

## EFFECT OF SULPIRIDE ON BODY WEIGHT AFTER CHRONIC ADMINISTRATION IN MALE MICE

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Although some studies indicate that sulpiride (an atypical neuroleptic drug) increases body weight in female rodents after long-term administration, this action is less clear in males. In this study, we examined the effect of three doses of sulpiride (40, 60 or 80 mg/kg, ip) or physiological saline, chronically administered during 9 consecutive days, on body weight in the OF.1 strain of adult male mice. All animals were housed in transparent plastic cages during four weeks (non-drug period) and weighed weekly. During the drug period, sulpiride was administered once daily for 9 days and body weights measured. Results showed that sulpiride did not vary body weight after chronic administration, suggesting that the action of some neuroleptics on body weight might be a sex-dependent phenomenon.

*Efecto de la administración crónica de sulpiride sobre el peso corporal en ratones macho.* Aunque investigaciones recientes han demostrado que el sulpiride (un neuroléptico atípico) incrementa el peso corporal en roedores hembras tras su administración crónica, no existen evidencias claras respecto a su acción en roedores machos. En el presente estudio examinamos el efecto de la administración crónica de tres dosis de sulpiride (40, 60 ó 80 mg/kg, ip), o suero salino, sobre el peso corporal de ratones machos adultos de la cepa OF.1. Todos los ratones fueron aislados en jaulas transparentes durante cuatro semanas (período sin tratamiento) y pesados semanalmente. Durante el período de tratamiento, los animales recibieron una inyección diaria de sulpiride durante 9 días, registrándose también sus pesos. Los resultados indicaron que ninguna de las dosis de sulpiride afectó significativamente el peso de los animales tras su administración crónica, en comparación con el grupo control. Estos resultados sugieren que el efecto de algunos neurolepticos sobre el peso corporal podría ser un fenómeno sexo-dependiente.

The influence of dopamine on feeding behaviour is a well-documented fact. However, while it seems evident that stimulation of D1 receptors produces a decreased body weight in rodents, the role of D2

receptors remains less clear (Ferrari, Pelloni and Giuliani, 1992).

Sulpiride is a substituted benzamide which selectively blocks dopamine D2 receptors (Jenner and Marsden, 1979), also exhibiting a high affinity for D3 receptors (Giros, 1991). Traditionally, it is considered as an atypical neuroleptic drug due to the low frequency of its extrapyramidal side effects and its antidepressant action

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(Gerlach, Behnke, Heltberg, Munk-Anderesen and Nielsen, 1985), being a potent stimulator of prolactin secretion (Kakigi, Maeda, Tanimoto, Kaneda and Shitani, 1992).

Sulpiride shows a wide range of behavioural actions in rodents, such as an antiaggressive specific profile after acute treatment (Redolat, Brain and Simón, 1991; Martín-López, Puigcerver, Vera and Navarro, 1993; Martín-López, Caño and Navarro, 1996), a significant increase in overall movement without any effect on defecation in the open-field test (Bruhwylter, Chleide, Liegeois, Delarge and Mercier, 1990) and catalepsy following intracerebroventricular administration of high doses of the drug (Motohashi, Takashima, Mataga, Nishikawa, Ogawa, Watanabe and Toru, 1992).

It is a well known fact that sulpiride increases body weight and feeding in female rats (Baptista, Parada and Hernández, 1987; Parada, Hernández and Hoebel, 1988; Parada, Hernández, Paez, Baptista, Puig and De Quijada, 1989). In contrast, there are few reports in relation to the effects of chronic administration of sulpiride on body weights in males, and most of these studies have used low doses of the drug. Thus, Baptista et al. (1987) found that chronic administration of sulpiride for 21 days (10 or 20 mg/kg, ip) did not increase body weight in male rats. Likewise, Parada et al. (1989) reported that sulpiride (20 mg/kg), even when the animals were on a high-fat diet, did not change either body weight nor food intake.

This work represents an attempt to study the effect of chronic administration of higher doses of sulpiride (40, 60 or 80 mg/kg, ip) on body weight in male mice.

## Method

### *Animals*

48 OF.1 strain albino male mice aged approximately 42 days (Servicio de Ani-

males de Laboratorio, Granada, Spain) and weighting 25-30 grams in arriving to the laboratory were used. Mice were housed in transparent plastic cages (24 x 13.5 x 13 cm) under standard laboratory conditions: constant temperature (21±20° C), a reversed light schedule (lights on: 01:00-13:00 hrs), normal lab chow (Panlab, Barcelona, Spain) and tap water available "ad libitum".

### *Procedure*

#### NON-DRUG PHASE

Animals, divided into four groups (12 per group), were allowed four weeks to accommodate to the standard laboratory conditions and changes in body weight were weekly measured (at the same hour of the day and once a week) using a digital balance.

#### DRUG TREATMENT PHASE

Sulpiride (Dogmatil®, Delagrangue, Madrid, Spain) was diluted in saline to provide appropriate doses for injection. After four weeks without drug treatment, animals received daily injections of three doses of sulpiride (40, 60 or 80 mg/kg, ip) or physiological saline (control group) for 9 consecutive days, being monitored daily for body weight. As statistical analysis, an ANOVA with repeated measures was used.

## Results

Figure 1 shows the evolution of mean body weight in all groups during non-drug phase. Body weight did not vary significantly in the experimental or control groups during the predrug phase.

Figure 2 illustrates the evolution of mean body weight in all groups during the drug treatment. As can be observed, no significant differences between experimental and control groups were found.

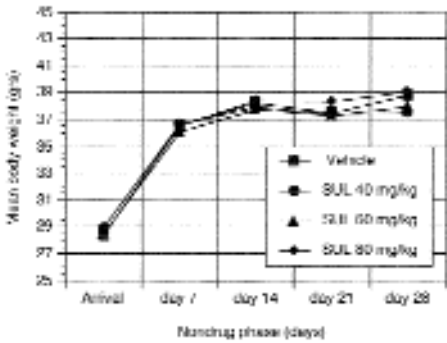


Figura 1. Mean values in the evolution on body weight (in grams) during the nondrug period of all groups.

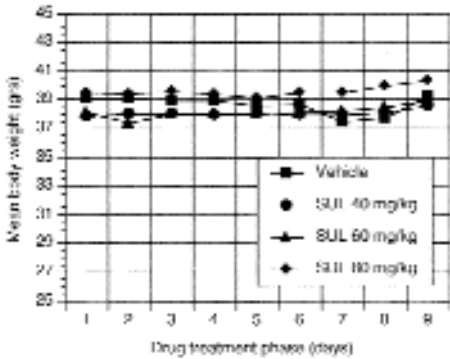


Figura 2. Mean values in the evolution on body weight (in grams) during the drug treatment phase

### Discussion

In this work, chronic treatment with relatively high doses of sulpiride (40, 60, 80

mg/kg) did not change body weights of male mice, supporting previous findings with rats (Baptista et al, 1987; Parada et al, 1988, 1989; Santacana, Sánchez and Muñoz, 1976) and mice (Redolat et al, 1991).

Our results suggest a sex-dependent effect of sulpiride on body weight, so that sulpiride is known to enhance certainly body weight and feeding in female rats. The mechanism by which sulpiride increases body weight in female rodents is relatively well known. Thus, Baptista, Hernández and Hoebel (1990) have indicated that this neuroleptic drug blocks D2 receptors in the lateral hypothalamus involved in satiety. Likewise, sulpiride also appears to block D2 receptors in the pituitary involved in the inhibition of prolactin release. This resulting hyperprolactinemia would cause a functional ovariectomy, which in turn would produce hyperphagia (Baptista, Murzi, Hernández and Burguera, 1991). This sex-dependent effect on body weight has been also reported following administration of other drugs such as lithium (Moore, Gerardo and Stern, 1986).

Summing up, the results indicate that sulpiride chronically administered does not affect weight significantly in male mice, and confirm that the action of some neuroleptic drugs on body weight might be a sex-dependent phenomenon, mediated mainly by blockade of D2 receptors.

### References

Baptista, T., Parada, M. and Hernández, L. (1987). Long-term administration of some antipsychotic drugs increase body weight and feeding in rats. Are D2 dopamine receptors involved?, *Pharmacology Biochemistry & Behavior*, 27, 399-405.

Baptista, T., Hernández, L. and Hoebel, B.G. (1990). Systemic sulpiride increases dopamine metabolites in the lateral hypothalamus, *Pharmacology Biochemistry & Behavior*, 37, 227-229.

Baptista, T., Murzi, E., Hernández, L., Burguera, J.L. and Burguera, M. (1991). Mecha-

- nism of the sex-dependent effect of lithium on body weight in rats, *Pharmacology Biochemistry & Behavior*, *38*, 533-537.
- Bruhwyler, J., Chleide, E., Liegeois, J.F., Delarge, J. and Mercier, M. (1990). Anxiolytic potential of sulpiride, clozapine and derivatives in the open-field test, *Pharmacology Biochemistry & Behavior*, *36*, 57-61.
- Ferrari, F., Pelloni, F. and Giuliani, D. (1992). Effects of the dopamine D2 agonists lisuride and CQ 32-084 on rat feeding behaviour, *Pharmacology Biochemistry & Behavior*, *41*, 683-688.
- Gerlach, J., Behnke, K., Heltberg, J., Munk-Andersen, E. and Nielsen, H. (1985). Sulpiride and haloperidol in schizophrenia. A double-blind cross over study of therapeutic effect, side effects and plasma concentrations, *British Journal of Psychiatry*, *147*, 283-288.
- Giros, B. (1991). Le troisieme recepteur de la dopamine, *Pathologie Biologie*, *39*, 252-254.
- Jenner, P. and Marsden, C.D. (1979). The substituted benzamides. A novel class of dopamine antagonists, *Life Sciences*, *25*, 479-485.
- Kakigi, T., Maeda, K., Tanimoto, K., Kaneda, H. and Shitani, T. (1992). Effect of substituted benzamides on prolactin secretion in the rat, *Biological Psychiatry*, *31*, 827-831.
- Martín-López, M., Puigcerver, A., Vera, F. and Navarro, J.F. (1993). Sulpiride shows an antiaggressive specific effect after acute treatment in male mice, *Medical Science Research*, *21*, 595-596.
- Martín-López, M., Caño, A. and Navarro, J.F. (1996). Effects of high doses of sulpiride on agonistic behavior in male mice, *Psicothema*, *8*, (161-166).
- Moore, B.J., Gerardo-Gettens, B.A. and Stern, J.S. (1986). Hyperprolactinemia stimulates food intake in the female rat, *Brain Research Bulletin*, *17*, 563-569.
- Motohashi, N., Takashima, M., Mataga, N., Nishikawa, T., Ogawa, A., Watanabe, S. and Toru, M. (1992). Effects of sulpiride and oxyperline on the dopaminergic system in the rat striatum, *Neuropsychobiology*, *25*, 29-33.
- Parada, M.A., Hernández, L. and Hoebel, B.G. (1988). Sulpiride injections in the lateral hypothalamus induce feeding and drinking, *Pharmacology Biochemistry & Behavior*, *30*, 917-923.
- Parada, M.A., Hernández, L., Paez, X., Baptista, T., Puig de Parada, M. and De Quijada, M. (1989). Mechanism of the body weight increase induced by systemic sulpiride, *Pharmacology Biochemistry & Behavior*, *33*, 45-50.
- Redolat, R., Brain, P.F. and Simón, V.M. (1991). Sulpiride has an antiaggressive effect in mice without markedly depressing motor activity, *Neuropharmacology*, *72*, 825-852.
- Santacana, M.G., Sánchez, E. and Muñoz, M.C. (1976). Effects of the administration of two doses of sulpiride on the behaviour of the rat, *Neuropharmacology*, *15*, 415-420.

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