both sides of the lumbar cord suggests that the size of facilitation is related to the number of synapses depolarizing primary afferent terminals. Increased facilitation of the DRPs conditioned by volleys spreading along the cord corroborates this hypothesis. Larger maximum and slower decay of facilitation of contralateral DRPs evoked by volleys spreading caudally implies that pathways descending from lumbar cord activate more synapses than those ascending from caudal segments. This finding gives evidence for different organization of pathways transmitting depolarization in both directions. The spread of the DRPs along the cord most probably occurs via substantia gelatinosa and Lissauer tract. However, anatomical studies did not disclose different numbers of synapses involved in transmitting depolarization in both directions[9]. We have found that ipsilateral DRPs spreading caudally decrease in more distant segments while contralateral potentials are increased[5]. The enhancement may be produced by volleys which traverse the cord from the ipsilateral side a few segments below a stimulated dorsal root. These volleys would activate additional synapses and increase facilitation of contralateral DRPs despite the lack of known accessory synaptic relays in descending pathways of the substantia gelatinosa.

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Supernormal responses to premature stimulation in Ca-dependent action potentials

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Summary. The responses of Ca-dependent action potentials to premature stimulation were studied in the isolated canine ventricular muscle. When very premature stimuli were applied, supernormally augmented responses with propagation occurred, while responses with long preceding intervals were small and not conducted.

In general, recovery from inactivation of slow Ca current is known to be delayed[2-4] and refractoriness of slow responses[5], whose depolarization depends on slow inward current, is thought to be prolonged. Sano et al.[6] reported that the effective refractory period was increased to more than 1 sec in ventricular muscle preparation in which slow responses were activated by isoproterenol in high K solutions. Recently, however, we examined the responses of Ca-dependent action potentials[7] (AP) to premature stimulation and revealed that supernormal responses occurred when very premature stimuli were applied, and this augmented premature response showed supernormal conduction. This agreed with our previous report[8] that Ca-influx might be enhanced during premature depolarization.

Material and methods. A small portion of the trabecular muscle was dissected from the right ventricle of dogs and mounted in a tissue bath perfused with tris buffer physiological solution. Premature stimuli (S_2) were applied at variable intervals after every 10th driving stimulus (S_1) of 0.5 Hz. APs (R_1 and R_2) elicited by S_1 and S_2 of equal strength and duration were recorded with conventional microelectrode methods as described previously[9] at the proximal (P) and distal points (D) which were at intervals of a few mm. Measurements were made of the amplitude (Amp), duration (APD), the maximal rising velocity of APs recorded at P and conduction time for P and D. The ratio of these parameters of R_2 to those of R_1 were calculated.

Results and discussion. In control solutions (K 4.5 mM, Ca 1.6 mM), both Amp_2/Amp_1 and APD_2/APD_1 were near unity at any S_1S_2-interval (figure 1). In high K (21 mM)-high Ca (10 mM) solutions, the basic responses were small and had a low rising velocity (8 to 23 V/sec). Both their amplitude and duration were depressed by verapamil (10^{-5} M), and were augmented by isoproterenol (10^{-6} g/ml). Moreover, the resting membrane potential in this solution decreased to -49 ± 1 mV (mean + SE) (ranged from -45 to -54 mV), resulting in complete inactivation of fast inward Na current. Thus, they were thought to be Ca-dependent APs. When a very premature stimulus was applied, R_2 greater than R_1 occurred. The rising velocity of R_2 was also greater. Figure 1 shows the relation between the degree of the augmentation of R_2 and S_1S_2-intervals. Amp_2/Amp_1 and APD_2/APD_1 were 1.9 ± 0.3 and 2.8 ± 0.4, respectively at a S_1S_2-interval of 180 msec. They declined progressively to unity with increasing the coupling interval to 500 msec. Asterisks above the value show the significance of change. This supernormal premature response, R_2 elicited by S_2 applied 200 msec after S_1, was conducted from P to D, while a basic beat (R_1) was not (figure 2, A). When the

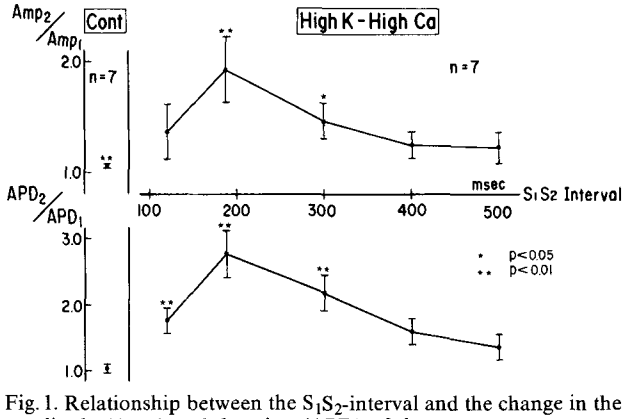

Fig. 1. Relationship between the S_1S_2-interval and the change in the amplitude (Amp) and duration (APD) of the premature response. On the left, the maximal ratio in the control solution is shown. Vertical bars indicate SEM. See text for additional explanation.

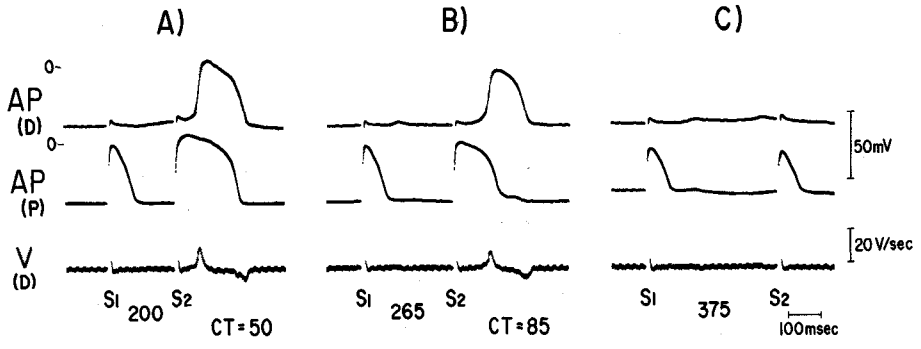

Fig. 2. Facilitated conduction in premature responses in high K-high Ca solutions. A basic and a premature AP which were recorded at distal (D, top trace) and proximal points (P, middle trace) are shown in a pair. In bottom trace rising velocity (V) of APs recorded at D is illustrated. See text for additional explanation.

coupling interval was increased to 265 msec, R_2, which was smaller than in A, was conducted to D with increased conduction time (figure 2, B). When S_2 was applied at a interval of 375 msec, R_2 as well as R_1 was blocked. In consequence of this supernormal conduction, the minimal coupling interval with propagated responses was shortened to 173±11 msec in high K- high Ca solutions from 239±9 msec in control. If extracellular accumulation of potassium ions occurs in the patient's heart muscle, the above-mentioned phenomenon may well be related to the genesis of Wedensky effect and bradycardia-dependent conduction disturbance, although another mechanism, oscillatory potentials[10], may play some role in such depolarized fibres. Moreover, the supernormal response may be involved in the genesis of extrasystoles, because the decreased minimum coupling interval with propagated responses, as well as delayed conduction, favours the occurrence of reentry[11].

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The effects of dopaminergic blocking agents on the glucose tolerance test in 6 humans and 6 dogs[1,2]

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Summary. Pre-treatment with low doses of sulpiride, an atypical dopaminergic blocking agent, but not haloperidol, a classical dopaminergic blocking agent, decreased tolerance to glucose and increased blood serotonin levels in 6 normal humans and 6 normal dogs investigated.

The administration of 2 different kinds of dopaminergic blocking agents (haloperidol + sulpiride) were successfully used in the treatment of more than 1500 headache, and other psychosomatic patients. A high percentage of the diabetics included in that casuistic showed significant reductions in their fasting serum glucose levels[4,5]. It was also found that haloperidol and sulpiride, administered separately, induce opposite effects on distal colon motility[6] and on whole blood serotonin levels[5]. For these reasons, we decided to investigate the effects of both drugs on the glucose tolerance test.

Material and methods. 4 consecutive oral glucose (100 g) tolerance tests (30-day intervals) were performed on 6 healthy volunteer humans (30–36 years old and 60–65 kg) and on 6 normal adult mongrel dogs (1.7 g/kg) weighing 25–30 kg. Peripheral blood samples were withdrawn for glucose[7], insulin[8], and serotonin[9] determinations at 0, 30, 60 and 120 min. Whole blood serotonin levels were assessed at 0 and 60 min only. All experiments began at 08.00 h, after 12 h (humans) and 16 h (dogs) fasting periods.

In 3 human subjects and 3 dogs, oral sulpiride (50 mg and 25 mg every 8 h, respectively) was administered for 8 days before the 2nd test; whereas oral haloperidol (0.5 mg and 0.3 mg every 8 h, respectively) was administered 8 days before the 4th test. In the 3 other human subjects and dogs, the sequence of the drug periods was inverted. Drug doses were similar to those employed in the treatment of headache patients[4]. In all the subjects and dogs, placebo was administered before the 3rd tests (control II). The humans did not change their habits during the duration of the investigation. They suffered no intercurrent diseases or oscillations of body weight during that time. No side effects were registered and no other drug was taken during the experimentation periods.

Dogs employed in the present study were maintained (under controlled conditions) in the home of one of us, where they ate their routine dog food (Perrarina). No