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## The effect of systemic cocaine on spinal nociceptive reflex activity in the rat

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In the anesthetized rat, cocaine (25 mg/kg i.p.), enhanced the frequency potentiation of nociceptively evoked polysynaptic discharges but did not affect the polysynaptic reflex discharge to single nociceptive stimuli or the habituation of this reflex to repetitive pinch stimuli. The non-nociceptive, short-latency reflex discharge was suppressed for 10–15 min after cocaine administration. The neurogenic extravasation response to antidromic cutaneous C-fiber stimulation was unaffected by cocaine. These findings suggest that systemic cocaine, in doses analgesic for the rat, does not suppress spinal nociceptive reflexes.

Early in this century, 3 short reports described general analgesia after the systemic administration of cocaine to dogs<sup>5,12</sup> and a human subject<sup>3</sup>. Furthermore, more recently Yang et al.<sup>17</sup> showed that cocaine applied intranasally attenuated ischemic pain (tourniquet test) in humans. Behavioral experiments in this laboratory demonstrated that, in the rat, cocaine (20–25 mg/kg i.p.) produces a profound, rapid onset (<10 min), short duration (~1 h) non sedative analgesia (formalin test) that is antagonized by chlorpromazine, but not naloxone<sup>7,8</sup>. Additional experiments have shown that analgesic doses of cocaine affect the spontaneous and nociceptively-evoked activity of caudally and rostrally projecting medial medullary reticular neurons over a time course paralleling the behavioral effects<sup>1</sup>. In the current study, we wished to determine if systemic cocaine in analgesic doses suppresses nociceptive spinal reflex activity by acting on central or peripheral mechanisms.

Seven adult male Sprague–Dawley rats (330–480 g) were anesthetized (chloral hydrate, 400 mg/kg i.p.), and a tracheal cannula was inserted. End-tidal CO<sub>2</sub> was continuously monitored and kept between

3.5 and 4.5%. A feedback-controlled heating pad kept the rectal temperature between 36.5 and 38.5 °C. The peripheral vascularization was checked by considering the color of the ears and extremities. The level of anesthesia was monitored by observing somatic and autonomic responses to a noxious stimulus, the size of the pupils, and muscle tone.

A pool made of skin was formed in the left popliteal fossa and filled with warm mineral oil. The sural nerve was cut and its central end was prepared for electrical stimulation. The common peroneal nerve was cut and thin filaments were dissected from its central end. After surgery, additional anesthetic was administered as necessary and the animal was paralysed with gallamine. The central end of the sural nerve was placed on stimulating electrodes and a thin filament of the central end of the common peroneal nerve was placed on a platinum–iridium recording electrode. Electrical stimuli (0.5 ms rectangular pulses) were delivered to the sural nerve from a constant unit. The stimulus rate was usually 0.25 Hz, except when studying the frequency potentiation. In some experiments, electrical stimuli were applied via

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two closely spaced needle electrodes through the glabrous skin of the foot pad. Neural responses to natural noxious stimuli were tested by applying a noxious pinch to the toes. The neural signals were led through an AC amplifier (band pass: 200 Hz–1 kHz) to a loudspeaker, a storage oscilloscope for photography, and through a window discriminator to a computer.

Cocaine (25 mg/kg) was given i.p. Special care was taken to avoid s.c. or i.m. injections. The effect of cocaine was tested in only one nerve filament in each rat.

In one rat, the peripheral end of a cut saphenous nerve was prepared for antidromic electrical stimulation at C-fiber intensity (0.5 ms, 5 mA pulses at a fre-

quency of 10 Hz for 10 min) after i.v. injection of Evans blue (50 mg/kg in saline vehicle; 50 mg/ml).

Electrical stimulation (50–150  $\mu$ A) of the sural nerve produced a 5–15 ms latency reflex discharge in the common peroneal nerve. At higher intensities (0.3–5.0 mA), a long-latency discharge could be elicited at latencies of 150–200 ms, and durations of up to several hundred ms. Occasionally, high-intensity stimulation elicited only a single reflex discharge which had a latency of 40–60 ms and a duration of 40–80 ms. Noxious pinch of the ipsilateral toes for 1 s also produced common peroneal nerve discharges but pinch of the contralateral toes was ineffective. Habituation of the response to repeated pinch was

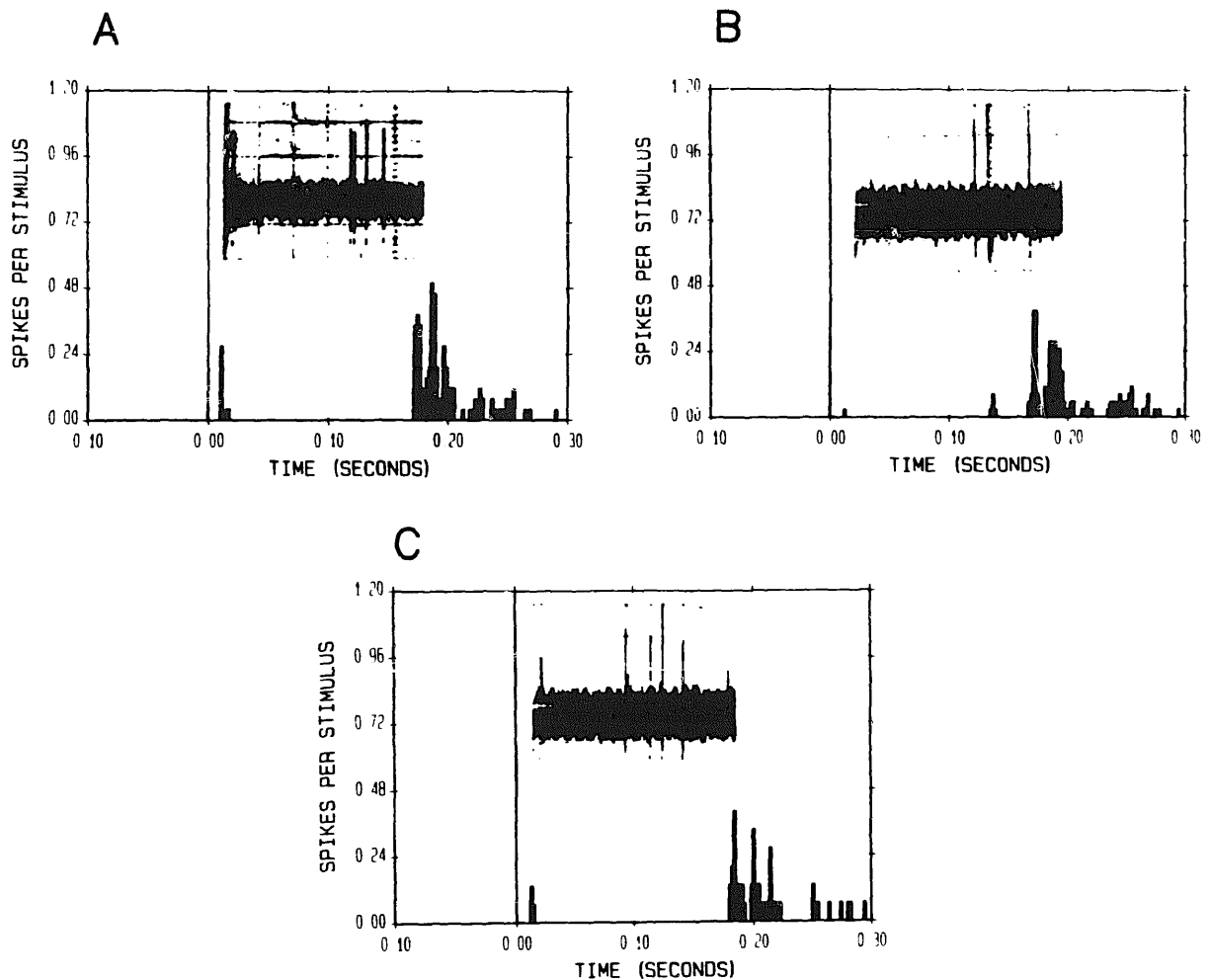


Fig. 1. Averaged peristimulus time histograms of short-latency non-nociceptive and nociceptive polysynaptic reflex discharges in a common peroneal nerve filament following electrical stimulation of the sural nerve at C-fiber intensity before (A), 10 min after (B) and 20 min after (C) cocaine administration (25 mg/kg). The insets show single sweep examples of the neuronal responses. The vertical line at time zero in the graphs and the beginning of the baseline in the insets indicates stimulus artifact. The baseline duration in the insets is 300 ms. A transient suppression of the short-latency discharge is seen 10 min after cocaine, but there is no change in the long-latency reflex discharge. The 95% confidence limits of the long-latency response histogram bins (evaluated using 300 ms bins) in each graph were overlapping. In each graph  $n = 32$ . The stimulus repetition rate (0.25 Hz) was too low for frequency potentiation of the nociceptive long-latency discharge.

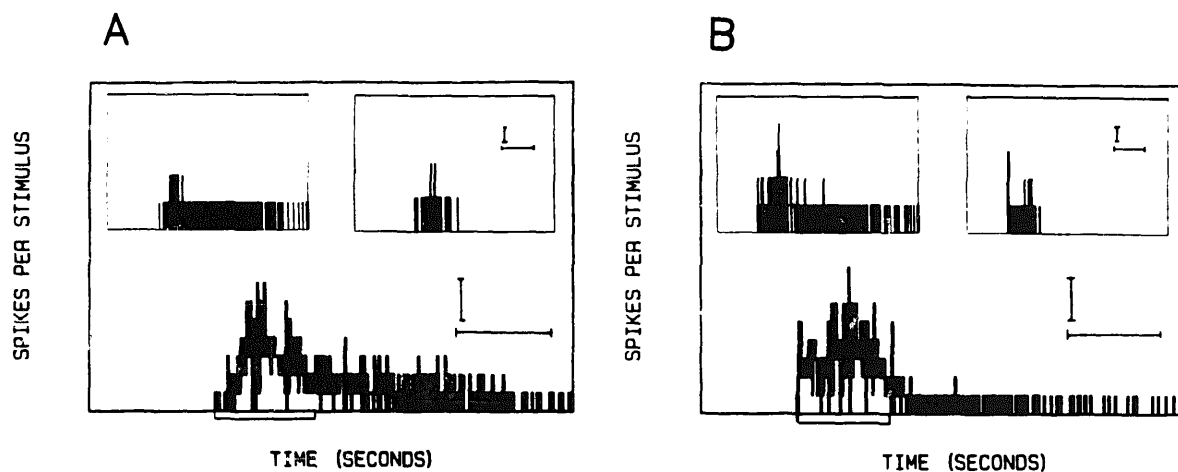


Fig. 2. Averaged peristimulus time histograms of reflex discharges in a common peroneal nerve filament following noxious pinch of the ipsilateral toes before (A) and 10 min after (B) cocaine administration;  $n = 6$  in both graphs. The interstimulus interval was 10 s. There was no change in the response to pinch after cocaine was injected. The insets demonstrate the marked habituation to repetitive pinch stimuli, and they also show that the habituation was not influenced by cocaine. The inset in the upper left corner of each graph shows the response to a single stimulus 5 trials later in a train of consecutive stimuli in each condition, and the inset in the upper right corner of each graph shows the response to a single pinch stimulus in each condition. This same nerve filament, however, showed enhanced frequency potentiation of nociceptive polysynaptic discharges with cocaine, as indicated by Fig. 3E-G. Horizontal calibration: 1 s. Vertical calibration: 1 impulse/s. The hollow bar under the abscissa indicates the stimulus duration.

observed when stimuli were applied at intervals of 10 s or less. Habituation to electrical stimulation of the sural nerve at 0.25 Hz was not observed. High-intensity electrical stimulation of the sural nerve at higher frequencies (0.35–0.4 Hz) potentiated the long-latency reflex discharge.

Cocaine (25 mg/kg i.p.) did not suppress the common peroneal reflex discharge to single high-intensity electric stimuli during the 30-min observation period ( $n = 6$ ). However, as shown in Fig. 1, in 2 rats the short-latency response was suppressed for 10–15 min after the cocaine administration. Cocaine did not affect the pinch-evoked reflex responses or the habituation to repetitive pinch stimuli (Fig. 2). However, the potentiation of polysynaptic discharge by higher-frequency stimulation was enhanced within 3 min after cocaine administration (Fig. 3).

In the rat treated with Evans blue, antidromic activation of the saphenous nerve at C-fiber intensity produced a clear and well-demarcated blue coloration in the skin innervated by the saphenous nerve. This neurogenic extravasation phenomenon, which indicates that impulses are being conducted into the terminal cutaneous branches of nociceptive afferent C-fibers<sup>4,6</sup>, was unaffected by analgesic doses of co-

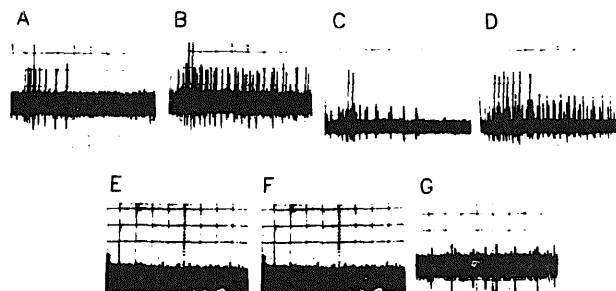


Fig. 3. Photographic examples of frequency potentiation of the reflex discharge in two separate nerve filaments (A–D and E–G) in the common peroneal nerve, before and after cocaine. The responses in the upper row are to sural nerve stimulation at C-fiber intensity (10 mA, 0.5 ms pulses), and at the frequency of 0.35 Hz. The responses in the lower row are to percutaneous skin stimulation via needle electrodes in the tibial nerve area at C-fiber intensity (10 mA, 5 ms pulses) and at a frequency of 0.4 Hz. Largest spike in A–D shows: A, the response to the first stimulus in a row before cocaine; B, the response to the 8th stimulus in a row before cocaine (note the modest frequency potentiation); C, the response to the first consecutive stimulus 5 min after cocaine; D, the response to the 8th consecutive stimulus 5 min after cocaine (note the strong frequency potentiation). The nerve filament in E–G responded only to pinch and not to electric stimuli (see Fig. 2). E, the response to the 16th stimulus in a row before cocaine; F, the response to the first stimulus in a row 10 min after cocaine; G, the response to the 16th stimulus in a row 10 min after cocaine. Bars: in A–D = 100 ms; in E–G = 50 ms. The beginning of baseline in each figure depicts the stimulus artifact.

caine administered before the antidromic stimulation.

The reflex discharges we recorded from the common peroneal nerve in response to sural nerve stimulation were similar to those described earlier<sup>9,13,14</sup>. Our observations are in accord with the interpretation that the low-threshold, short-latency discharge is a non-nociceptive reflex whereas the long-latency high-threshold response is a nociceptive flexor reflex elicited by A- $\delta$ - or C-fiber stimulation. We also observed that the flexor reflex was rapidly habituated by repetitive natural stimuli<sup>14</sup> and potentiated by high-intensity electrical stimulation at frequencies exceeding 0.3 Hz<sup>10,11,13</sup>.

Systemic cocaine, in doses analgesic for the rat, did not depress nociceptive polysynaptic flexor reflex discharges and had no effect on the conduction of impulses into the cutaneous terminals of afferent C-fibers as tested by the neurogenic extravasation phenomenon<sup>3,6</sup>. Indeed, the only effect of cocaine that we observed was an enhancement of the flexor reflex potentiation produced by repetitive electrical stimulation at C-fiber intensities. The mechanism by which cocaine produces this increased responsiveness is not known. Our results suggest that cocaine may enhance selectively the excitatory effect of specific input pathways to flexor motoneurons because the low threshold, short latency reflex was briefly suppressed and habituation of the flexor reflex was preserved.

It has been reported recently that another local an-

esthetic, tocainide, when administered systemically, preferentially suppresses polysynaptic flexion reflexes<sup>15</sup>. Thus cocaine and tocainide appear to produce central analgesia via at least partially different mechanisms.

Prevailing theories of the mechanisms mediating systemic analgesia have emphasized the importance of supraspinal neurons that suppress the nociceptive responsiveness of spinal cord cells<sup>2</sup>. It is reasonable to expect that cocaine would activate or enhance this descending inhibition by potentiating the monoaminergic synaptic transmission that, in part, mediates it<sup>16</sup>. Furthermore, we have shown that an analgesic dose of cocaine dramatically alters the spontaneous and somatically evoked activity of identified medullary reticulospinal neurons over a time course paralleling the behavioral analgesia<sup>1</sup>. However, our experiments demonstrate that cocaine does not uniformly depress spinal segmental nociceptive mechanisms. It is possible that systemic cocaine depresses the nociceptive responses of rostrally projecting spinal neurons, which we did not identify. Alternatively, systemic cocaine may produce analgesia by affecting supraspinal mechanisms exclusively.

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