Theobromine found in Chocolate can induce weight-loss and testicular atrophy in rats

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Theobromine, a bioactive compound found in Cocoa beans has long gone under-researched due to attention being focused on its central-nervous-system stimulating cousin, Caffeine. It is evident though that Theobromine is a pharmacologically active substance that induces growth-stimulating, smooth muscle relaxation, cough suppressing, and glucose-lowering effects. (Hendrik, 2011) It is also known that dogs are very susceptible to theobromine poisoning from eating chocolate — reports from studies on dogs are not very helpful because they metabolize theobromine very slowly compared to humans (Finlay. 2005) — and so further investigation was required to assess safety for humans. (Tarka et al., 1982)

Study 1

A chronic study, by Tarka et al. (1991), of 4 groups of SD rats fed a diet that consists of 0.0 (control), 1.5, 3.5, and 5.0% Cocoa Powder (CP). The 4 groups were bred from 3 generations of ancestors that were fed the same diets. Theobromine compromised 2.6% of the CP and thus the rats were fed about 0, 19, 46, and 64 mg of Theobromine per kg of body weight per day. After the 104 weeks study was concluded, there was no evidence found that involved any treatment-related clinical disease nor carcinogenic effects from the dietary CP. There was a slight increase in testicular atrophy, kidney and cardiac lesions, interstitial fibrosis, and non-suppurative myocarditis in the highest dosage group, but not significantly divergent from the control group. The 3.5 and 5% groups ended up with a modest reduction in body weight. Since no increase in mortality was measured, no LOAEL or LD50 values can be determined. Tarka et al. conclude that a NOAEL value can be determined to be 64 mg/kg in this chronical protocol and that CP is a safe substance to be used as a food additive. (Tarka et al., 1991)

Study 2

Another study showed that the consumption of a 10% cocoa diet for 2 weeks in diabetic rats lowered and improved tolerance to glucose levels while increasing insulin levels. The rats were split into three groups: a reference group (RG), a cocoa group (CG) fed a diet

containing 10% CP (2.5% theobromine), and a Theobromine group (TG) fed a 0.25% theobromine diet. Fecal fat content, examined after 7 days of the diet, was lower in CG and TG in comparison to RG. CG and TC groups showed a 15% decrease in LDL-c (unhealthy cholesterol) content, while at the same time HDL-c (healthy cholesterol) values have increased by 24–41% in CG and TG. In fasting conditions (after 18 days), CG and TG had higher plasma glucose concentrations than the RG The rats from CG and TG showed higher ghrelin ("hunger hormone") concentrations and lower glucagon (main catabolic hormone) levels than the RG. (Mariona et al., 2019) No LD50 or NOEAL was reported.

Study 3

Another study was conducted by Kaikai and his team in 2015; after orally administering up to 800mg/kg of cacao tea water extract (CWE) — analyzed to have 10% theobromine — in Sprague Dawley (SD) rats, for 28 consecutive days, no mortality or toxicity was observed. The SD rats, 70–100 g and 6 weeks old, received doses of 200, 400 and 800 mg/kg body weight/day by 1 mL/100 g bodyweight gavage with CWE dissolved in distilled water. There were no adverse effects found in body weight, food consumption, relative organ weight, haematological parameters, gross pathology and histopathology between treatment and control groups with 0, 20, 40 and 80 mg/kg of theobromine doses. Though, the bodyweight of the male receiving the highest dose was noticeably smaller compared with the control rats. (Kaikai et al., 2015) No LD50 or NOEAL was reported.

Carcinogenicity

Theobromine has shown very limited carcinogenic potential. Brusick et al. (1985) reports that even though it exhibited some clastogenic activity in cultured human lymphocytes, theobromine has shown limited genotoxic activity. Rosenkranz And Ennever (1987) go on to explain that even though theobromine scores positively on a few of short-term genotoxicity tests, CPBS (an algorithm used to evaluate the cancerogenic risk from multiple genotoxicity tests) predicts a low probability of theobromine being a carcinogen. And more importantly, theobromine has been officially classified by IARC as a class 3 compound.

Conclusion

Outcomes from high-dose long-term exposure include apparent weight-loss and inconsistent, barely-significant appearances of atrophies and legions. Since no frequency of exposure was specified, 3 times per day was assumed to be the frequency as that would be so for a diet. After extensive research through the literature, it does not seem that a LOAEL for theobromine was ever determined. All the research we examined cited an "Oral LD50 values … to be 1000 mg/kg" from (Tarka et al., 1982), which in turn cites a PhD thesis — by the same author — that cannot be found, and indicates that the actual data for that figure was never published. LOAELs for cats and dogs have been published before, but since they are much more sensitive to theobromine than humans and rats, there are not good values to base extrapolations on.

It does seem that reporting on theobromine toxicity in humans is still a bit unclear. It is evident though — from testing on rats and rabbits, and the lack of human medical cases — that any "sane" consumption of a cacao product should be safe. So unless an 80kg person is eating close to 0.24-1.6 kg of dark-milk chocolate daily in a long-term manner, there should be no concern of having any noticeable side effects.

One noted observation is that many of these studies were supported by chocolate manufacturers, notably Hershey Corp.

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