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Hypothermic effects of MK-212, a 5-hydroxytryptaminergic stimulant, in normotensive Wistar-Kyoto and spontaneously hypertensive rats

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Previous research has revealed that spontaneously hypertensive rats (SHRs) differ from normotensive Wistar-Kyoto rats (WKYs) in many noncardiovascular aspects, including response to centrally acting drugs. For instance, we have reported that SHRs are more sensitive to the hypothermic effects of the dopamine stimulants apomorphine and L-dopa (Martin & Quock 1980, 1984) as well as the narcotic analgesic drug morphine (Quock et al 1985). This letter reports preliminary findings from an investigation designed to ascertain whether SHRs might also differ from WKYs in their body temperature response to 6-chloro-2-(1-piperazinyl)pyrazine (MK-212), a centrally acting 5-hydroxytryptaminergic stimulant (Clineschmidt & McGuffin 1978).

Female normotensive Wistar-Kyoto rats (WKYs) and Okamoto-Aoki spontaneously hypertensive rats (SHRs), 200–250 g, were bred from male and female WKYs and SHRs purchased from Charles River Laboratories (Wilmington, Massachusetts). They were maintained on a standard light-dark schedule (light, 0600–1800h) with free access to food and water. Experiments were consistently conducted at the same time each day (1300–1600h) at an ambient temperature of 22 ± 1 °C.

Systolic blood pressures were determined during the week before the temperature experiment by plethysmography (Buñag & Butterfield 1982). Rats were placed into Plexiglas cylinders to which they had previously been conditioned and their systolic blood pressures measured via a tail cuff, using a photoelectric sensor and a pressure amplifier/monitor and recorder (I.I.T.C., Woodland Hills, California). An average systolic blood pressure for each animal was determined from the mean of five determinations. The mean systolic blood pressures of animals used in this study were 147·8 ± 2·8 mmHg for WKYs ($n > 20$) and 187·1 ± 1·9 mmHg for SHRs ($n > 20$) ($P < 0·05$, Student's t-test).

Body temperature experiments were conducted with animals housed two per cage (24 × 30 × 15 cm) following a 60 min acclimatization period. Rectal temperatures were measured with a rectal thermistor probe inserted to a depth of 3·5 cm and connected to an electronic telethermometer (Yellow Springs Instruments, Yellow Springs, Ohio). Temperature readings were recorded at 15 min intervals for 60 min before and 90 min following drug challenge. Time-response curves were constructed from the temperature data and the areas under the temperature response curves were determined as thermal response indices per animal (Clark & Cumby 1978). The mean thermal response indices for various groups of test animals were compared, using a one-way analysis of variance (ANOVA) and Duncan's multiple range test.

6-Chloro-2-(1-piperazinyl)-pyrazine hydrochloride (MK-212) (Merck) was dissolved in distilled water and administered intraperitoneally in a volume of 0·1 ml per 100 g. The doses represent the weights of the hydrochloride salt. Each test animal was challenged with only a single dose of MK-212 then discarded.

Treatment with distilled water failed to evoke any significant alteration in body temperature of WKYs and SHRs. Administration of increasing doses of MK-212 resulted in dose-related hypothermic responses in both WKYs and SHRs. The time courses of the temperature responses to four challenge doses of MK-212 are presented in Fig. 1. Analysis of the mean thermal response indices of these eight test groups of animals

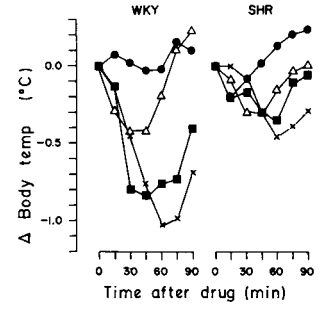

FIG. 1. Time-response curves of WKYs and SHRs to increasing challenge doses of MK-212: ●, 1·0 mg kg^{-1}; △, 2·0 mg kg^{-1}; ■, 3·0 mg kg^{-1}; and ×, 5·0 mg kg^{-1}. Symbols represent the mean of 6–14 rats per group. Refer to Table 1 for statistical analysis of mean thermal response indices.

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Table 1. Comparison of mean thermal response indices of WKYs and SHRs treated with various doses of MK-212.

Challenge dose of MK-212 (mg kg^{-1})	Mean thermal response index (°C-min) ± s.e.m. WKY	SHR
1·0	+ 0·8 ± 7·9[a]	+ 3·0 ± 7·2[a]
2·0	−16·6 ± 4·7[a]	−12·8 ± 8·9[a]
3·0	−51·3 ± 6·6[b]	−17·1 ± 11·5[a]
5·0	−54·7 ± 10·7[b]	−20·7 ± 6·5[a]

Figures represent the mean thermal response indices of groups of 6–14 rats each. Superscript letters indicate homogeneous subsets which are significantly different ($P < 0·05$) from other subsets.

indicate a similarity of WKY and SHR response to 1·0 and 2·0 mg kg^{-1} of MK-212 (Table 1). However, SHRs appear to be significantly less sensitive than WKYs to the hypothermic effect of the two higher doses of MK-212 (3·0 and 5·0 mg kg^{-1}).

MK-212 at 1·0 and 2·0 mg kg^{-1} evoked no overt behavioural response in either WKYs or SHRs. However, higher doses (3·0 and 5·0 mg kg^{-1}) induced a state of behavioural depression, wherein animals of both strains appeared sedated, immobile and slow to react to tactile stimulation. This condition lasted approximately 45–60 min in SHRs but as long as 60–90 min in WKYs.

Since SHRs exhibited a lesser degree of hypothermia than did WKYs and since SHRs also appeared to recover more rapidly than WKYs from the drug-induced behavioural syndrome, we are tempted to speculate that the reduction in body temperature might be secondary to the state of behavioural depression. It has been previously shown that SHRs are more resistant than WKYs to sedative-hypnotic drugs (Czyzewska-Szafran et al 1979; Czyzewska-Szafran & Wutkiewicz 1980). It is plausible that the reduced hypothermic effect of MK-212 in SHRs is a manifestation of the reduced susceptibility of this strain to centrally acting depressant drugs. On the other hand, a hyperfunction of brain 5-hydroxytryptaminergic systems in the SHR has been demonstrated (Rosecrans & Adams 1976; Nagaoka & Lovenberg 1977). Since 5-hydroxytryptamine plays an important, albeit complex, role in control of body temperature (Myers 1981), an alternative explanation of our findings might be that the reduced hypothermic effect of MK-212 in SHRs is associated with an alteration of brain 5-hydroxytryptaminergic receptors in SHRs, as has been shown for dopaminergic (LeFur et al 1983) and opiate mechanisms (Martucci & Hahn 1979). Whether this can be demonstrated as a difference in binding of 5-hydroxytryptaminergic ligands in the brains of WKYs and SHRs remains to be seen.

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