脊髄イヌの血圧,心拍数および心電図に対するキシラジンの影響

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Effects of Xylazine on Arterial Blood Pressure, Heart Rate and Electrocardiogram in Spinal Dogs

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Xylazine is widely used in veterinary medicine as a sedative agent. This drug is known to induce bradycardia, occasional atrioventricular block, and a transient rise in blood pressure followed by a long-lasting decrease in most domestic animals [5]. Recent pharmacological studies have revealed that the α_2-adrenoceptor mediates both the sedative and the cardiovascular effects of xylazine [1, 2], because these effects are antagonized by yohimbine, α_2-adrenoceptor blocking agent [3, 4]. However, it is still unclear whether the cardiovascular effects of xylazine result from the activation of α_2-adrenoceptors in the central nervous system (CNS) or those in the peripheral vascular tissues.

To assess the peripheral effects of xylazine on the circulatory system, we investigated the effects of xylazine on arterial blood pressure (ABP), heart rate (HR) and electrocardiogram (ECG) in the spinal dogs.

Seventeen healthy mongrel dogs of both sexes weighing from 7 to 18 kg were used. In order to avoid the efferent effects of the sympathetic nervous system, the spinal cord was transected under pentobarbital sodium (30mg/kg, i.v.) anesthesia. At first, the dogs were artificially ventilated with 40% oxygen via an endotracheal tube connected to a positive pressure ventilator. Twenty min later, the dura mater was incised and the spinal cord was tightly ligated at the center of the second cervical vertebra. Ventilation was maintained at the rate of 10 times/min and with a peak inspiratory pressure of about 10 mmHg throughout the experiment. The cephalic vein, the femoral vein and artery were cannulated for giving drugs, collecting blood samples, and recording ABP, respectively.

The administration of the drugs was begun 60 min after the transection of the spinal cord. The dogs of group 1 (n=5) recieved xylazine alone (3 mg/kg, i.v.). The dogs of group 2 (n=5) recieved xylazine (3 mg/kg, i.v.), and then after 5 min, yohimbine (0.5 mg/kg, i.v.). The dogs of group 3 (n=4) recieved xylazine (3 mg/kg, i.v.) 3 min after the injection of hexamethonium (C_6, 10 mg/kg, i.v.), a ganglion blocking agent, and 5 min later they received yohimbine (0.5 mg/kg, i.v.). The dogs of group 4 (n=3) were pretreated with C_6 (10 mg/kg, i.v.), atropine sulfate (0.5 mg/kg, i.v.), and prazosin (10 mg/kg, i.v.), an α_1-adrenoceptor blocking agent. After 3 min, they were given xylazine and then yohimbine in the same manner as group 3. HR and ECG (lead

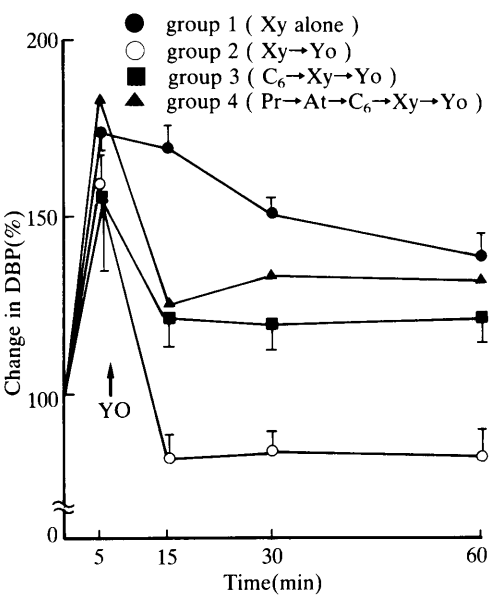

Fig. 1. Changes in DBP following injections of xylazine and yohimbine in spinal dogs of each groups. Each value represents a mean±SE (n=3–4). Xy; Xylazine, Yo; Yohimbine, C_6; Hexamethonium, Pr; Prazosin, At; Atropine.

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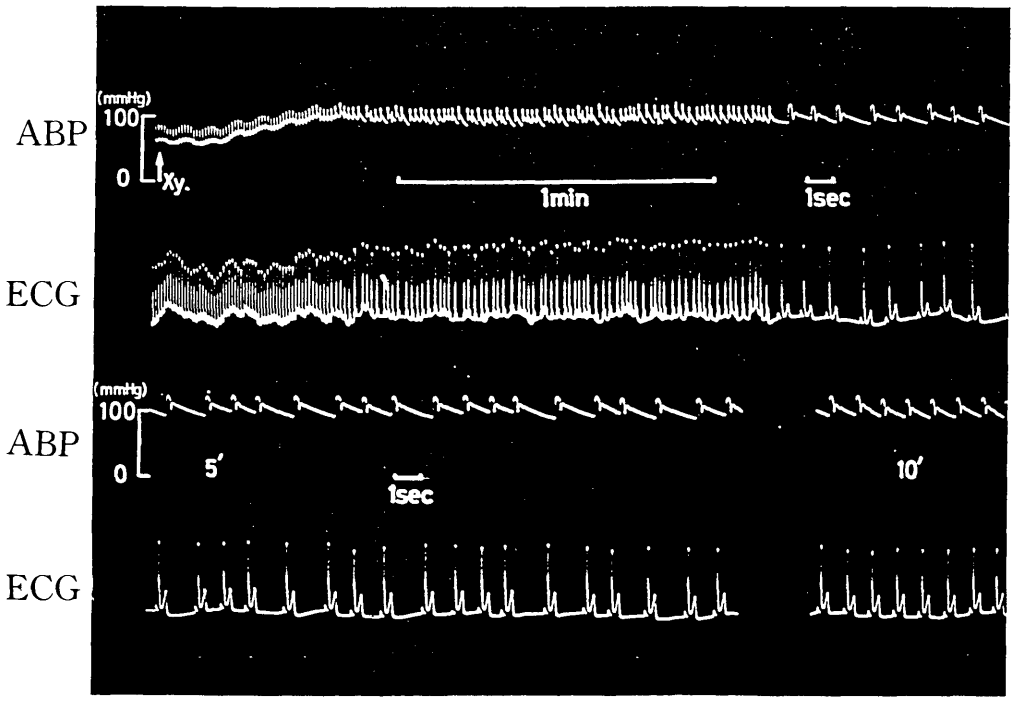

Fig. 2. Changes in ABP and ECG after xylazine injection in a dog of group 1. Xy; Xylazine (3 mg/kg, i.v.), ABP; arterial blood pressure, ECG; electrocardiogram.

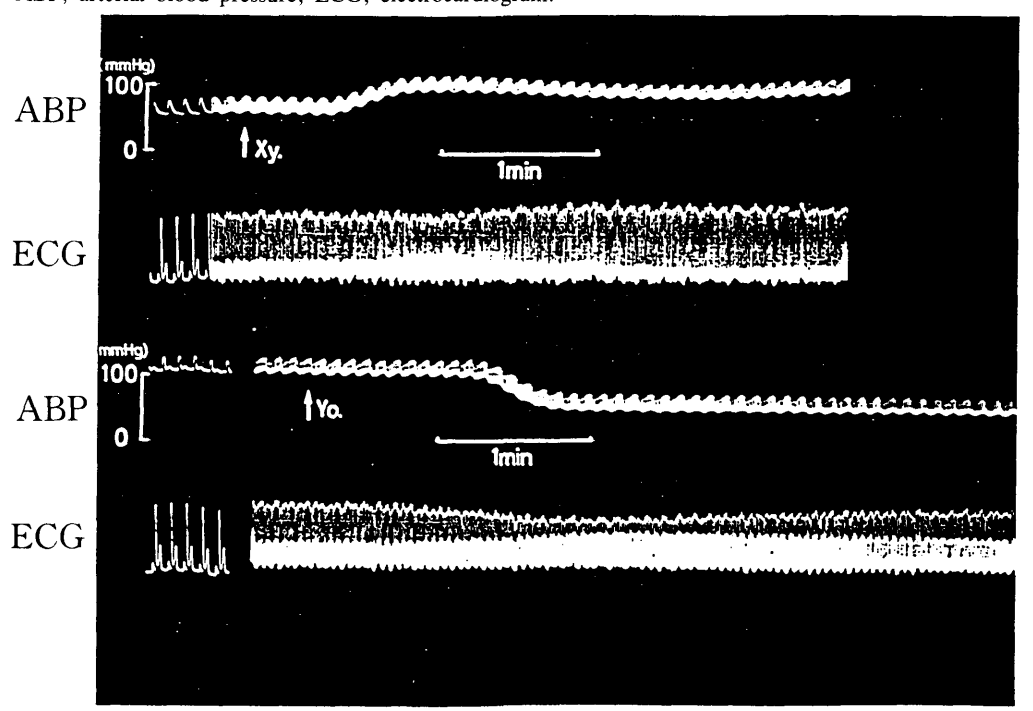

Fig. 3. Changes in ABP and ECG after injections of xylazine and yohimbine (5 min later) in a dog of group 2. Xy; Xylazine (3 mg/kg, i.v.), Yo; Yohimbine (0.5 mg/kg, i.v.).

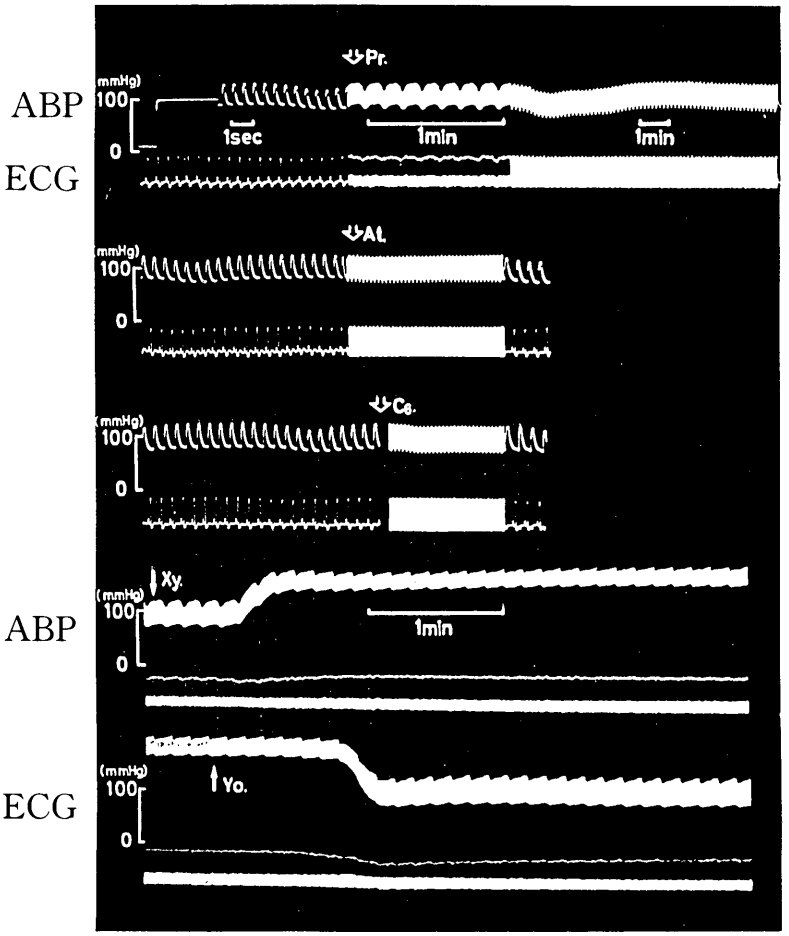

Fig. 4. Changes in ABP and ECG after injections of xylazine and yohimbine under the premedication with prazosin, atropine and C_6 in a dog of group 4. Xy; Xylazine (3 mg/kg, i.v.), Yo; Yohimbine (0.5 mg/kg, i.v.), C_6; Hexamethonium (10 mg/kg, i.v.), Pr; Prazosin (10 mg/kg, i.v.), At; Atropine (0.5 mg/kg, i.v.).

II) were continuously monitored throughout the experiment.

Fig. 1 shows the changes in diastolic blood pressure (DBP) following the injection of xylazine and yohimbine in the dogs of each group. DBP decreased from 118 mmHg at the preligation state to 65 mmHg at 60 min after the spinal ligation. DBP was immediately elevated after the injection of xylazine in all groups (Figs. 2–4). In the dogs of group 1, which did not receive yohimbine, a xylazine-induced rise in blood pressure sustained throughout the 60 min measurement peirod without the subsequent hypotension reported in intact dogs [4]. This pressor effect was antagonized by yohimbine (Groups 2, 3 and 4 in Figs. 1, 3 and 4). In the dogs of group 3, premedication with C_6 did not affect either the pressor effect of xylazine or the inhibitory effect of yohimbine. Furthermore, combination of prazosin, C_6, and a large dose of atropine (parasympatholytic agent) also did not modify the effects elicited by xylazine and yohimbine in 3 dogs (Fig. 4). From these results, the hypotensive effect of xylazine in intact dogs is thought to be mediated by CNS α_2-adrenoceptors. The yohimbine-sensitive α_2-adrenoceptor is known to exist on vascular smooth muscle cells, and its activation results in vasoconstriction [8]. Therefore, it is conceivable that the pressor effect is mediated by postsynaptic α_2-adrenoceptors located in vascular tissues.

Changes of HR in each group are shown in Fig.

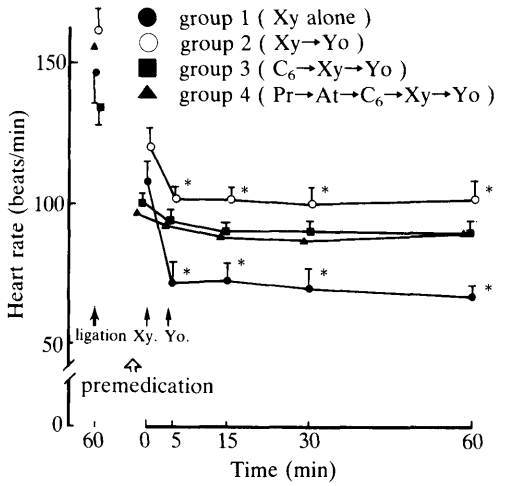

Fig. 5. Changes in HR following injections of Xy and Yo in spinal dogs of each group. Each value represents a mean±SE (n=3–4). The mark (*) represents a significant decrease ($p<0.05$) compared with the value at 0 time. Xy; Xylazine, Yo; Yohimbine, C_6; Hexamethonium, Pr; Prazosin, At; Atropine.

5. In group 1, HR significantly decreased from the pre-xylazine level (60 min after the spinal ligation). Yohimbine partially antagonized the bradycardic effect of xylazine (Group 2 in Fig. 5). On the other hand, in groups 3 and 4, xylazine-induced bradycardia did not occur after premedication with C_6 (Group 3) or combination of C_6 plus atropine (Group 4). These results indicate that the site of the bradycardic action by xylazine is supraganglionic and that the presynaptic α_2 receptor in postganglionic fibers does not influence the effect in dogs whose sympathetic outflow is blockd. Recently, it was reported that α_2-adrenoceptors in the CNS modulated the vagus activity and thereby induced bradycardia via the parasympathetic nerve [6, 7]. Therefore, these results suggest that xylazine-induced bradycardia is mediated by α_2-adrenoceptors related to the activation of the parasympathetic nervous system in a site of CNS and/or a supraganglionic site of the parasympathetic nervous system.

Although no second-degree atrioventricular block was observed in any dogs examined, 4 of 10 dogs in groups 1 and 2 exhibited sinus arrhythmia after the xylazine injection. In group 1, sinus arrhythmia subsided about 10 min after the xylazine injection and restored normal sinus rhythm (Fig. 2). In group 2, sinus arrhythmia immediately disappeared after the yohimbine injection and converted to normal sinus rhythm. The sinus arrhythmia was not observed in dogs of groups 3 and 4, which had received C_6 and a large dose of atropine. In this experiment, since the sympathetic outflow from CNS was blocked by the transection of the spinal cord, the results suggest that xylazine-induced sinus arrhythmia is also mediated by α_2-adrenoceptors located in the parasympathetic nervous system in the central region as discussed above.

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要　約

脊髄イヌの血圧，心拍数および心電図に対するキシラジンの影響（短報）：田原秀樹・小川博之・大塚宏光・伊藤勝昭[1]（宮崎大学農学部家畜外科学教室，[1]家畜薬理学教室）——脊髄イヌに神経遮断薬アトロピン，C_6，プラゾシンおよびヨヒンビンを投与し，キシラジンの循環器系に及ぼす効果とその作用機序を検討した。キシラジンによる持続性血圧上昇は末梢血管の α_2 受容体を介するものであり，徐脈と洞性不整脈は中枢神経（脊髄を除く）もしくは神経節より上位の副交感神経に存在する α_2 受容体の活性化によることが示唆された。