**Short communication**

# Effect of Long-term Administration of Stobadine to Rats on Selective Variables of Spontaneous Behaviour of their Offspring

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**Abstract.** The present study investigated the effect of long-term administration of the cardioprotective drug stobadine (STB) to dams on selective variables of spontaneous behaviour of their offspring in open field (horizontal and vertical activities, frequency and duration of grooming, and duration of total activity and immobility) tested on day 60 of age. The treatment of dams with STB significantly increased horizontal activity of offspring in both sexes. The other variables studied were not affected, with the exception of a significant increase in the frequency and duration of grooming and in the duration of total activity in females compared to males from STB treated dams.

**Key words:** Stobadine — Spontaneous behaviour — Rat — Offspring

Stobadine, (-)-cis-2,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido [4,3-b] indole, CAS 95751-51-2, STB, (Chemical Abstracts 1987) is an effective cardioprotective drug with antiarrhythmic (Štolc et al. 1983) and antihypoxic effects on the myocardium (Styk et al. 1986) and the central nervous system (Štolc and Horáková 1988). It is derived from the $\gamma$-carboline antidepressant and neuroleptic drug Carbidine® (Barkov 1973) as its active (-)-enantiomer. Results of our previous experiments in rats (Dubovický et al. 1994) indicated that long-term administration of STB to dams induced alterations both in their exploratory behaviour and in that of their offspring. In the light of these findings we decided to determine selected variables of spontaneous behaviour of their offspring in a more comprehensive approach.

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*Animals:* Rats (SPF Wistar strain) from the breeding facility IEF SAS Dobrá Voda, Slovakia were used. The animals were kept under controlled conditions at 22 °C ± 2 °C and 55 ± 5% relative humidity. The colony rooms were exposed to natural photoperiod. Food and tap water were available ad libitum.
*Drug:* STB in the form of dipalmitate salt DP 1031 (m.w. 715.2, 99.5% purity) was synthesised at the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague. The chemicophysical properties of this salt and its chemical purity were described earlier (Beneš and Štolc 1989).
*Experimental procedure:* The dams (10 animals) were treated daily by oral gavage with DP 1031 at the dose of 50 mg/kg dissolved in 0.5% Methocell suspension (MC 4000 cP, Fluka, AG, Busch SG, Switzerland) at a constant dosage volume of 0.5 ml/100g body weight over 14 days before mating, and during the gestation and lactation (up to weaning of pups on day 21 post partum – pp). The dose employed represented 10 times the anticipated maximum daily oral human therapeutic dose. The control group (10 animals) received as vehicle 0.5% Methocell suspension over the same time interval.
*Behavioural testing:* From each dam two pups were taken (one male and one female) and tested on day 60 pp. Selective variables of the spontaneous behaviour – horizontal (horizontal movement of the rat) and vertical (rearing, both forepaws lifted off the floor) activities, frequency and duration of grooming and duration of total activity (horizontal, vertical and grooming) and immobility (total lack of movement) were observed in an open field test. The horizontal and vertical activities were recorded by an electronic apparatus IMAK 48 (developed in the Department of Psychology, Philosophical Faculty, Comenius University, Bratislava, Slovakia), the walls of which contained photocells – 32 infraemitters and 32 infrareceptors, 45 mm above the floor of the experimental box for the recording of horizontal activity, and 16 infraemitters and 16 infrareceptors, 125 mm above the floor for vertical exploratory activity recording (Jurišová et al. 1993). The pup was placed in the centre of the experimental box, sized 42 × 42 cm, constructed of transparent glass. Simultaneously with this testing the other activities in open field (grooming, total activity and immobility) were recorded by a videocamera. All animals were tested in a 6-min session once daily for four consecutive days in the same daytime period between 8.00–12.00 a.m
*Statistical evaluation:* The significance of differences between the values of the control and the DP 1031 groups as well as between males and females was done by Student's $t$-test ($P \leq 0.05$) The number of animals in each group was 10. Values are expressed as mean ± S.E.M.

The horizontal activity of the offspring was significantly increased in both sexes compared to control groups (Fig. 1). Vertical and total activities, grooming and immobility were not significantly influenced in comparison with the controls (data not shown). Chronic treatment of dams with DP 1031 caused a non-significant

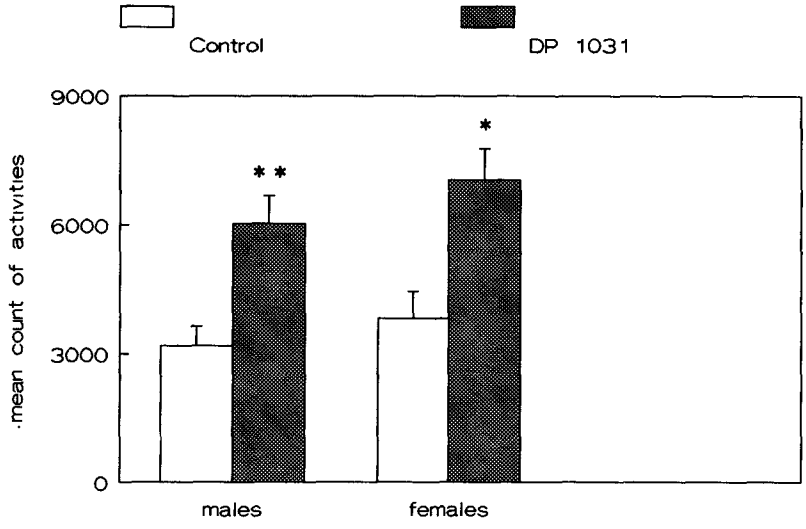


**Figure 1.** Horizontal activity in offspring of dams treated with DP 1031. $^{*}p \leq 0.01$, $^{**}p \leq 0.002$

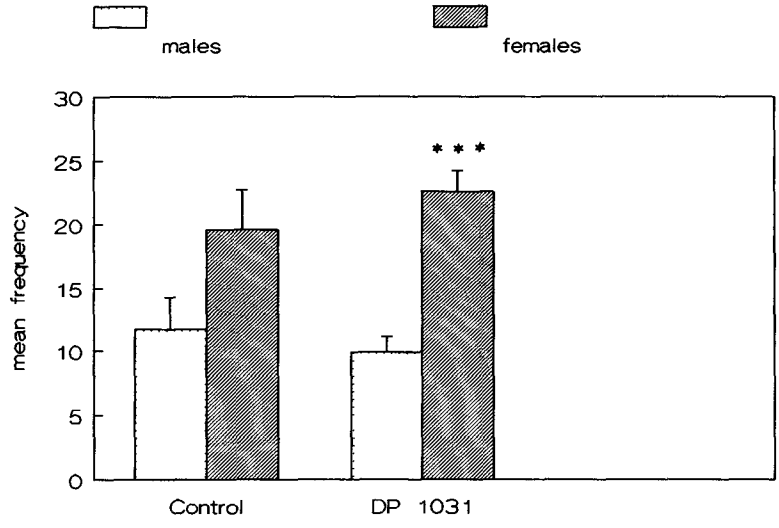


**Figure 2.** Frequency of grooming in offspring of dams treated with DP 1031. $^{***}p \leq 0.001$

decrease of grooming activities in male and an increase in female offspring. It finally resulted in significant intersexual differences in these activities as well as in the

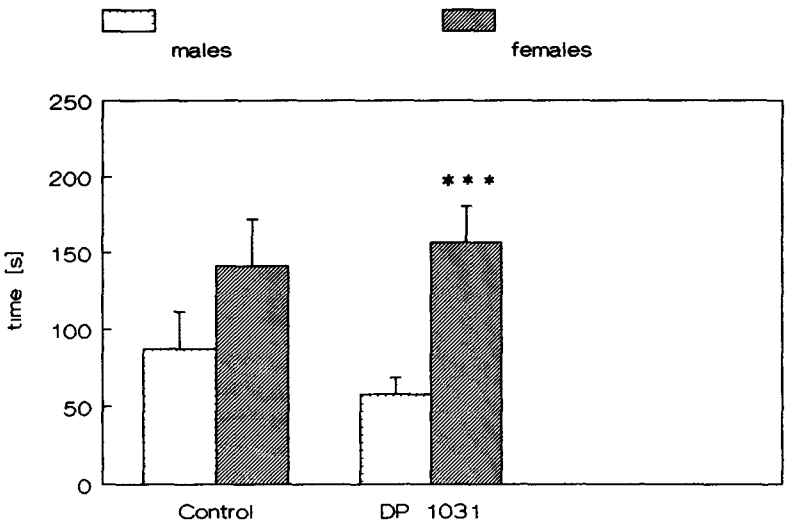


**Figure 3.** Duration of grooming in offspring of dams treated with DP 1031. $***p \leq 0.001$

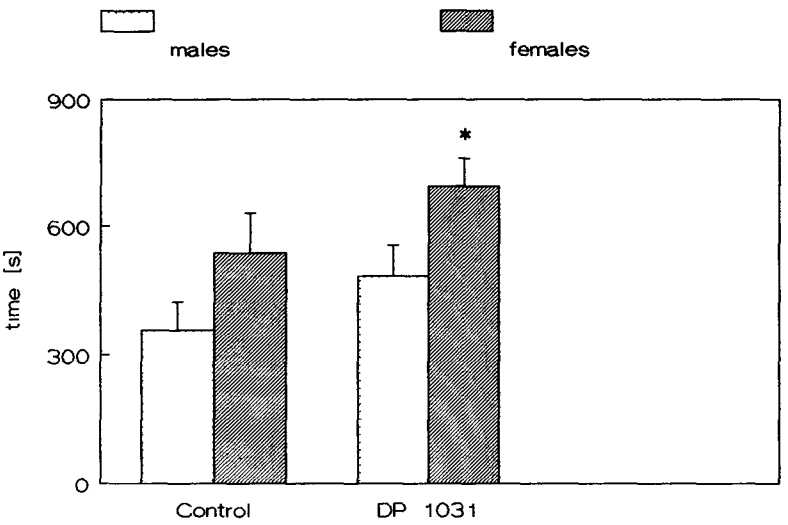


**Figure 4.** Duration of total activity in offspring of dams treated with DP 1031. $*p \leq 0.05$

duration of total activity in the DP 1031 groups (Fig. 2, 3 and 4).

Spontaneous behaviour is a natural activity of animals and a common indicator of their arousal state. It consists of a number of acts and postures (Hliňák et

al. 1990). Our study revealed that long-term administration of DP 1031 to dams increased the horizontal activity of their offspring of both sexes, and underlined the intersexual differences in grooming activities and in the duration of total activity. In contrast to our investigation, Mock et al. (1993) in a behavioural and teratological study of DP 1031 (50 mg/kg) in rats observed increased horizontal activity only in the male offspring of mothers treated with DP 1031 (6–15, 6–20 days of gestation). This discrepancy may be explained by the different methodological approaches (different timing of treatment and different schedules of open field testing). The fact that DP 1031 can induce (though non-significantly) both a decrease and an increase of grooming activities appears to be contradictory. These results however contributed to the knowledge that some variable changes of spontaneous behaviour and characteristics of these changes are sex dependent (Mullenix et al. 1983).

Long-term administration of DP 1031 to dams resulted in increased horizontal activity of their offspring in both sexes and increased the frequency and the duration of grooming as well as the duration of total activity in females compared to males.

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