A review on *As (Est-2)* autosomal locus in the rabbit and the heritable condition of different pharmacological responses to atropine

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Abstract. Atropinesterase is a carboxylesterase enzyme involved in the hydrolysis of various aromatic and aliphatic esters, including atropine. This action is well known in the rabbit, although not all rabbits express atropinesterase activity or this activity is not resumed only at rabbits. Various factors of influence, such as the breed, the gender, the age of life, or the season, are important for estimating the atropinesterase activity in the rabbit. This enzyme is encoded by a single autosomal locus *(As,* recently named *Est-2*), an interaction of incomplete dominance being reported between alleles. A close linkage with *Est-1,* which is the locus of cocainesterase, and other serum and red blood cell esterases were demonstrated throughout the time, by considering the frequencies of recombinants in linkage experiments. This review aims at comprehensively debating on atropinesterase coding locus and its relationship with other loci in the rabbit genome, the consequences of atropine enzymatic hydrolysis starting with its medical use, and the other possible interventions in the ester-type drugs metabolism.
Key Words: *Oryctolagus cuniculus*, atropine, atropinesterase, hydrolysis.

Introduction. The rabbits' ability to use in their diet leaves of belladonna, which contain atropine, without side effects, is known since 1852 (Cauthen et al 1976). Only certain rabbits have this ability and it was considered by more recent studies as a heritable condition which makes certain animals insensitive to atropine. In fact, a process of metabolic detoxication involving atropinesterase (EC 3.1.1.10 or EC 3.1.1.0, atropine acyl-hydrolase, AtropE), a member of the large enzyme family of carboxylesterases, is involved, through a process of hydrolysis, more polar compounds being formed and easily excreted. Broadly speaking, carboxylesterases can hydrolyse esters, thioesters, and amide bonds of endogenous chemicals or various xenobiotics, producing carboxylic acid and an alcohol, a thiol, or an amine, respectively (Cashman et al 1996).

Although atropinesterase can be found in various tissues, the richest of its sources remains the serum. However, liver is the most likely site of ester hydrolysing, although it has less atropinesterase activity than serum (reviewed by Forster & Hannafin 1979). Greene & Wade (1968) suggested, besides serum and liver, the intestine as another tissue of atropinesterase presence, while Liebenberg & Linn (1980) reviewed the atropinesterase activity also in the iris, kidney, spleen, adrenal glands, cardiac muscle and lacrimal glands of the rabbit.

The atropinesterase activity is variable, depending on the rabbit strains. Margolis & Feigelson (1963) observed atropinesterase activity in 21% of albino and in 50% of chinchilla tested individuals. Liebenberg & Linn (1980) reported atropinesterase activity in 61.17% of the New Zealand white rabbits, with a large variability of results, compared to other reports cited by the authors (25 or 25.7%), mainly based on the greater number of individuals included in their study. An early report of Sawin & Glick (1943) found atropine esterase activity in 50% of the Chinchilla breed individuals, but no activity in the New Zealand white breed.

Contradictory reports to Liebenberg & Linn (1980) showed variations among the gender of the individuals investigated for atropiesterase activity. Although not considered as a sex-linked trait, but only as possibly influenced by sex, Liebenberg & Linn (1980)

reported more males positive for atropinesterase activity than females (62.28% versus 56.94%, respectively) and when the seasonal factor was included, this variation was associated with both winter and summer seasons. Ecobichon & Comeau (1974) reported a 50% frequency of atropinesterase in either sex. Sawin (1955) reviewed a tendency of occurring in a higher percentage of females and in greater concentration than in males. Regarding the age, the first atropinesterase activity was reported not earlier than after one month of life. Some of the rabbits with inconsistent atropinesterase activity at the age of one month of life increased it at subsequent examinations, at two and three months (Sawin & Glick 1943). No precursor protein formation was reported during the course of the developmental increase of enzyme activity, and the lack of atropinesterase activity in negative rabbits was assumed either to an inactive genome in the atropinesterase region, due either to its absence or to an incomplete suppression, or to an aberrant message that cannot be used in the protein synthesizing process (Margolis & Feigelson 1964).

Besides the rabbit, some plants are known to contain atropinesterase. The hydrolytic cleavage of atropine to tropine and tropic acid by atropinesterase was reported in the root sap of Jimson weed *(Datura stramonium* L.), whose activity reached a maximum potential in a later vegetation phase (during the 20^{th} week of plant growth), at a pH of 5.0-5.8, which corresponds to the pH of the cell sap of Datura (5.2-5.7), but is lower than the optimum of 8.3 in the rabbit serum (Jindra et al 1963).

Confusing results on its presence in rats and guinea-pigs were revised by Harrison et al (2006). They assessed the capacity of other species (dog, goat, guinea-pig, human, pig, rhesus) to hydrolyse atropine in their plasma and found different metabolic rates compared to the rabbits and that traces of activity may be related to the presence of other carboxylesterases, such as cocainesterase, with low affinity for atropine, or to small amounts of atropinesterase. Their lower atropinesterase activity in *Rhesus* monkey compared to other tested species was justified by the low sample size (Harrison et al 2006).

In the context of all previous aspects discussed, the aim of this paper was to review genetic and physiological aspects of atropinesterase encoding, synthesis, action, and metabolism variability in rabbits.

Material and Method. Genotypic and phenotypic aspects of atropinesterase and its involvement in atropine hydrolysis in some but not all of the rabbits were mainly debated here in a comprehensive presentation. This is a review study based on 31 scientific papers selected for their scientific relevance for the subject matter.

Results and Discussion

The atropine and its medical use. Atropine (DL-hyoscyamine) is an organic ester consisting of an aromatic *tropic acid* and a complex organic base tropine*.* It is mainly known to be produced by *Atropa belladonna* or the Deadly nightshade plant. Other members of the *Solanaceae* family were reported to produce atropine (e.g. *Datura, Henbane*), but also a related alkaloid, the hyoscine. Atropine has a parasympatholytic mechanism of action, blocking the muscarinic receptors in the postganglionic synapses of the parasympathetic nervous system. These cholinergic sites use acetylcholine as mediator and more elevated atropine doses than necessary affect other cholinergic sites, such as the neuromuscular junction (Shutt & Bowes 1979).

The usual anticholinergic effect of atropine is related to an increased heart rate, which seems to be variable depending on the the dose, even reaching the contradictory parasympathomimetic effect of bradycardia, in small doses (Kottmeier & Gravenstein 1968). The aforementioned cited authors verified the hypotheses of vagal centers and/or direct effect on the heart by testing atropine suphate, which crosses the blood-brain barrier, and its more potent derivative in accelerating the heart rate, namely the atropine methylbromide, which has no access to the brain, and the peripheral parasympathomimetic effects on the heart were also included. 1 mg of atropine sulfate 70 kg^{-1} was used to accelerate the heart rate in 79 human patients aged from six weeks

to 79 years, with a relatively more atropine needed to obtain this effect in young people than in adults. Arrhythmias were rather reported in young individuals and were rather associated with small doses of this drug than with large ones (Dauchot & Gravenstein 1971). Forster & Hannafin (1979) reviewed a dose of 2 mg kg^{-1} i.v. for the rabbit, as recommended for its anticholinergic effects, and a LD50 of 71 mg kg^{-1}.

Controversial uses of atropine to sustain the cardiac function during the chloroform anaesthesia were discussed by Shutt & Bowes (1979). On the other hand, Olson et al (1993) reviewed the beneficial effects of anticholinergic agents in preventing bradycardia and the accumulation of salivary secretions during anaesthesia and surgical manipulations. Their use for premedication may counteract the bradycardia caused by alpha-2 adrenergic agents, such as the injectable anaesthetic xylasine or the vagal stimulation by endotracheal intubation or surgical manipulation of viscera (Olson et al 1993).

Shutt & Bowes (1979) also included the atropine use as a morphine's antidote, considering its effect of mydriasis (dilating the pupils).

Its action of mydriasis induction by blocking the parasympathetic innervation of the pupil and the ciliary muscle was reviewed by Mori et al (2019). The mydriatic effect of atropine applied as drops to the conjunctival sacs, described by Goldsmith et al (1977), is common in most humans, being slower in individuals with dark irides but hyper-reactive in individuals with Down syndrome. Considering the atropine ability to be bound by the melanin of pigment cells, its less effective action in the pigmented than in the albino rabbit’s iris was also discussed by Akesson et al (1983). Besides, the limitation of atropine at the level of the receptor in the smooth muscle of iris, due to its enzymatic hydrolysis in aqueous humor, was also considered as a limiting factor, by Akesson et al (1983). Kuiper et al (1997) presented the atropine sulfate as a long-acting mydriatic agent (more than 24 h), fact which may lead to a deleterious effect on the retinal function. The overexposure to light was also incriminated into retinal degeneration in sensitive strains (Kuiper et al 1997).

The effect of atropine in decreasing the myopia was demonstrated by Bedrossian (1979), when sixty-two children were treated with atropine in one eye for one year, the other eye being of control. The atropine effects related to the prevention of myopia progression and of iris adhesion to the anterior lens or to its use to treat the iris inflammation and anterior uveitis were also reviewed by Mori et al (2019).

The vasodilatation effect of atropine is nowadays used in the prevention of death in patients with bacteremic or hemorrhagic shock, or to increase the body temperature, especially in infants and small children. Atropine inhibits the activity of sweat glands and its effect of vasodilation is kept even in species that do no sweat, such as dogs (Liu et al 2004). Although the vasodilation effect of atropine was supposed as a result of blocking the M-cholinoceptors located on the vascular wall, this direct action was not supported by the results of Liu et al (2004) on the sympathetic denervated rabbit ear blood vessels (complete resection of the auricular branch of the vagus), the hypothesis α-adrenoceptors blocking being supposed.

Rapid-testing for atropinesterase activity prevents failures in rabbit medical research. In the same way of various drugs inactivation through the action of various carboxyesterases, the efficacy of atropine as a preanesthetic agent may be of a relative effectiveness mainly as a result of its rapid hydrolysis by the serum atropinesterase in some but not all rabbits (Ecobichon & Comeau 1974; Forster & Hannafin 1979; Margolis & Feigelson 1964; Stormont & Suzuki 1970).

The shortcoming of atropine enzymatic destruction in various rabbit subjects in medical research or therapeutics can be prevented by pre-testing individuals for positive atropinesterase activity. A rapid screening test may be used in this regard. As Liebenberg & Linn (1980) reported, at 45 minutes after the subcutaneous injection of 0.5 mg atropine sulfate per animal (1.0 mL of an 0.5 mg mL^{-1} solution) in about 3 months old rabbits and of 2-3 kg each, a light from a hand-held disposable penlight was shone directly into the eyes of each rabbit, the lack of atropinesterase activity being translated into a prolonged mydriatic effect of atropine, in absence of the pupillary light reflex.

Stormont & Suzuki (1970) reviewed with the same aim of pupil reflex time recovery measuring the ocular adding of a 0.05 mL of a 2% solution of atropine sulfate in 0.9% saline. A revised information in Forster & Hannafin (1979) demonstrated that "atropine esterase-free" rabbits present no light reflex, but only a persistent mydriasis for less than 1.25 to 5 or more hours, while in "containing atropine esterase" rabbits this reflex recovered within 8 to 42 minutes. Ecobichon & Comeau (1974) reported a marked pupillary dilation within 30 minutes after the s.c. administration of atropine sulfate (20 mg) in both rabbit types, with "low" and "high" enzymatic activity, reaching the maximum pupillary diameter 60 minutes after administration. Rabbits with "high" atropinesterase activity recovered a normal pupil diameter 5 hours after drug administration while rabbits with "low" activity completely lost the light reflex for up to ten hours. The authors reported a markedly dilated pupil around 48 hours after injection, regaining its normal size at 72 hours (Ecobichon & Comeau 1974).

Forster & Hannafin (1979) discussed on a quick screening test based on a single dose of 1 mg kg^{-1} i.v., eliminating the rabbits in which the bradycardial reflex response to smoke apnea disappeared within 20-25 minutes.

Olson et al (1993) reported no vagolytic effect of atropine even in rabbits without a detectable atropine esterase activity and reported glycopyrrolate, a synthetic anticholinergic agent with a longer lasting action than atropine sulfate, being effective in preventing the heart rate depression in rabbits receiving ketamine:xylazine. Although the recommended anticholinergic dose of atropine for the rabbit is of 2 mg kg^{-1} i.v., in individuals with high atropinesterase activity its effect on inhibiting the bradycardial response was abolished within 10 minutes. Even a massive dose of 100 mg kg^{-1}, (more than the LD50 of 71 mg kg^{-1}) injected 70 minutes after the first recommended dose, was quickly degraded after 40 minutes, in the same individual. In order to sustain the anticholinergic action of atropine in rabbits with high atropinesterase activity, a dose of 1 mg kg^{-1} i.v. should have to be repeated at every 3 minutes (Forster & Hannafin 1979).

The As (also named Est-2) locus and its assumed linked position on the fifth rabbit chromosome. Atropinesterase locus and its enzyme product are inherited and expressed as a result of the incomplete domination interaction between involved alleles (Ecobichon & Comeau 1974; Margolis & Feigelson 1963). Originally, Sawin & Glick (1943) considered a single autosomal gene noted with *As*.

The inheritance and expression of the atropinesterase gene, in a context of incomplete Mendelian domination, determine variable phenotypes, considering the homozygote or heterozygote genotypes. However, a larger amount of atropinesterase is expected in the blood of homozygous positive individuals than in heterozygous, where a single allele is active, and no circulating enzyme is expected in the blood of homozygous negative individuals (Forster & Hannafin 1979; Liebenberg & Linn 1980). Sawin (1955) interestingly pointed out the enzyme dominance over its absence of activity. The ability to produce the enzyme as dominant over its absence was also mentioned in an earlier report from 1943 (Sawin & Glick).

Sawin (1955) and Liebenberg & Linn (1980), studied the chromosomal location of the encoded gene of atropinesterase, initially named *As* gene, showing a linkage with the *E* gene for developing the black pigment in the pelt. The original consideration of this fact, by Sawin & Glick's 1943 report, included these genes as members of the sixth linkage group of the rabbit. Based on the original report of Sawin & Glick (1943), Fox & van Zutphen (1979) identified a map distance of 26.2±6.8 cM between *As* and *e* genes. They also demonstrated that this group of linkage in rabbit shares homologies with the mouse *(Mus musculus)* chromosome 8 and with the rat *(Rattus norvegicus)* linkage group (LG) V.

Further investigations in the rabbit revealed, in fact, two closely linked loci, *Est-1* and *Est-2*. The former codes for the production of cocainesterase and the latter was considered analogous to the *As* gene and therefore it encodes for atropinesterase (Forster & Hannafin 1979; Fox & Van Zutphen 1977, 1979). Considering the localized activity of atropine- and cocaine-esterase in an anodal region of the electrophoretic gels, related to the albumins, they are defined as prealbumin esterases (Van Zutphen 1974a).

A third locus, *Est-3*, was demonstrated to segregate independently of the previous two, for which critical recombinant individuals were not reviewed (Fox & Van Zutphen 1979). All of them give rise to ten phenotypes which are involved in the metabolism of esterified drugs such as atropine, procaine, and cocaine (Forster & Hannafin 1979). Kelus (1981) described the third serum esterase locus (*Est-3*) as a "dependent" prealbumin carboxylesterase and classified the red blood cell and platelet esterase (*Es*) into red blood cell carboxylesterase-1 (*Es-1*), platelet carboxylesterase-2 (*Es-2*) and red blood cell carboxylesterase-3 (*Es-3*). The *Es-1* locus has two alleles and is closely linked to the *Es-2* locus, which also includes two alleles, while the *Es-3* locus, with its three alleles, is not linked to the previous two loci. Studying the polymorphism of rabbit erythrocyte esterases, Schiff & Stormont (1970) discussed each two alleles (A and B) controlling *Es-1, -2,* and *-3* loci, respectively, with codominant autosomal alleles for each three phenotypes described. However, the electrophoretic profile showed the last system migration as the most anodal of all three, and the second one between the first one and the last one (Schiff & Stormont 1970). Since 1981, a post-albumin locus (*Pa*) was reported in New Zealand white and White of Dendermonde rabbits, including two codominant autosomal alleles, Pa^F and Pa^S (Juneja et al 1981).

Based on various reviewed linkage experiments and on their owns', Fox & Van Zutphen (1979) established in rabbits two tightly linked group of genes, one including the red cell esterase *Es-1* and *Es-2*, and the second one, the serum esterase loci, *Est-1* and *Est-2*, with a frequency of recombinants less than 0.5% between the last two genes (frequency reported in Van Zutphen 1974b). There is a larger distance between the *Est-1* and *Est-2* group, and the *e* locus, compared to the chromosomal distance between the *Es-1* and *Es-2* group and the group of serum esterase (*Est-1* and *Est-2*). Various data included 4.8±2.7 cM (centimorgans) or 6.3±2.1cM/7.6±3.3 cM, as the chromosomal distance between *Es-1* and *Est-1,2* or *Es-1* and *Est-1*, respectively, and of 13.6±4.2 cM or 18.5±3.7 cM between *Est-1* and *e*. Interestingly, a higher frequency of recombinants (26.19%) was reviewed for *Est-2* and *e* loci. However, the arrangement of *Es-1,2 – Est-1,2 – e* loci in the rabbit chromosome is certain. The investigations on serum and tissue esterases *Est-2, Est-4, Est-5, Est-6,* and red blood cell esterases, *Es-1* and *Es-3*, revealed polymorphic loci in two rabbit inbred stains (AX/JU and IIIVO/JU). The results on linkage studies corroborated with other reported ones, showed the tissue esterase *Est-5* to be linked to the *C* locus already assigned to chromosome 1, at a distance between genes of 24 cM. A linkage between *Es-1* and *Est-2* with a map distance of 6.4 cM was confirmed for LG VI. Although this group was not assigned to a specific chromosome, suggestions based on other reports were made for rabbit chromosome 5. No linkage was reported between *Es-3* and the esterase loci of LG VI, concluding that this locus is a separate part of the esterase cluster within LG VI (Korstanje et al 2001).

Final remarks on atropinesterase classification, other effects and interactions which affect its action. Trials to include atropinesterase in the group of metabolizing enzymes reveal its individuality, being distinct from the group of lipases and cholinesterases or A and C esterases. Atropinesterase can rather be considered as a B esterase due to its ability to hydrolyze alkyl and aryl esters, including here nitrogen-containing esters, such as atropine, at a optimum pH of 8.3 for this latter case (Margolis & Feigelson 1963). Liebenberg & Linn (1980) defined more specifically atropinesterase as a carboxylesterase, together with two other rabbit serum esterases: cocainesterase and tropacocaine esterase, whose substrates of action are different and specific. At the same time, serum atropinesterase activity was reviewed in the dog, goat, guinea-pig and rat, but no activity of the two previously mentioned enzymes was observed. The site of action for atropinesterase seems also to be variable and not only in the iris or lacrimal gland, but also in liver, intestinal mucosa, kidney, spleen, adrenal glands, cardiac muscle of the rabbit, as reviewed by Liebenberg & Linn (1980). An earlier report of Ecobichon & Comeau (1974) stated that atropinesterase is a non-specific carboxylesterase. Van Zutphen (1974a) also included atropine- and cocaine-esterase in the class of carboxylesterases, both enzymes being able to hydrolyze aromatic and aliphatic esters.

The effect of atropinesterase (*As, Est-2*), as a non-specific carboxyesterase, concerns not only the atropine hydrolysis, but also other ester-type drugs, such as α-naphthyl acetate, procaine and benzoylcholine, as noticed by Forster & Hannafin (1979). Therefore, the atropine induced mydriasis and procaine-induced convulsions in rabbits depend on their expression by the presence or by the lack or deficiency of this plasma carboxylesterase. Forster & Hannafin (1979) found that procaine and benzoylcholine were competitive inhibitors of atropine. Competitive inhibition of the hydrolysis of each other, including here procaine, atropine and benzoylcholine was demonstrated by Ecobichon & Comeau (1974). On the other hand, an earlier report of Greene & Wade (1968) stated that animals with intermediate procaine esterase activity also metabolized atropine, whereas those with low activity usually did not. Van Zutphen (1974a) discussed the dependence between cocaine- and atropine-esterase, the activity of atropinesterase being dependent on the presence of cocainesterase. Sawin (1955) underlined the ability of atropinesterase to destroy monoacetyl-morphine. An early report of Sawin & Glick (1943) showed that although the initial rate of "monoacetyllmorphinease" activity is somewhat greater than its "atropinesterase" activity, the time required for their complete hydrolysis is about the same.

Conclusions. Atropine is an anticholinergic drug whose metabolism is genetically influenced by individual factors such as species, breed, age and, the most important, the genetic structre for the atropinesterase locus. Although humans and other species do not have a specific atropinesterase activity, this was reported in rabbits containing the synthesyzing allele either in homozygoute or heterozygoute genotypote, but with differences in the rate of its metabolism. Linkage experiments and modern studies assigned this locus to LG VI and the fifth rabbit chromosome, in different linkage relationships with other loci. The differences in the enzymes activities between rabbits and humans are related to the the rabbit's general use as a human experimental model.

Conflict of interest. The author declares no conflict of interest.

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