140. *The Diuretic Action of Caffeine and Other Purine Derivatives on Mammals.*

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In studying the mode of the diuretic action of caffeine and its allies, it is important to determine or to analyse the relative importance of the extra-renal and renal effects of these drugs in producing diuresis.

Our experiments were performed on rabbits, dogs and cats, observing (1) the changes in the renal blood flow and the urine excretion induced by caffeine and other purine derivatives, (2) the extent of diuresis caused by these drugs during hydraemia, and (3) the oxygen consumption of the kidney during diuresis in those animals.

Changes in the renal circulation. Changes induced by caffeine and other purine derivatives in the renal blood flow have been examined by many investigators. Some of them insist on a marked increase in the renal circulation (Loewi¹⁾ and others), while others are inclined to deny the claim (Schwarz²⁾, Richards and Plant³⁾). One of us (Tamura) and Miwa⁴⁾ found that the caffeine diuresis could be caused without any increase in the renal blood flow. Cushny and Lambie⁵⁾ observed some increase in the renal blood flow by caffeine, and the fact found by them that the diuresis preceded the augmentation of the renal blood flow and lasted long after the latter had become normal, led them to conclude that the diuretic action was rather independent of the changes in the blood supply, and was due to the changes in the renal cells. Recently M. Ozaki⁶⁾, however, observed the increased renal circulation preceding the diuresis by caffeine administration.

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- 1) Loewi, Fletscher and Henderson. Arch. f. exp. Path. u. Pharm., 53 (1905), 57.
 - 2) Schwarz. Arch. f. exp. Path. u. Pharm., 43 (1899), 1.
 - 3) Richards and Plant. Journ. Physiol. 7 (1915), 485.
 - 4) Tamura and Miwa. Mitt. med. Fak. Kaiser. Univ. Tokio, 23 (1920), 317.
 - 5) Cushny and Lambie. Journ. Physiol., 55 (1921), 276.
 - 6) M. Ozaki. Hokkaido Med. Journ., 3 (1925), 9.

In our experiments, various doses of caffeine was injected intravenously into rabbits, cats and dogs which had been prepared after Barcroft and Brodie's method. In rabbits weighing from 2-3.5 Kgrms, almost with every dose of caffeine used (0.01-0.2 grms, intravenously) a marked diuresis occurred, after the increase of blood flow through the kidney which had appeared before the recovery of the blood pressure from its temporary fall directly following the injection took place. This must be interpreted as due to the dilatation of renal vessels. But at the height of the diuresis, the renal blood flow returned almost to its normal level as reported by Tamura and Miwa¹⁾, and even after the blood pressure and renal blood flow had recovered from the effect of caffeine, the diuresis continued for a considerable period, as shown in Fig. I.

Fig. I. Graphs of the arterial pressure (A.P.), Renal blood flow (R.B.F.), and excretion of urine (U.) of a rabbit after the injection of caffeine.

In dogs, the blood pressure fell and the renal blood flow increased directly after injection of caffeine just as in rabbits. The diuresis,

1) K. Tamura u. M. Miwa. Mitt. med. Fak. Kaiser. Univ. Tokio, 23 (1920), 317.

however, was less marked or often failed to appear, as indicated in Fig. II.

Fig. II. Graphs of the arterial pressure (A.P.), renal blood flow (R.B.F.), and excretion of urine (U.) of a dog after the injection of caffeine.

As in rabbits and dogs, the experiments on cats showed similar changes of the blood pressure and renal circulation, while in the majority of cases no diuresis was recognised (Fig. III.)

Directly after the injection of a very large dose of caffeine into rabbits, the blood pressure fell pronouncedly, with the blood flow diminishing, but already, as they were recovering, diuresis followed.

From these experimental results, we know that equally in rabbits, dogs and cats caffeine causes a marked dilatation of the renal vessels to such an extent as to increase the renal blood flow even during the fall of the general blood pressure after the injection, but the caffeine diuresis is marked in rabbits, indefinite in dogs and absent in cats; the beginning of diuresis in rabbits lags behind the changes in the renal circulation.

From these findings we conclude that the diuretic action of caffeine

is independent of the changes in the renal blood circulation, although it would certainly be more pronounced if it be preceded by the increased blood flow through the kidney.

Fig. III. Graphs of the arterial pressure (A.P.), renal blood flow (R.B.F.), and excretion of urine (U.) of a cat after the injection of caffeine.

Caffeine diuresis during a Ringer hydraemia. The next step is to decide whether caffeine increases urine excretion by its specific stimulant effect upon the kidney or by some of its extra-renal actions.

We investigated the effect of caffeine, just as Heymans¹⁾ tested allyl-theobromine, on the animals, in which hydraemia and diuresis were caused by the constant infusion of Ringer's solution.

In normal rabbits, a small dose of caffeine and its allies caused clearly a diuresis as mentioned above. By infusing the animal constantly with Ringer's solution and causing hydraemia and diuresis, caffeine of the same dose induced a more marked diuresis. Similarly, a frequently repeated injection of small doses caused a pronounced diuresis, especially with theophylline (Fig. IV.).

1) Heymans. Arch. internat. de Pharm., 25 (1921).

Fig. IV. Graphs of blood proteins (B.P.) and excretion of urine (U.) of a rabbit after the injection of caffeine during a Ringer hydraemia. The time of infusion is indicated on the base line. The diuresis caused by caffeine is greater during Ringer hydraemia than under normal conditions.

In cats, however, almost invariably no diuretic action appeared, as shown in Fig. V.

Judging from the action of caffeine in hydraemic rabbits and cats, we are inclined to suggest that caffeine diuresis may be accelerated to some extent under the reduction of the swelling pressure of the body albumine, causing hydraemia as reported by Ellinger and others¹⁾, but the chief cause of diuresis by caffeine is to be found in its renal action.

In case if the diuresis is set up by saline infusion, the reabsorption of water in the tubules greatly diminishes or fails altogether as found by Magnus²⁾ in dogs and by Cushny³⁾ in rabbits. Accordingly, our experiments in which caffeine diuresis is greater during Ringer hydraemia than under normal conditions, shows that the diuretic action of caffeine

1) Ellinger, Heymann and Klein. Arch. f. exp. Path. u. Pharm. 90, 91 (1921).

2) Magnus. Arch. f. exp. Path. u. Pharm., 44 (1900), 68.

3) Cushny. Journ. Physiol., 23 (1902), 431.

lies primarily in the augmentation of the glomerular filtration, not so much in the diminution of reabsorption of water.

Fig. V. Graphs of blood proteins (B.P.) and excretion of urine (U.) of cat after the injection of caffeine during Ringer hydraemia. The time of infusion is indicated on the base line.

Gaseous metabolism during caffeine diuresis. Tamura and Miwa¹⁾ found that in diuresis caused by caffeine and other purine derivatives, there was no appreciable change in the oxygen consumption of the kidney; contrary to which Tashiro and Abe²⁾ reported later that a small dose of caffeine, in most cases, augmented more or less the oxygen-intake of the kidney, while the use of a larger dose depressed it.

We, therefore, thought it worth while to reinvestigate the problem under more thoroughly controlled conditions taking special care of the doses of drugs administered. The experimental method and the apparatus used being the same as mentioned before.

The experiments on rabbits with caffeine showed clearly diuresis both in the cases of small doses as well as of large ones; the oxygen absorbed in the kidney, however, showed no change from that in normal conditions, although in the case of diuretin-diuresis oxygen consumption increased distinctly (Table I.).

1) Tamura u. Miwa. l.c.

2) Tashiro and Abe. Tohoku Journ. exp. Med., 3 (1922), 142.

Table I.

No. of exp.	Animal	Normal		At the height of diuresis		Dose of drugs, in grms
		Urine per min., in drops	Oxygen consumption of kidneys per gm per min., in c.c. (0°C, 760mm Hg)	Urine per min., in drops	Oxygen consumption of kidneys per gm per min., in c.c. (0°C, 760mm Hg)	
I.	Rabbit	3-4	0.072	12-13	0.071	0.006 (caffeine)
II.	"	3-3	0.058	11-14	0.058	0.04 "
III.	"	3-2	0.071	12-12	0.071	0.12 "
IV.	"	3-3	0.076	19-20	0.169	0.075 (diuretin)

In some dogs, a slight diuresis was found without accompanying any change of the oxygen consumption in the kidney; in most cases of the experiments on cats no change was detected both in diuresis and in oxygen consumption. (Table II.).

Table II.

No. of exp.	Animal	Normal		At the height of diuresis		Dose of drugs, in grms
		Urine per min., in drops	Oxygen consumption of kidneys per gm per min., in c.c. (0°C, 760mm Hg)	Urine per min., in drops	Oxygen consumption of kidneys per gm per min., in c.c. (0°C, 760mm Hg)	
I.	dog	6-5	0.053	10-12	0.050	0.06 (caffeine)
II.	cat	2-3	0.053	3-4	0.059	0.02 "
III.	cat	5-5	0.040	4-6	0.040	0.02 "

In short, caffeine causes equally in the rabbit, dog and cat the fall of the general blood pressure and the dilatation of the renal vessels directly after the injection, but the diuresis induced is most marked in rabbits, while in dogs it is indefinite, and in cats there appears almost no change of the urine outflow. Moreover, when diuresis is caused by caffeine in rabbits and dogs it does not accompany the increase of renal blood flow,

but it is set up after the blood flow has returned to its normal condition ; and by a large dose of caffeine, marked diuresis occurs without showing any increase of the renal blood flow throughout the experiment. The caffeine diuresis, therefore, does not depend on the renal vaso-dilatation although its existence may facilitate the occurrence of diuresis to some extent.

The facts that the caffeine diuresis in rabbits is more marked during the hydraemia caused by saline infusion than in the normal condition and that caffeine does not act on cats both in the hydraemic stage as well as in normal conditions, suggest that the caffeine hydraemia, which is understood by many to be an extra-renal action of caffeine, has no great significance in causing diuresis, and its renal action depends primarily on the increase of glomerular filtration and not so much on the possible lessening of the reabsorption in the tubules.

In other words, caffeine diuresis is caused chiefly by the increased permeability of the glomerular capsule, to a lesser degree by hydraemia and tubule diarrhoea, and only occasionally by renal vaso-dilatation.

In the kidney, unlike in other glands, its gaseous metabolism undergoes no appreciable change during an increased excretion induced by such a specific stimulant as caffeine, while the increase of the urine excretion caused by a kidney irritant like diuretin accompanies an increase of oxygen-intake.