Recovery of noradrenaline levels after reserpine compared with the life-span of amine storage granules in rat and rabbit

SIR,—After reserpine treatment the noradrenaline in peripheral tissues and in the central nervous system (CNS) rapidly decreases to very low levels, and the recovery takes place slowly over several weeks (Carlsson, Rosengren, Bertler & Nilsson, 1957). The mechanism appears to be a longlasting blockage of the storage mechanism in the amine granules (Bertler, Hillarp & Rosengren, 1961, Carlsson, Hillarp & Waldeck, 1963; Lundborg, 1963; Dahlström, Fuxe & Hillarp, 1965). However, the recovery time for the cell bodies is much shorter (24–48 hr) both centrally (Dahlström & Fuxe, 1964a) and peripherally (Norberg & Hamberger, 1964). Thus, a great difference exists between the recovery time after reserpine treatment in the adrenergic nerve cell bodies and in their terminals. This difference may be explained by the fact that the storage granules are formed in the pericarya of the neurones and transported down the axons to the terminals (see, *inter alia*, Dahlström, 1965).

The recovery time for noradrenaline after reserpine has in this study been examined in different tissues of the rat and rabbit. Brain, heart and skeletal muscle (gastrocnemius) were examined.

Male albino rats (Sprague-Dawley, 200 g) and male albino rabbits (1·4–2·0 kg) were injected with reserpine (Serpasil ampoules, 2·5 mg/ml, diluted with isotonic glucose solution) intraperitoneally (rats, 1 and 10 mg/kg) and intravenously (rabbits, 0·2 and 2 mg/kg). The animals were killed 48 hr, 1, 2, 3, 4, 5, and 6 weeks (rat) or 48 hr, 1, 2, 4 and 6 weeks (rabbit) after the injection. Noradrenaline was measured spectrophotofluorimetrically (Bertler, Carlsson & Rosengren, 1958; Häggendal, 1963).

The recovery of noradrenaline after reserpine administration could be represented graphically as an approximately straight line for all the tissues examined. The time required for a total recovery was between 4 and 5 weeks for the rat after both 1 and 10 mg/kg doses. For the rabbit the corresponding time was about 7 weeks after the high dose (2 mg/kg); at this dose the amines decreased initially to very low levels. After the lower dose of 0·2 mg/kg, the initial decrease was less marked and the recovery time was about 6 weeks. However, if the recovery curve for this latter group of rabbits was extrapolated to zero level of noradrenaline the total time for recovery was about 7 weeks.

These findings are supported by results obtained by Häggendal & Lindqvist (1964) on the effect of a single dose of reserpine (0·2 and 1 mg/kg) on the catecholamine levels in brain and heart of the albino rabbit. If the recovery curves of both brain and heart noradrenaline were extrapolated to zero and to normal levels the time required for a total recovery would be about 6 weeks.

The storage granules being synthesised in the cell body and transported via the axons to the adrenergic terminals have a course of transport which has been found to be linear (Dahlström & Häggendal, 1966a, b). The adrenergic nerve terminals are thus supplied with newly formed granules at a rate which is in all probability fairly steady. The time required for a total exchange of granules in the terminals (the life-span of the granules) has been calculated for hind-leg skeletal muscle of rat to be about 5 weeks (Dahlström & Häggendal, 1966a), and for the rabbit about 7 weeks (Dahlström & Häggendal, 1966b).

The straightness of the noradrenaline recovery curve of rat and rabbit after reserpine treatment and the fact that the time required for a total recovery for both species is close to the calculated life-span of the amine granules, indicate that the course of the noradrenaline recovery after reserpine reflects the downward-transport of the newly formed storage granules, unaffected by reserpine.

The straight course of the noradrenaline recovery is contrary to the view that *in vivo* the reserpine-blocked granules in the terminals would be able to regain their normal ability to take up and store noradrenaline again during their lifetime (at least after a high dose of reserpine). In the latter instance the recovery curve ought to resemble a logarithmic curve rather than a straight line.

It has been found that after axotomy of monoamine-containing nerve fibres in the CNS accumulations of the respective amine rapidly occur proximal to the lesion (Dahlström & Fuxe, 1964a, b). This indicates that the transport of amine granules is high also in the CNS. Since the recovery time for noradrenaline in both rat and rabbit brains was about the same as in the peripheral tissues of the respective species, and likewise followed an approximately straight line, it seems likely that the life-span of amine granules in the CNS is about the same as in the peripheral terminals.

After a single dose of reserpine (or after cessation of chronic reserpine treatment) the functional recovery occurs largely within 1 to 3 days, both in central and peripheral neurones. The first granules, formed in the cell bodies and unaffected by reserpine, have reached the mid-part of the sciatic nerve of the rat as early as 18 hr after a single dose of the drug (Dahlström, 1966). Hence it is reasonable to assume that fresh granules have reached the terminals at the time when the first signs of functional recovery are observed. The possibility of a causal relationship between the two phenomena should be considered. Such a relationship may not be contradicted by the findings of Andén, Magnusson & Waldeck (1964) that during reserpine recovery (during the second to third day after a single dose of reserpine to a rat) the capacity of the tissues to take up and retain labelled noradrenaline is high compared with the noradrenaline levels. It might be that such a high capacity is characteristic of the newly formed downward-transported granules.

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Diethyldithiocarbamate and amphetamine stereotype behaviour

SIR,—Pfeifer, Galambos & György (1966) described the sedative effects of diethyldithiocarbamate (DDC) including antagonism of amphetamine-induced hypermotility. The authors assumed this antagonism to be due to the effect of DDC in decreasing brain noradrenaline by inhibiting the synthesis of noradrenaline from dopamine.

We found the effect of DDC on the stereotype behaviour (constant sniffing, licking or biting) exhibited by rats (16) and mice (20) made hyperactive by amphetamine (3 and 6 mg/kg base s.c. respectively) was not antagonised by DDC 500 mg/kg s.c. or even after repeated doses (2 or 3 × 500 mg/kg) given from 7 hr to ¼ hr previous to the amphetamine. Also, two groups of six mice given amphetamine (6 mg/kg) and either DDC or a placebo 7, 4 and 1 hr previously, showed a similar onset of stereotype activity (68 min ± 29 s.d.) but the activity terminated at 289 min ± 52 (s.d.) for DDC and at 151 min ± 9 (s.d.) for the placebo. All the animals treated with DDC were strongly sedated and the reduction in amphetamine hypermotility (locomotion) reported by Pfeifer & others (1966) was obvious. Thus the effect of DDC is in sharp contrast to compounds which decrease the synthesis of both dopamine and noradrenaline by inhibition of the tyrosinehydroxylase (α-methyltyrosine and some of its derivatives). These compounds in relatively low doses change the amphetamine-induced stereotype hyperactivity into a more varied behaviour, which besides sniffing includes locomotion and grooming. This effect of α-methyltyrosine is reversed by dopa (Randrup & Munkvad, 1966; Weissmann, Koe & Tenen, 1966). The reversing effect of dopa is not inhibited by DDC (4 rats, two with 500, two with 2 × 500 mg/kg s.c. DDC given before amphetamine + dopa). The evidence thus indicates that dopamine rather than noradrenaline is associated with the stereotype behaviour, while the motility may be more related to noradrenaline.

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