Endosulfan Induced Polydypsia In Adult Wistar Rats
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Abstract
The effect of Endosulfan on water and food intake of adult wistar rats was studied. Endosulfan, an organochlorine insecticide from the cyclodiene group was administered daily and orally to male and female albino wistar rats. Different doses of Endosulfan 0.2, 5 and 10mg/kg body weight were given to different groups for twenty eight (28) days. For the control group, n-saline was administered. Measured amount of water and food were given to all the dose groups four hourly daily. At each end of the four hours, volume of water and weight of food taken were measured and calculated in all the dose groups. There was an increase in water consumption dose dependently in the treated groups when compared with the control for the twenty eight days of the study. The groups administered with 5 and 10mg Endosulfan/kg elicited a statistically significant (P<0.05) increase in water consumption in the third and fourth weeks of the study. For the food intake, a dose dependent decrease was elicited by Endosulfan. The result for the water and food intake indicate alteration in the hypothalamus. The pesticide, Endosulfan may have induced polydypsia through central or nephrogenic mechanisms by stimulating the paraventricular nucleus in the hypothalamus to release Arginine vasopressin (AVP). Similarly, decrease in food intake may have occurred through the Ventromedial nucleus of the hypothalamus.

INTRODUCTION
Polydypsia has been shown to represent a compensatory mechanism in order to maintain total body fluids within normal limits (Johan, 2008). Most disorders of water balance are due to the inability of the kidney to conserve water because of the anti-diuretic hormone, AVP deficiency or renal insensitivity to AVP. Primary polydypsia, causes certain behavioral or neurological disorders with prolonged intake of large amounts of water resulting in renal medullary washout and the production of large amounts of dilute solute-free urine (1). It has been reported that the stimulation of the paraventricular nucleus (PVN) in the hypothalamus causes the release of AVP (Bisset et al, 1967). Hypothalamus participates in the control of appetite with the lateral nuclei serving as the feeding centre. When this feeding centre is stimulated hyperphagia occurs and when destroyed causes lack of appetite and progressive inanition, a condition characterized by loss of weight, decreased metabolism and muscle weakness (Guyton and Hall, 2006).

Endosulfan, an organochlorine insecticide with contact and stomach action has been in world-wide use since its introduction in the 1950's. (Maier-Bode, 1968). It is used in the control of sucking, checking, and boring insects and mites on a wide range of crops and also as a wood preservative (Anon, 1984). In the last two decades, many countries have recognized the hazards of wide application of this pesticide and have banned or restricted its use (Anon, 2003). Food is the major source of toxicity to the general populace. Cases of poisoning due to consumption of Endosulfan-contaminated food have been reported in Nigeria. After laboratory investigation in May, 2008 by National Agency for Food, Drug and Administration Control (NAFDAC), it was reported that Endosulfan was among the pesticides that caused food poisoning in Bekwarra Local Government Area (LGA) of Cross River State where 112 people were hospitalised and two children died after eating contaminated moi-moi and beans. Also in Doma, Gombe State, 120 students were hospitalised after consuming a meal of beans suspected to have been preserved with poisonous chemicals (Inalegwu, 2008). Fish from India, (Anon, 2002a) Kenya and Nigeria were heavily contaminated with Endosulfan (Anon, 2003b). There is experimental evidence that Endosulfan exposure in male children may delay sexual maturity and interfere with sex hormone synthesis (Saiyed et al, 2003). It directly affects the central nervous system, causes liver and kidney (chronic glumerulonephrosis) damage in rats and mice. It also impairs the reproductory system of rats (Dalsenti et al. 1999). Endosulfan is a proven endocrine disruptor (Soto et al, 1994) and has potential to
Endosulfan Induced Polydypsia In Adult Wistar Rats

induce hypothyroidism (Anon, 2001).

The effects of pesticides on non target organisms and the environment have been a source of world wide concern for more than a decade (Ware, 1983) even in Nigeria where it is been used to preserve beans. Therefore in this paper, the effect of Endosulfan on the drinking and eating pattern of laboratory animals was investigated.

MATERIALS AND METHODS

CHEMICALS

Emulsified concentrate of Endosulfan was purchased from Jubaili Agrotech in Kano Nigeria. Normal saline obtained from May and Baker Nigeria limited.

ANIMALS

Adult male and female wistar rats weighing between 170 – 270g obtained from the Animal house, Faculty of Pharmaceutical Sciences, Ahmadu Bello University Zaria, Nigeria were used for the study. All the animals were housed in separate, sawdust bedded plastic cages (55cm x 33.5cm x 20cm) in a well ventilated laboratory observed for one week prior to the study. The temperature of the laboratory was about 33°C and 12 – 12hr light and dark cycle. They were fed with standard rat feed and given water ad-libitum except when fasting was needed during the period of the study. On attainment of stable water and food baselines by all the groups, dosing of the animals with Endosulfan commenced. Moribund animals were not used in this study. The doses administered ranged below the acute LD₅₀ level of toxicity (Fahmy, 1970).

DETERMINATION OF WATER AND FOOD INTAKE

Using the guidelines given by OPPTS (US EPA. 1998) fifteen rats were group caged by sex, fed from the same batch of food and given same water till they maintained a steady eating and drinking habit. At this baseline, the administration of drugs commenced. Four dose groups of fifteen rats each were used for the study. Groups 1-3 received 0.2, 5 and 10mg Endosulfa/kg body weight respectively while group four received n-saline. One of the standard tests used to study thirst in humans and animals is the drinking pattern after depriving them of water in a diurnal cycle and making food available since they influence water intake (Kooi et al, 2001). Five hundred milliliter of water and weighed amount of food were offered to the animals in each group four hourly daily (2hrs in the morning (11.00 - 1.00pm) and 2hrs in the evening (4.00 - 6.00pm)).

This was done daily for twenty eight (28) days. The different doses of Endosulfan were administered to each group once daily two hours after deprivation of food and water. Each day the animals were deprived of food and water for 20hrs. From the volume of water left, the water consumption in ml/100g rat/24hrs was calculated as shown below;

Water intake in mls (W) = Vol of water given – Vol of water not taken

Time Interval (T) = 4hrs

Weight of animals /cage = B grams

Therefore 100 g rat drank

\[ W \times \frac{4}{B} \times 100 \]

In the same way, the amount of food consumed was also calculated using the above formula in g/100g rat/ 24hrs

STATISTICAL ANALYSIS

All results are expressed as the mean ± standard error of mean (SEM) and significance of difference between means of the control and treated were determined using paired student t-test. P values < 0.05 were taken to be statistically significant.

RESULTS

DETERMINATION OF WATER AND FOOD INTAKE

Endosulfan dose dependently increased the intake of water in adult wistar rats during the period of study. (See figures 1-4)
The highest water intake was observed in the group administered with 10mg Endosulfan/kg body weight while the group administered with 0.2mg Endosulfan/kg consumed the least from the treated groups. The 5 and 10mg
Endosulfan/kg body weight produced a statistically significant \((P<0.05)\) increase in the fourth week when compared with the control.

During the twenty eight days of the study, food consumption by the rats in all the groups was slightly decreased (See fig. 5 below).

**Figure 5**

The mean weekly food consumption decreased in all the groups. The control group had the highest rate of feed intake followed by the 0.2 mg/ kg Endosulfan treated group while the 10 mg/ kg group showed the lowest rate of feed intake. None of the treated groups showed any statistical difference from the control at \(P<0.05\)

**DISCUSSION**

In this present study, the effect of Endosulfan pesticide on water and food intake in adult albino wistar rats was investigated for twenty eight days. The water consumption by the rats increased dose dependently from week one to week four. In the second week of the study, 0.2mg Endosulfan/kg showed a fall in the volume of water taken which could be as a result of the body’s physiological process in adjusting to the inhibition of vasopressin by a foreign substance. Meanwhile this volume of water intake gradually rose to the level of the control by the fourth week. The 5 and 10mg Endosulfan/kg body weight produced an increase in water intake throughout the period of the study but was statistically significant \((P<0.05)\) in the 4th week when compared with the control. Since water consumption is under the control of the hypothalamus, any alteration signifies that the hypothalamus has been affected (Smith and McCann, 1962). If the hypothalamus is altered there is a tendency of increased water intake (diabetes insipidus) which occurs when there is lack of secretion of Antidiuretic hormone (ADH) centrally or even when released could be nephrogenic. (Rang et al, 2003). The balance between water loss and water intake results from interactions between the hypothalamus, the pituitary gland and the kidney, and is maintained by thirst and renal excretion of water and salt. (Johan, 2008)

Hypothalamus also participates in the control of appetite as the lateral nuclei serve as the feeding centre which when stimulated causes hyperphagia (Guyton and Hall, 2006). The destruction of lateral hypothalamus causes lack of appetite and progressive inanition, this is a condition characterized by loss of weight, decreased metabolism and muscle weakness (Guyton and hall, 2006). In view of this, the decrease in food intake observed in this study could be as a result of loss of appetite which may have resulted from the destruction of the lateral hypothalamus by the increased doses of Endosulfan. It has been established that there is a difference in function between paraventricular nucleus (PVN) and ventromedial nucleus (VMN) of the hypothalamus in the drinking and eating patterns in rats (Sakata et al, 1988). Feeding modulation occurs through the histaminergic pathways in the VMN while drinking behaviors are mediated in the PVN (Sakata et al, 1988). From electrophysiological and behavioral findings, neuronal histamine in the hypothalamus has been found to modulate feeding and drinking behaviors through H-1 receptors (Fukagawa K. et al, 1989). It has also been reported that a lot of pharmacological agents that modify the neurotransmitter level would act at the level of the hypothalamus to affect food and water intake (McCann, 1982). Furthermore, some of these pharmacological agents like the environmental contaminants such as heavy metal cadmium and Endosulfan pesticide have been shown to influence motor and feeding behaviors in Ornate Wrasse (Thasoma Pavo) through cerebral histamine receptor subtypes (Giuseppina, 2005). From the findings of this present study, there was a slight decrease in feed intake caused by different doses of Endosulfan and based on the reports above, the observed effects may have occurred through the histaminergic pathway of VMN in the hypothalamus. Hence the increase in water intake may also have been mediated through the PVN.
Endosulfan Induced Polydypsia In Adult Wistar Rats

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