The Acute Effect of Timiperone on the Alpha-MT-Induced Dopamine Fluorescence in Rat Brain

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Received for publication August 17, 1982

Key words: quantitative microfluorimetry — timiperone — haloperidol — dopamine turnover — rat brain

It has been reported that timiperone, a new butyrophenone, 4'-fluoro-4-[4-(2-thioxo-1-benzimidazolynyl) piperidino] butyrophenone, possesses potent antipsychotic activity (Yamasaki et al. 1977; Sato et al. 1978). Tachizawa and co-workers (1979), using a[^H]-spiroperidol binding assay, showed that timiperone inhibited specific[^H]-spiroperidol binding in vitro at low concentrations similarly to spiroperidol and was 5 times as potent as haloperidol. In the present fluorescent histochemical investigation, we studied on the effect of timiperone on rat central dopaminergic systems in comparison with that of haloperidol by means of formaldehyde-induced fluorescence microscopy (Falck et al. 1962) and quantitative microfluorimetry (Jonsson, 1971).

The Wistar strain male rats (200-300 g) were used. Timiperone (0.1 mg/kg - 0.4 mg/kg) and haloperidol (0.5 mg/kg - 2.0 mg/kg) were orally given to rats 5 h. before decapitation and DL-alpha-methyl-paratyrosine (alpha-MT, 250 mg/kg) was injected i.p. 1 h. after the drug administration. Control rats were treated with 0.3 % C.M.C (1 ml/kg) and alpha-MT in the same way as the neuroleptics treated rats. The brains were immediately frozen in isopentane cooled with liquid nitrogen, freeze-dried and treated with formaldehyde gas in accordance with the specific method for cellular demonstration of biogenic monoamines described by Falck and Hillarp (Falck et al. 1962). The formaldehyde gas treatment was performed at 80°C for 1 h. using paraformaldehyde equilibrated at 75% relative humidity. The specimens were embedded in paraffin. The frontal sections including the following three dopaminergic terminals [1. n. caudatus putamen, 2. n. accumbens and 3. median eminence (lateral palisade zone)] were made according to the atlas of König and Klippel (König and Klippel, 1963). A Zeiss fluorescence microscope (MPM01 system), with a 100 W high pressure mercury lamp, a BP 405/8 exciter filter, a FT 425 dichroic mirror and a LP 450 barrier filter, was employed for the quantitative measurement of the dopamine fluorescence intensity. The signal of the photomultiplier was led into a digital voltmeter for the recording of the fluorescence. Fluorescence was measured in 50 circular areas in the above mentioned regions. Background fluorescence was obtained by measuring tissue fluorescence in the region of the anterior commissure and the ventromedial nucleus which showed no specific fluorescence. Net dopamine fluorescence was obtained by subtraction of background fluorescence. Results were analysed by Student’s t-test.

Fig. 1 shows effects of timiperone and haloperidol on the alpha-MT-induced dopa-
Fig. 1. Effects of timiperone and haloperidol on the alpha-MT-induced dopamine fluorescence disappearance in the n. caudatus putamen. Note that the reduction in the dopamine fluorescence intensity was not found after administration of 0.1 mg/kg of timiperone.

Dopamine fluorescence disappearance in the n. caudatus putamen. The reduction of the dopamine fluorescence intensity was not observed after administration of 0.1 mg/kg of timiperone. Timiperone in a dose of 0.4 mg/kg, however, caused a significant increase in the dopamine turnover (61.10 ± 7.65%). The dopamine fluorescence intensities in haloperidol (0.5 mg/kg and 2.0 mg/kg)-treated rats were 76.32 ± 4.73% (P < 0.05) and 73.97 ± 11.23%, respectively. Effects of timiperone and haloperidol on the alpha-MT induced dopamine fluorescence disappearance in the n. accumbens have been shown in Fig. 2. Timiperone treatment resulted in a marked increase in the dopamine turnover. The dopamine fluorescence intensities in timiperone (0.1 mg/kg and 0.4 mg/kg)-treated rats were 66.14 ± 5.22% (P < 0.05) and 51.08 ± 5.18% (P < 0.01), respectively. These were similar to those in haloperidol-treated rats. On the other hand, acute treatment with timiperone and haloperidol did not change the dopamine turnover in the median eminence under the present condition (Fig. 3).

The fact that 0.1 mg/kg of timiperone induced the reduction of the dopamine fluorescence in the n. accumbens (not in the n. caudatus putamen) suggests that a small dose of timiperone would suppress...
selectively the dopamine receptors of the meso-limbic system, and supports strongly the experimental data that timiperone possesses potent antipsychotic activity with less likelihood of extrapyramidal adverse reactions (Yamasaki et al. 1977; Sato et al. 1978).

Furthermore, it was histochemically found that timiperone was approximately 5 times as potent as haloperidol in accelerating the meso-limbic dopamine turnover in rat after oral administration of either drug. This supports the recent biochemical finding that the specific $^3$H-spiroperidol binding inhibition due to timiperone was 5 times as potent as haloperidol (Tachizawa et al. 1979).

Acknowledgements: For generous supply of timiperone the authors are indebted to Daiichi Seiyaku Co., Ltd., Tokyo, Japan.

References


