Sibutramine is a Serotonin-Norepinephrine Re-uptake Inhibitor (SNRI) which was widely used in the treatment of obesity as it acts on the central nervous system influencing satiety as well as energy expenditure. Although now withdrawn from most markets, sibutramine is often a hidden ingredient in “natural” weight loss agents which have been shown to contain far higher concentrations of this compound than the original prescription drug. In light of the obesity epidemic and the associated comorbidities, some are of the opinion that the benefits associated with sibutramine use outweigh the possible risks. Comprehensive risk assessment of this compound is essential in order to fully define the safety and efficacy of its use.

Numerous adverse events have been associated with sibutramine use, with cardiovascular complications being most predominant. This study was aimed at investigating the effect of sibutramine on the ultrastructure of platelets and fibrin networks by using scanning electron microscopy. Male Sprague-Dawley rats, treated with a low (LD; 1.32mg/kg) and high dose (HD; 13.2mg/kg) of sibutramine for 28 days were used in this study and were compared to control animals. Blood samples were collected on the day of termination via cardiac puncture and plasma smears were prepared for the evaluation of platelet morphology. To evaluate fibrin clot structure thrombin was added to the plasma to form the coagulum.

Compared to controls, platelets from exposed animals presented with pseudopodia formation as well as membrane spreading (Fig. 1). Upon higher magnification signs of necrosis, such as membrane tears, were also evident, characteristic of over activation (Fig. 2). The fibrin clots of the sibutramine-treated animals revealed fused thick fibres with thin fibres forming a net-like architecture, covering the thick fibres (Fig. 3). Fibrin network formation was also seen without the addition of thrombin (Fig. 1C). This may be due to elevated concentrations of coagulatory factors which is associated with the over activated phenotype. These results are typical of a hypercoagulable state, as has been previously described in cases such as thromboembolic ischaemic stroke.

It can therefore be concluded that sibutramine alters the ultrastructure of platelets and fibrin networks to that typical of a hypercoagulable state. This could contribute to the increase in blood pressure and heart rate associated with sibutramine use. This effect may occur through peripheral noradrenergic stimulation, which further activates various physiological processes in response to shear stress. In depth biochemical investigations are required to identify the molecules and regulatory process involved to fully understand the mechanisms whereby sibutramine affects platelet function.

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Fig. 1: Platelets from the different experimental groups. A: Control; single pseudopod is visible (arrow); B: LD Sibutramine; Activated platelet, numerous pseudopodia (thick arrows) and membrane spreading (thin arrows); C: HD Sibutramine; numerous pseudopodia (arrows), matted thick fibres (white star) and platelet interaction is visible.

Fig. 2: Higher magnification of platelets from the different experimental groups. A: Control; smooth surface and open canalicular pores visible (arrows); B: LD Sibutramine; platelet membrane appears granular; C: HD Sibutramine; membrane appears necrotic (arrows) with membrane tears (white star).

Fig. 3: Fibrin networks of animals in the different experimental groups. A: Control; major thick (thick arrows) and minor thin (thin arrows) fibres; B: LD Sibutramine; fused thick fibres (thick arrows) and minor fibres forming a net-like structure (thin arrows); C: HD Sibutramine; minor fibres (thin arrows) covering the thick fibres (thick arrows).