EFFECTS OF ATROPINE AND VAGOTOMY ON VOCALIZATION OF THE RABBIT

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Vocalization (squeal, cry) has been used as a signal of pain by a number of investigators (1, 2). Since atropine increases the threshold of vocalization induced by electrical stimulation of the rat tail, Herold and Cahn (3) considered that in the rat, cholinergic neurons were related to the conduction of pain sensory transmission in the central nervous system. In a previous study, we reported that in the rabbit, vocalization could be induced by electrical stimulation of the sciatic nerve (4). The present study was undertaken to examine the effect of atropine and vagotomy on vocalization of the rabbit in order to determine whether the transmission of pain impulses in the rabbit was also conducted by a central cholinergic mechanism, as claimed by Herold et al. (3) in the rat.

Female rabbits (2-3 kg) anesthetized with urethane (1 g/kg s.c.) were vocalized by afferent stimulation of the sciatic nerve cut off, using 30 V at square pulses and a duration

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of 0.1 msec for 10 sec through bipolar platinum wire electrodes. The number of vocalizations produced by this stimulus intensity at 10 min intervals was almost constant for at least four hours. Vocalization was recorded on an ink-writing recorder (Nihon Kohden, WI-260) through integral circuits (5) mounted with a biophysical amplifier (Nihon Kohden, RB-2). According to Carroll et al. (2), vocalization was classified into the following two parameters; vocalization during the stimulation (Vd) and vocalization continuing after the stimulus had ceased (Va), and in each rabbit the number of Vd and Va was counted, respectively. In the experiment of bilateral vagotomy, the effect of vagotomy on the number of Vd and Va was measured 30 min after cutting of the vagus nerve. Results were expressed as the percent of the change to the values of the control, as shown in Fig. 1.

At doses of 2.5–20 mg/kg, atropine decreased the number of Vd dose-dependently,
while atropine produced an increase in the number of Va at doses of 2.5–5 mg/kg and a
decrease in that of Va at dose of 20 mg/kg. The decreasing effect of atropine in a dose of
20 mg/kg on the number of Vd and Va is similar to that of vagotomy which decreases the
number of Vd and Va simultaneously. It is known that the contraction of the vocal
cord is mainly controlled by the recurrent nerve, rami of the vagus nerve and that
disturbance in the function of the vagus nerve evokes the voice disorders by inhibiting
the conduction of nerve impulses to the vocal cord and by disordering the rhythm of the re-
spiratory movement closely related with vocalization (6). Therefore, this decrease in the
number of Vd and Va produced by a dose of 20 mg/kg of atropine may be explained by
inhibition of the vagus nerve as based on the peripheral anticholinergic action of atropine.

At doses of 2.5–5 mg/kg, atropine decreased the number of Vd and increased the number
of Va. This contrary change in the number of Vd and Va is not interpreted as the peripheral
anticholinergic action of atropine on the vagus nerve, since inhibition of the vagus nerve
evokes a decrease of both the number of Vd and Va as was quite evident in the experiment
using a vagotomy procedure. Therefore, this contrary change with low doses of atropine
may be due to inhibition of central cholinergic neurons produced by the central antichol-
inergic action of atropine (7). If atropine decreases the number of Vd by inhibiting central
cholinergic neurons, our finding that atropine increased the number of Va suggests the
possibility that atropine increased that of Va by inhibiting inhibitory cholinergic neurons in
the central nervous system. Inhibitory cholinergic neurons exist in the peripheral nervous
system (8, 9), but have not been demonstrated in the central nervous system (10, 11, 12).
Further investigation is necessary to validate our hypothesis.

The present finding that cholinergic neurons participate not only in the peripheral
mechanism but also in the central mechanism on vocalization of the rabbit is in agreement
with the finding of Herold et al. (3), that atropine increased the threshold of vocalization in
the rat. Herold and Cahn (3) claimed from their results that pain sensory transmission in
the rat is under the control of acetylcholine and 5-hydroxytryptamine in the central nervous
system. Therefore, as claimed by Herold et al. (3) in the rat, there is the possibility that
central cholinergic neurons may also play some role in pain sensory transmission in the
rabbit.

REFERENCES
1) BROLIE, D.C., LUEONGWAT, E. AND SMITH, JR. G.E.: A note on a modification of a method for
evaluating salicyl-type analgesics. J. Am. Pharm. Ass. 41, 48–49 (1952); 2) CARROLL, M.N.
AND LIM, R.K.S.: Observations on the neuropharmacology of morphine and morphine-like anal-
gesia. Archs int. Pharmacodynam. Thér. 125, 383–403 (1960); 3) HEROLD, M. AND CAHN, J.: Phar-
cmacology of Pain, Edited by LIM, R.K.S., ARMSTRONG, D. AND PARDO, E.G., p. 87–99, Academic
Press, New York and London (1967); 4) MURAI, S. AND OGURA, Y.: Pharmacological studies
99P (1975); 5) TAIWA, N., NAKAYAMA, K. AND HASHIMOTO, K.: Vocalization response of puppies
to intra-arterial administration of bradykinin and other algesic agents and mode of actions of
blocking agents. Tohoku J. exp. Med. 96, 365–377 (1968); 6) KIRIKAE, I.: Modern Oto-Rhino-
Laryngology, p. 474–482, Nanzando Company, Tokyo (1974); 7) INNES, I.R. AND NICKERSON,
M.: The Pharmacological Basis of Therapeutics, Fourth edition, Edited by GOODMAN, L.S. and

**NONSPECIFIC RELAXATION OF INTESTINAL SMOOTH MUSCLE INDUCED BY ANTISPASMODICS AND MOVEMENT OF CALCIUM IONS**

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Benactyzine relaxes the intestinal smooth muscle in high concentrations of $10^{-3}$ to $10^{-2}$ M and has been found to have little inhibitory action on cyclic AMP phosphodiesterase (1), while papaverine, in the concentrations which have a relaxing action, inhibits cyclic AMP phosphodiesterase in intestinal smooth muscle (1, 2) from the guinea pig. In the present work, we examined the effects of benactyzine and papaverine on Ca-uptake by a microsomal fraction obtained from rabbit taenia coli and Ca-contraction of a KCl-depolarized smooth muscle, and influence of external Ca ions on inhibitory actions of the drugs on the smooth muscle contraction induced by histamine.

The taenia coli isolated from male rabbits, weighing 2.0 to 3.0 kg, was suspended in a 30 ml organ bath filled with Locke Ringer solution kept at 32°C and bubbled with air. The pH of the bathing medium under these conditions was 7.6. Responses to drugs were recorded isotonically. The Locke Ringer solution used had the following composition (mM): NaCl 154, KCl 5.6, CaCl$_2$ 2.2, MgCl$_2$ 2.1, NaHCO$_3$ 5.9 and glucose 2.8. To test the effects of an increase of external Ca ions on noncompetitive antagonistic activities of benactyzine and papaverine, the concentration of CaCl$_2$ in the Locke Ringer solution was increased 10 times (high Ca-Locke Ringer solution). In some experiments the taenia coli was suspended in the same bath filled with Ca-free KCl-Locke Ringer solution (KCl 159.6, MgCl$_2$ 2.1, NaHCO$_3$ 5.9 and glucose 2.8 mM), bubbled with air and kept at 32°C. After an initial incubation (lasting about 60 min), CaCl$_2$ was added cumulatively and the contraction induced by CaCl$_2$ was recorded isotonically. Benactyzine was added to the bath 3 min before the addition of CaCl$_2$.

Estimation of Ca-uptake by the microsomal fraction was done by the method of Carsten (3) and as modified by Takayanagi et al. (4). Rabbits, weighing 2.0 to 3.0 kg were sacrificed by a blow on the neck and taenia coli was immediately removed and washed with ice-cold...