which the dose-response curve of succinylcholine was determined on the right and the left normal nictitating membranes of the same cat. It is evident that there was no difference in sensitivity to succinylcholine between the two normal nictitating membranes.

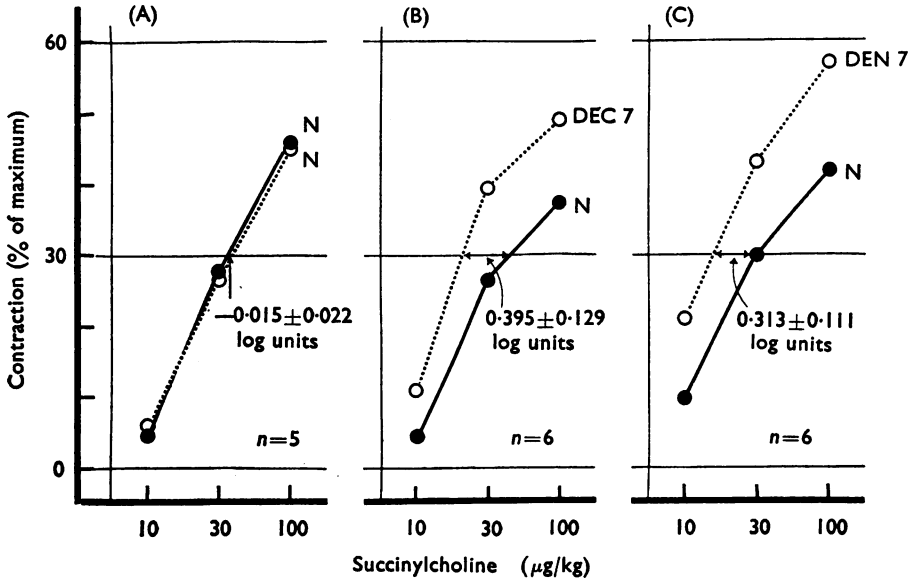

FIG. 1. Response of the nictitating membrane of the spinal cat to succinylcholine. The mean responses are shown of (A) the left (solid line) and the right (broken line) normal nictitating membrane, (B) the decentralized and the contralateral normal nictitating membrane and (C) the denervated and the contralateral normal nictitating membrane. N=normal membrane; DEC7=7 days after decentralization; DEN7=7 days after denervation. Log units shown are means and their standard errors of (A) log ED30 determined on the left minus log ED30 determined on the right normal membrane, (B) log ED30 determined on the normal minus log ED30 determined on the contralateral decentralized membrane and (C) log ED30 determined on the normal minus log ED30 determined on the contralateral denervated membrane. n=number of experiments.

However, when the right nictitating membrane was either decentralized or denervated for seven days, it became more sensitive to succinylcholine than the contralateral normal nictitating membrane (Fig. 1B and 1C); the dose-response curve of succinylcholine was significantly shifted to the left and the degree of shift, as measured at the level of ED30, was approximately 2·0 to 3·0 fold. It is also evident that there was no difference between the decentralization- and the denervation-induced supersensitivity to succinylcholine.

Discussion.—The present results clearly demonstrate that both chronic decentralization and denervation induced an apparent supersensitivity of the nictitating membrane to succinylcholine. Since succinylcholine causes a contraction of the nictitating membrane solely through its action on the extraocular muscles and has no effect on the smooth muscle of the nictitating membrane (Thompson, 1958; Paton & Thompson, 1970), it must be concluded that the supersensitivity observed is due to the increased sensitivity of the extraocular muscles to succinylcholine.

The supersensitivity to succinylcholine obtained in the present experiments is of a moderate degree and shows little difference between the degrees of supersensitivity induced by decentralization and denervation. Earlier experiments on the nictitating membrane of the cat, *in vivo*, also

showed similar results with acetylcholine (Fleming, 1963 ; Trendelenburg & Weiner, 1962), methoxamine (Trendelenburg, Maxwell & Pluchino, 1970) and isoprenaline (Pluchino & Trendelenburg, 1968). According to current concepts of the mechanism of supersensitivity of the nictitating membrane (Trendelenburg, 1966), these characteristics are typical of the decentralization type of supersensitivity for those agents which are not taken up by the adrenergic nerve endings. The results, therefore, suggest that the supersensitivity to succinylcholine developed in the extraocular muscle is of a type similar to the decentralization type of supersensitivity developed in the nictitating membrane to other agonists.

The mechanism of decentralization supersensitivity developed *in vivo* in the nictitating membrane of the cat is considered to be due either to a change in the smooth muscle of the nictitating membrane (Fleming, 1963 ; Trendelenburg & Weiner, 1962 ; Langer, Draskoczy & Trendelenburg, 1967) or to the relatively pronounced vasodilatation and the consequent better delivery of the drugs to the nictitating membrane (Cervoni, Reit & McCullough, 1970). The similarities between the type of decentralization supersensitivity which develops in extraocular muscles and the nictitating membrane to succinylcholine and other agonists, respectively, suggest that both share a common mechanism. The most likely one would be the relatively pronounced vasodilatation after section of the cervical sympathetic nerves. This would facilitate the delivery of the injected drugs not only to the nictitating membrane but also to the extraocular muscle and thus result in supersensitivity. Alternatively, since the contraction of the extraocular muscle can lead to an apparent contraction of the nictitating membrane (Paton & Thompson, 1970) and agents such as adrenaline and acetylcholine which are known to be enhanced by decentralization can cause contraction of both the nictitating membrane and the extraocular muscle (Eakins & Katz, 1967 ; Sanghvi, 1967 ; Paton & Thompson, 1970), it is also possible that the increase in sensitivity of the extraocular muscle *per se* can indirectly result in an increase in response of the nictitating membrane to those agonists. Further studies on the decentralization supersensitivity of the extraocular muscle (*in vivo* and *in vitro*) to other agonists such as acetylcholine and noradrenaline should clarify the contribution of this muscle to the mechanism of decentralization supersensitivity in the nictitating membrane of the cat.

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(*Received January* 9, 1973)