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Effects of Antidepressant Drug on Sexual Behavior and Fitness Parameters of *Drosophila ananassae*

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Abstract: *Drosophila* is a suitable model organism in the field of toxicological science. The objective of this study was to explore the potential of doxepin, an antidepressant drug, on sexual behavior and fitness of *Drosophila ananassae*. Sexual behavior such as mating latency and copulation duration was higher as concentration of antidepressant increases in both larval and adult feeding methods, decrease in the fecundity and fertility was also observed in adult feeding than larval feeding methods. According to the Chi-Square, the percentage of the hatchability is decreased in treated compared with one control and significant difference in viability in adult feeding method. Our findings show the adult one which are exposed are more sensitive comparatively with larval stage. It was also noticed that antidepressant effects some behavioral aspects of *Drosophila*.

Keywords: Mating, Fecundity, Fertility, Hatchability, Viability.

1. Introduction

Everyone occasionally feels blue or sad, but these fleeting pass within a couple of days. When a person has a depressive disorder it interfaces with daily life, normal functioning and causes pain for both the person with the disorder and those who care about him or her (Baldwin, 2001). Major depressive disorder, also called major depression is characterized by a combination of symptoms which adversely affects a person's family, work or school life, sleeping, eating habits and general health (Hadzi-Pavlovic, 2000). Major depression is disability and prevents a person from functioning normally. An episode of major depression may occur only once in a person's lifetime, but more often, it recurs throughout a person's lifetime.

Antidepressants form one class of drugs administrated against depression. There are two most common groups of Antidepressants available today and they are:

- Tricyclic Antidepressants
- SSRI's (Selective Serotonin Receptive Inhibitors).

Antidepressant drugs are currently the mainstay of treatment for all but the mildest forms of depression. Their effectiveness in the management of depressive illness is undisputed and their effectiveness in preventing suicide, while not proven, may be assumed (Henry, 1997). Nevertheless of all the drugs that are taken with lethal overdose antidepressants are the most common. Epidemiological studies from several countries have provided evidence of marked differences in overdose toxicity between drug classes and in some cases between individual drugs within a class. However, use of antidepressant in high concentration may be associated with cellular toxicity (Strumper *et al*., 2003). A fatal toxicity index (death per million: National Health Service prescriptions) was calculated for antidepressant drugs on sale during the years 1975-84 in England (Wales & Scotland). The tricyclic drugs introduced before 1970 had a higher index than the mean for all drugs studied (Cassidy & Henry, 1987).

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The anticholinergic effects of tricyclic drugs are a major drawback and the risk of interactions limits the usefulness of monoamine oxidase inhibitors (MAOIs). Generally, newer drugs include doxepin have a more favorable adverse effect profile. Although a number of drugs produce rare but serious adverse effects, overdose toxicity is a matter of greater importance especially in patients who are at risk of suicide. Toxicity indices, calculated from the number of deaths per million prescriptions for each drug enable comparisons between drugs to be made. These show that several of the older tricyclic drugs have relatively high mortality in overdose. Many of the new drugs including doxepin and fluoxetine have a good record of safety in overdose and the forms an important part of their risk-benefit profile (Henry, 1992). There are a few reports on the side effects of antidepressant drugs (Rao & Rao, 1980) conducted studies in mutagenic effects of fluphenazine hydrochloride in *D. melanogaster* (Van Schaik & Graf, 1991 & 1993) conducted studies of five tricyclic antidepressants and recommended the wing somatic mutations and recombination test of *D. melanogaster* for evaluation of mutagenicity and genotoxicity of these drugs. Further, they have also studied the structure activity relationship of tricyclic antidepressant and related compounds in *D. melanogaster* (Henry, 1992) conducted a study on the toxicity of antidepressant and compared with fluoxetine. Although, the survey of literature shows that antidepressant have side effects and no efforts have been made to analyze their effect on mating behavior and fitness in *Drosophila* or its toxicity in any test system. *Drosophila* is best suitable organism to screen some drugs. *D. ananassae* belongs to *D. melanogaster* species group and found along with human habitation. Here, the author has tried to study the effect of mating behavior and reproductive fitness in *Drosophila.*

2. Materials and Methods

To study the effect of toxicity of doxepin antidepressant drugs on some parameters of *D. ananassae* flies were obtained from the *Drosophila* stock center, Mysore was used. The pure culture of these flies was maintained under standard food medium (Hedge *et al.*, 2001).

Doxepin is an antidepressant drug belonging to tricyclic group. It is chemically called (*E,Z*)-3-(dibenzo[*b,e*]oxepin-*N,N*-dimethylpropan-1-amine. Its molecular formula is $C_{19}H_{21}NO$ with a molecular weight of 279.376g/mol. The drug is freely soluble in water, chloroform and alcohol. In order to fix the concentration for the study of antidepressant LC_{50} of doxepin for the larval feeding and adult feeding methods were estimated (0.28% and 2.84% for food media, respectively) by using log-dose/probit. Then, sublethal concentrations of 0.05% (500 ppm), 0.1% (1000 ppm) and 0.2% (2000 ppm) of doxepin for larval feeding and also 0.5% (5000 ppm), 1% (10000 ppm) and 2% (20000 ppm) concentrations of doxepin for adult feeding methods were selected. For this study, eggs of the same age ± 3 hours collected by procedure of Delcour (1969) were placed in vials containing normal medium at a density of 25 eggs per vial.

To study, the effect of doxepin an antidepressant drug in larval and adult feeding methods, different concentrations of the drug were thoroughly mixed with wheat cream agar medium. In larval feeding technique, newly hatched larvae were continuously fed on food medium supplemented with different concentration (above mention concentration). Virgin females and bachelor males emerged from the normal and treated media were isolated under ether anesthesia within 3 hrs of eclosion and maintained them separately in normal media for 5 days. In adult feeding technique, virgin females and bachelor males emerged from the normal media were isolated under ether anesthesia within 3 hours of eclosion and maintained them separately in normal media for 3 days and then transferred separately to treated media of different concentrations and fed for 2 days (48 hrs). Thus, they were aged for 5 days. These flies were used to study some sexual behavior (Hedge & Krishnamurthy, 1979; Hedge & Krishna, 1997; Speith, 1966) such as mating latency and copulation duration.

For observation of sexual behavior a virgin female and bachelor male of *D. ananassae* were introduced into an Elens-Wattiaux mating chamber (5cm x 5cm circular glass chamber with a lid to facilitate easy observation) according to Hedge and Krishna (1997) because maximum mating occurs during morning hours, observation was made between 7 and 11 a.m. Sexual behavioral acts such as courtship latency (time between introduction of male and female together into mating chamber and orientation of male towards female) mating latency (time between introduction of males and females into mating chamber and initiation of copulation of each pair), copulation duration (time between initiation and termination of copulation of each pair) were recorded. A minimum of 25 pairs involving each isofemale line was observed.

Fitness parameters such as fecundity, hatchability, fertility and viability were analyzed for fecundity, virgin females and bachelor males aged for 5 days were pairs mated. The single mated females was then transferred to vials containing normal food media and were allowed to lay eggs for 24 hours. After 24 hours, the flies were individually transferred to a fresh vial containing food media. The number of eggs laid during the following ten days was scored for both control and treated groups. Ten replicates were maintained for each of the concentrations and control under study. The egg hatchability was also measured by counting the number of the eggs hatched after 48 hours from the pair mated. The fertility of treated groups and control was measured by counting the number of the progeny produced by a

single mated female. For testing fertility, each mated female was kept in an individual food vial for a period of one day and then transferred to a fresh food vial every day. Ten successive changes were made and the total number of flies that emerged from each vial was counted. Ten replicates were maintained for each of the concentrations and control under study. Data were pooled and the mean number of flies per female was calculated. To study the viability (survival value) the number of flies emerged out of each vial are recorded every day until the last day of emergence. One way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) and Chi-Square Test was applied for all parameters using SPSS 10.5 software.

3. Results

Effect of doxepin on sexual behavior of *D. ananassae* in control and sublethal concentrations in both the larval and adult feeding methods is shown in Table 1.

Table 1. Effect of doxepin on sexual behavior in *D. ananassae* (Values are representing mean duration in minutes and their standard errors).

	Parameters / concentrations	Mating latency	Copulation duration
Larval Feeding	Control	13.40 ± 1.60	18.60 ± 0.75
	0.05%	20.90 ± 5.89	20.40 ± 0.60
	0.1%	23.40 ± 4.98	21.10 ± 0.92
	0.2%	24.10 ± 3.59	24.40 ± 0.92
	F value	4.219*	4.122*
Adult Feeding	Control	10.50 ± 1.69	24.90 ± 0.71
	0.5%	13.40 ± 2.20	28.40 ± 0.81
	1%	16.45 ± 2.60	29.10 ± 0.86
	2%	22.15 ± 3.47	31.40 ± 0.81
	F value	4.761*	8.240*

*Mean difference is significant at 0.05 levels according to ANOVA.

Mean mating latency and copulation duration in both feeding methods was increased, when compared to control. The maximum mating latency (24.10 ± 3.59; larval feeding 22.15 ± 3.47; adult feeding) and copulation duration (24.40 ± 0.92; larval feeding, 31.40 ± 0.81 adults feeding) was observed in highest concentration and proportionately increased with increased concentration. Shortest sexual behavior was observed in the control. There was significant difference in various concentrations and control in both methods (copulation duration F= 4.219, 4.761; mating latency; F=4.122, 8.240; copulation duration, P<0.05).

In the larval feeding method (Table 2), fecundity in all concentrations was increased compared to control (122.10 ± 6.3 eggs per female) and highest fecundity was found in 0.05% concentration (191.21 ± 12.1 eggs per female). On the contrary, in adult feeding method (Table 2), fecundity decreased with increasing concentration (2% = 36.15 ± 5.15 eggs per female). ANOVA depicts that in both feeding methods fecundity was significant compared to control (F= 79.533 larval feeding and F= 15.203 adults feeding; P<0.05). Table 2 also shows the fertility, here the same trend is continued like fecundity in both larval feeding methods highest fertility was counted at 0.05% (156.8 ± 0.60 adults per female) compare with control (120.6 ± 5.37 adults per female F= 67.731; P<0.05).

Table 2. Effect of doxepin on toxicity in *D. ananassae* (values are represented mean and their standard errors).

	Parameters / concentrations	Fecundity Eggs/female	Fertility Adults/female
Larval Feeding	Control	122.10 ± 6.3	120.6± 5.37
	0.05%	191.21 ± 12.1	156.8 ± 0.60
	0.1%	180.20 ± 12.7	146.4 ± 0.92
	0.2%	126.13 ± 5.2	90.00± 0.92
	F value	79.533*	67.731*
Adult Feeding	Control	119.20 ± 4.2	102.90 ± 5.20
	0.5%	63.40 ± 11.14	28.40 ± 5.05
	1%	61.60 ± 12.60	26.10 ± 7.86
	2%	36.15 ± 5.15	22.40 ± 0.81
	F value	15.203*	13.665*

*Mean difference is significant at 0.05 levels according to ANOVA.

In adult feeding methods this is opposite, where the fertility decreased with increase in concentration (Control = 102.90 ± 5.20; 0.5%=28.40 ± 5.05; 1%=26.10 ± 7.86; 2%=22.40 ± 0.81) and significant difference between treated one and control (F=13.665; P<0.05).

Table 3 incorporates the results of the effect of doxepin on egg hatchability of. In control groups of the both larval and adult feeding methods hatching is 96% and 95% respectively. Hatching was reduced to 90.1% and 90.4% in the highest concentration in both feeding methods respectively. Hatching was highest in 0.1% (97.4%) concentration in larval feeding methods, which was even more than that of control. The total number of the eggs laid is more in control compared to other concentration (Fig. 1).

Chi-Square test for both larval and adult feeding shows that there was non-significant difference in hatching between control and treated batches. In other words, hatching was unaffected by the treatment of doxepin either by larval or adult feeding methods. Data obtained in Table 3 also shows the effect of doxepin on viability in various concentrations in both larval and adult feeding methods. Viability in the control group is higher compared to different concentration (Fig. 2). In larval feeding, method viability was 90.5% and in adult feeding, it was 85.4%. Viability decreased in all concentrations of all treated groups for both the feeding techniques. However, lowest percent of viabilities in larval feeding were 71% (0.2% in larval feeding method) and 44.2% (0.5% in adult feeding method). The difference in viability between control and different concentrations compared statistically significant (P <0.05) in adult feeding to the larval feeding method according to the Chi-Square.

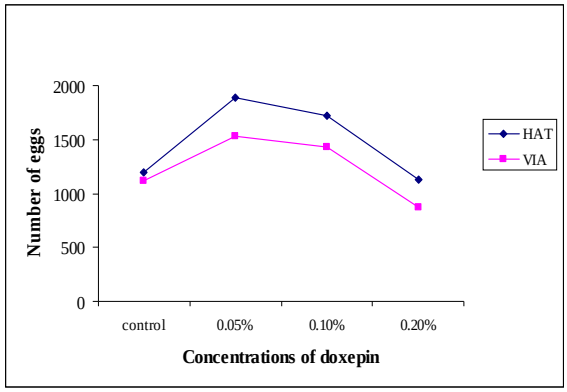

Fig. 1. Effect of doxepin during larval feeding on Hatchability (HAT) and Viability (VIA) of *Drosophila ananassae*.

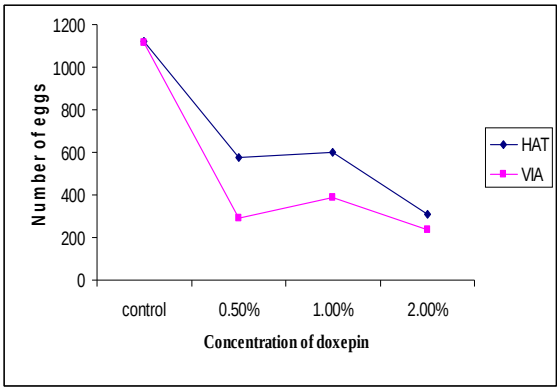

Fig. 2. Effect of doxepin during adult feeding on Hatchability (HAT) and Viability (VIA) of *Drosophila ananassae*.

Table 3. Effect of doxepin on toxicity of *D. ananassae* on Hatchability and Viability.

	Parameters / concentrations	Total eggs laid	Hatching (%)	λ^2 for hatching	Viability	λ^2 for Viability
	Control	1238	1200 (96%)		1122 (90.5%)	
Larval	0.05%	1935	1886(97.4%)	0.012	1528 (79.1%)	6.231
Feeding	0.1%	1826	1718(94.1%)	0.316	1426(78.0)	7.311
	0.2%	1245	1128(90.1%)	1.381	875 (71.0%)	18.621
	Control	1177	1121(95%)		1115 (85.4%)	
Adult	0.5%	660	574(87.1%)	1.556	289 (44.2%)	68.403*
Feeding	1%	640	598(93.4%)	0.138	390(61.2%)	22.001
	2%	335	309(90.4%)	0.169	235(69.3%)	5.041*

*significant by λ^2 test at the 5% level, when compared to control

4. Discussion

Sexually reproducing animals are endowed with special features, first to produce fertile offspring and second to adapt to a particular environment. The reproduction is preceded by a series of courtship acts wherein males and females show unique rituals to attract each other, mate and produce the offspring. The courtship and mating although are genetic, are also influenced by various factors acoustic, visual, chemical and tactile signals that culminate in copulation (Ewing, 1983; Speith & Ringo, 1983; Tomaru *et al.*, 1998). Such signals are also species specific and carry information about species, gender or receptivity (Guruprasad & Hegde, 2009). This behavior not only is influenced by the mutual stimuli and response generated by courting individuals but also by the environmental factors (Guruprasad & Hegde, 2008). In the present study, an effort is made to study the effect of doxepin (antidepressant drug) on the mating behavior of *D. ananassae*.

The present observation of sexual behavior of *D. ananassae* control and treated batches of flies agrees with the pattern described by (Speith, 1966). The mating latency indicates both vigors of male's receptivity of females. It is the time required for both the sex to initiate copulation. Higher the vigor of males and receptivity of females, the shorter is the mating latency. During this period, courtship acts are performed mostly by males, to increase receptivity of females and to make her sexually excited (Speith, 1968). A male with high vigor has to perform a same courtship act number of times to a non-receptive female than to a receptive female. In the present studies, there was a sharp increase in mating latency in different concentration of doxepin drug (Table 1) Indicating that this antidepressant drug affects the vigor of males and or receptivity of females.

Mating latency is a prerequisite for copulation in *D. ananassae* (Hegde & Krishna, 1997; Guruprasad *et al*., 2008, 2009; Speiss, 1970). It is quite natural that copulation is severely affected when courtship activity is affected. During copulation sperms from the male is transferred to the female reproductive tract and therefore the duration of copulation has a lot of significance in an animal's life (Speith, 1978). Perusal of Table 1 shows that copulation duration of *D. ananassae* in both feeding methods was affected by different concentration of doxepin with significant difference (DMRT and ANOVA). Copulation duration is very high as concentration increases. Interestingly this is high in the adult diet compare to larval feeding although there is no study which shows the effect of drugs or other chemicals on the vigor of males and receptivity of females. This is very similar to findings of Dithane M-45 a pesticide increase the mating latency and copulation duration of *D. melanogaster* (Vasudev & Krishnamurthy, 2002).

Viability (survival values) is one of the adoptive traits of any population and determines the rate of

increases or decrease of population in an environment. Therefore, it is one of the fitness parameters, which could be used to analyze the toxicity of any drug or chemical. Any change in viability reflects the somatic effect induced by them (Luning, 1966) provided the analysis is made in a uniform environment. Environmental factors which would affect the viability mainly include such as temperature, food, space and population density (Andrewantha & Birch, 1954). In the present experiment, temperature and space were uniform for both control and treated batches. Same number of eggs were allotted to vials, same strain of flies were used in the experiment, thus leaving the food medium supplemented with antidepressant drugs.

In *Drosophila*, the fecundity remains one of the less known quantitative traits. Along with fecundity, fertility, hatchability and viability are fitness parameters. Estimation of fecundity and fertility is important in routine toxicology testing of various chemicals. This gives an insight into the extent of effect on ovarioles and physiological factors, which is expressed in the terms of egg and offspring production. Table 2 reveals that mean fecundity eggs/female in the larval feeding methods was more than control this is completely reversed in case of adult feeding methods. According to ANOVA and DMRT have shown that increased fecundity in larval feeding and decreased in adult feeding were significant ($P<0.05$). This indicates that the mode of administration is also important factor, which one should consider while assessing the effect of any chemical on any biological system.

In the present study, fecundity is more in larval compared to the adult feeding method. This is due to larva has undifferentiated ovary. Perhaps antidepressant enhances the capacity of egg production when they develop into adults. When the larva develops into adults, the effect of the drug would vanish hence lay more eggs. In contrast to this in adult feeding, the decrease in fecundity may be accounted for the fact that the flies are under the influence of drugs, hence they might not have been able to lay eggs rather than producing less egg. This finding agrees with the observation of (Gruwes *et al*., 1971) where they noticed oviposition rhythm in *D. melanogaster* (Vogel, 1972) has demonstrated that certain aziridine analogous have a discernible effect on fecundity in *Drosophila*. Table 2 also shows mean fertility per female in the adult diet with doxepin was seriously impaired at all concentrations, and they were less fertile than control, compared to larval diet ($P<0.05$ by ANOVA and DMRT). Several workers have made studies on the effect of different chemicals on fertility in *D. melanogaster* (Nazir *et al*., 2001; Twinkle *et al.*, 2003; Vasudeva & Krishnamurthy, 1983). The present study of the author agrees with them.

Egg hatchability in control and treated in doxepin is given in Table 3. The date was insignificant ($P<0.05$, λ^2 test). It is possible that the chemicals have not affected the hatching of *D. ananassae* in all treated versus control, by larval and adult feeding methods. This is also observed in the Fig. 1. Viability (survival values) is one of the adoptive traits of any population and determines the rate of increases or decrease of population in an environment. Any change in viability reflects the somatic effect induced by them (Luning, 1966) provided the analysis is made in a uniform environment. Environmental factors which would affect the viability mainly include such as temperature, food, space and population density (Andrewantha and Birch, 1954). Viability of *D. ananassae* in both the feeding methods is shown in Table 3 in controls viability was very high, comparable to treat one. On the other hand in adult feeding method viability was seriously reduced compared to the larva, which is depleted in Fig. 2 and Table 3. There is the significant difference in adult feeding ($P<0.05$, λ^2 test) in 0.5% and 2% concentration in control versus treated one, this agrees the earlier work of (Nagabhushana, 2002; Shabhana *et al*., 1999).

5. Conclusion

Thus, it can be concluded from the above discussion that doxepin antidepressant drug have affected the mating behavior and fitness parameters of *D. ananassae* in both larval and adult feeding methods. Some parameters such as fecundity, fertility, total eggs laid hatching and viability are more affected in the adult feeding effect than larval feeding effect.

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