Effects of cholinergic and anticholinergic drugs on ketamine-induced linguopharyngeal motor activity

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Abstract. Benztropine mesylate (Cogentin) and physostigmine salicylate (Antilirium), were tested for changes in tongue protrusions, retrusions, and swallowing acts in rats anesthetized with a 100 mg/kg IM injection of ketamine hydrochloride. These ketamine-induced linguopharyngeal events were monitored by means of a force displacement transducer fed onto a polygraph. Benztropine (0.05–1 mg/kg) caused mild to moderate reductions in the rate of these events for a short period of time, up to about 30 min. With physostigmine (5–25 µg/kg), linguopharyngeal activity was markedly increased, up to 50-fold by the highest dose within 5 min and returned almost to the baseline within 60 min. With lower doses, more moderate responses were obtained. If methscopolamine (1.4, 3, 6 mg/kg IM) preceded physostigmine, the physostigmine enhancement was preserved.

Key words: Cholinergic state – Linguopharyngeal events – Dyskinesia – Tongue retrusions – Tongue protrusions – Swallows – Ketamine

Ketamine-induced tongue retrusions (Aldes et al. 1988), protrusions (Marco et al., submitted) and swallows (Marco et al. 1988) have been recently demonstrated in rats in our laboratory. We proposed that these ketamine-induced linguopharyngeal events (KILPE) may be used as a pharmacological model of neuroleptic-induced dyskinesia. In humans, the evidence of involvement of cholinergic mechanisms in dyskinetic syndromes is less solid than for dopamine, and the specific effects of cholinergics and anticholinergics are controversial and inconsistent. Some authors have suggested that a relative cholinergic hypofunction may play a role in dyskinetic conditions (Barbeau et al. 1973; Fann et al. 1974; McGeer and McGeer 1976). In tardive dyskinesia, due to chronic neuroleptic administration, no effect at all was observed with administration of physostigmine intravenously by some authors (Tarsy et al. 1974), but amelioration in Huntington’s choreiform symptoms has been reported by others (Klawans et al. 1974), including those of tardive dyskinesia (Fann et al. 1974). Beneficial effects of acetylcholine precursors on tardive dyskinesia have also been reported (Growdon et al. 1977, 1978; Jackson et al. 1979). Conversely, administration of anticholinergics may induce abnormal involuntary movements (Birket-Smith 1974) or aggravate dyskinesia according to most reports (Crane 1968; Klawans and McKendal 1971; Klawans and Rubovits 1974), but a few authors have reported the opposite effects. We wanted to determine the specific effects of agents capable of altering the central cholinergic state on our model of KILPE. The results described below demonstrate that benztropine mesylate (Cogentin), a central anticholinergic drug, and physostigmine salicylate (Antilirium), a central cholinergic drug, have ephemeral but clear effects on these motor activities in rats. We chose benztropine because it is routinely used jointly with neuroleptics, despite the fact that it is an inhibitor of DA reuptake and there are other cleaner anticholinergic agents.

Method

Thirty-five Sprague-Dawley female rats weighing between 200 and 250 g were anesthetized by ketamine hydrochloride IM injection at an initial dose of 100 mg/kg. After becoming listless and unresponsive to paw and pinna pinch, the animals were mounted in a stereotaxic frame. An additional dose, half the initial dose of ketamine hydrochloride was injected, if necessary, on an hourly basis. As in previous reports (Aldes et al. 1988; Marco et al. 1988), the tongue was pierced at about 2 mm from the tip with a curved suturing needle and a piece of nylon thread (4-0) attached to it before mounting. The nylon thread was sutured to a rigid arm extending from the beam shaft of the cantilever of a Grass force displacement transducer (FDT). The position of the FDT was adjusted such that the tongue was free from both upper and lower teeth, lying as normally as possible, and stretched not more than about 2 mm beyond the insertion of the lower teeth. Counts of KILPE (retrusions or R, protrusions or P, and swallows or S) were made from the paper recordings at regular intervals for a duration of 5 min before and after the administration of the cholinergic or anticholinergic agent. These counts of R, P, and S at different times and under the different pharmacological conditions were plotted on graph paper. Due to the findings that the mean and standard deviation were equivalent, all scores were normalized by square root transformations, as described by Walker and Lev (1953) and Winer (1962).

In eight experiments, methscopolamine was injected IM 15 min prior to physostigmine injection, to block the peripheral effects of the latter agent. The doses of methscopolamine were 1.4, 3, and 6 mg/kg.
Fig. 1. A Representative curves of effects of benztropine at two different doses of 1 mg/kg (upper) and 0.5 mg/kg (lower). Note the short-lived attenuation of linguopharyngeal events and return to about baseline within 60 min. B Upper curve represents the effects of physostigmine 15 µg/kg at time zero on ketamine-induced linguopharyngeal events monitored from time –15 min. Lower curve represents the effects of a higher dose of physostigmine, 25 µg/kg, when methscopolamine (6 mg/kg) had been injected following ketamine injection, 15 min before physostigmine. Note the equivalent time course of effects despite a clear slowing and mitigation of physostigmine effects by methscopolamine. Abscissa represents time in minutes. Ordinate represents the square root transformation of each event count for 5-min intervals of time.

Discussion

The most interesting finding of these experiments is that the changes in KILPE caused by physostigmine and benztropine were in the opposite direction to those most often reported in the clinical literature. Our results are, however, in agreement with several other reports which, themselves, are at variance with the general trend. For example, Gerlach and Faurbye (1960) to improve dyskinesia. The decrease in KILPE by benztropine and the increase by physostigmine parallel the results of Rupniak et al. (1982). It is to be noted that in their experiments rats had been subjected to a chronic schedule of neuroleptic administration prior to the challenge with the anticholinergic and cholinergic agents. Thus, in the rat model it does not appear to make much difference whether the model is more acute, as, ours or chronic, as elsewhere (Marco et al. 1988), there are no agents better capable of inducing acute dyskinesia or dystonia than those which cause tardive dyskinesia. Analysis of other animal models of neuroleptic-induced dyskinesia (Domino and Kovic 1983; Goetz et al. 1983) appear to suggest that acute dyskinesia is more readily obtained than chronic dyskinesia in several species. The increase in KILPE persisted even after the peripheral effects were blocked by methscopolamine, a peripherally acting anticholinergic drug. Severance of the hypoglossal nerve eliminates ketamine-induced tongue contractions (Aldes et al. 1988). Thus, neither are the KILPE peripheral nor can the enhancing effects of physostigmine be explained as being entirely peripheral in origin. The finding that methscopolamine slowed and mitigated the physostigmine effects suggests either that physostigmine contributes an effect at the periphery (muscle), which is...