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# A possible synaptic mechanism underlying the similar behavioural effects of adrenaline-like and acetylcholine-like drugs

There are many situations in which adrenaline-like and acetylcholine-like compounds produce similar effects. Amphetamine, a drug that increases activity at adrenoceptive synapses by preventing the reuptake of released noradrenaline (Rutledge, 1970), has behavioural effects very similar to those produced by the two closely related muscarinic blockers hyoscine and atropine. Both amphetamine and atropine disrupt timing behaviour on Fixed Interval (Ray & Bivens, 1968) and on differential reinforcement of low rates of response (Carlton, 1963; Bivens & Ray, 1968) operant conditioning schedules; both increase response rates on a Sidman avoidance schedule (Carlton, 1963; Ray & Bivens, 1968); and both increase responding during periods of non-reward in a discrete trial bar press task (Heise, Laughlin & Keller, 1970). A behavioural tolerance is quickly formed to chronic doses of both amphetamine (Schuster & Zimmerman, 1961) and hyoscine (Bignami & Gatti, 1968) in situations where the initial drug effect is a reduction in reinforcement. This suggests that the same behavioural effects produced by adrenergic stimulation and cholinergic blockade could arise from a common neural mechanism rather than necessarily from two complimentary neural systems.

The existence of a common mechanism is also suggested by the demonstration that subthreshold doses of atropine and amphetamine, when given simultaneously, act additively to give the same effect as do larger doses of either drug given alone (Carlton, 1963; Bivens & Ray, 1968; Ray & Bivens, 1968). Although these facts might be reconciled by postulating reciprocally acting adrenergic and cholinergic systems with adrenergic stimulation having the same behavioural effect as cholinergic blockade, the demonstration that adrenergic activation also produces the same effect as cholinergic activation does not fit the reciprocally acting systems hypothesis. Intracranial self-stimulation of the lateral hypothalamus is depressed by adrenaline (Mogenson, Russek & Stevenson, 1969), by noradrenaline (Olds, Yuwiler & others, 1964), by amphetamine (Umemoto & Kido, 1967) as well as by the centrally-active cholinergic agonist physostigmine (Domino & Olds, 1968; Stark, Totty & others, 1968; Olds & Domino, 1969a, 1969b). The lateral hypothalamus in turn makes adrenergic inhibitory synapses in the amygdala (Stein & Wise, 1969) and cholinergic inhibitory

synapses in the cortex (Phillis & York, 1968), but the behavioural significance of these output systems of the lateral hypothalamus has not yet been elucidated.

As suggested by the two types of inhibitory synapses made by the lateral hypothalamus, noradrenaline and acetylcholine also produce the same electroencephalographic responses. Cortical e.e.g. arousal is produced by both adrenaline (White & Daigneault, 1959) and acetylcholine (Domino, Dren & Yamamoto, 1967). Both neurotransmitters cause excitation of the caudate putamen region (York, 1968) and of some Renshaw cells in the spinal cord (Weight & Salmonoiraghi, 1966), although Renshaw cells are more typically excited by acetylcholine and depressed by noradrenaline (Salmoiraghi, 1966). A further interrelation of adrenaline-like and acetylcholine-like neurotransmitters is seen by the demonstration that hyoscine blocks the e.e.g. activation produced by amphetamine or adrenaline (White & Daigneault, 1959) or by acetylcholine (Domino & others, 1967). Conversely, Phillis (1970) reported that phentolamine blocks the cortical depressant effects of acetylcholine as well as the depressant effects of noradrenaline. Thus the neurotransmitter effects of synaptic blockade need not be limited to the neurotransmitter system being blocked.

In certain peripheral organs, acetylcholine activity seems to be very closely related to noradrenaline activity too. Increasing cholinergic activity by blocking the deactivation of acetylcholine with injections of physostigmine produces an adrenergic hypertensive response (Varagić & Krstić, 1966). The synaptic mechanism involved may be deduced from evidence (Belej, Papacostas & others, 1968; Muscholl, 1970) demonstrating a nicotinic acetylcholine-induced release of noradrenaline in isolated heart tissue that is inhibited after several seconds by a muscarinic acetylcholine action (Muscholl, 1970). The acetylcholine-induced release of noradrenaline, first demonstrated in the sympathetic nervous system by Burn & Rand (1959, 1962), has been observed recently in thalamocortical recruitment (Karczmar, 1969) and in the hypothalamus (Philippu, Heyd & Burger, 1970). The hypothesis that acetylcholine may be involved in the release of noradrenaline into the synapse following a nerve impulse received histological support by the demonstration of acetylcholinesterases and catecholamine (typically noradrenaline) in the same nerve trunk (Jacobowitz, 1965; Jacobowitz & Koelle, 1965; Eranko, 1966). Philippu & others (1970) noted that the presence of calcium ions was necessary for the occurrence of acetylcholine-induced release of noradrenaline. The mechanisms presented by Karczmar (1969) and Philippu (1970) account for the role of calcium in this system. That an analogous acetylcholine-5-hydroxytryptamine relation does not exist is suggested by the data presented by Katz & Kopin (1969) that demonstrated that 5-HT release is not calcium dependent.

The hypothesis of acetylcholine-mediated release of noradrenaline accounts for all of the evidence presented above showing identical effects of cholinergic and adrenergic stimulation. Philippu (1970) also reported that the acetylcholine-induced release of noradrenaline is increased by atropine, a finding that would be expected since Muscholl (1970) demonstrated that the nicotinic release of noradrenaline in the heart is blocked by muscarinic activity. Therefore the similar behavioural effects of amphetamine and hyoscine discussed above are also accommodated by this hypothesis. Amphetamine increases adrenergic activity by blocking reuptake of noradrenaline while hyoscine increases adrenergic activity by preventing the muscarinic inhibition of the acetylcholine-induced release of noradrenaline. The net effect of both drugs is an increase of noradrenaline in the synapse. Although both Koelle (1969) and Karczmar (1969) confirm the existence of a pure cholinergic synapse, i.e. one in which only acetylcholine participates in neurotransmission, the histological and behavioural separation of dual and pure cholinergic synapses remains to be accomplished.

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