

The pathophysiology of lifelong premature ejaculation

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Abstract: For many decades it has been thought that lifelong premature ejaculation (PE) is only characterized by persistent early ejaculations. Despite enormous progress of *in vivo* animal research, and neurobiological, genetic and pharmacological research in men with lifelong PE, our current understanding of the mechanisms behind early ejaculations is far from complete. The new classification of PE into four PE subtypes has shown that the symptomatology of lifelong PE strongly differs from acquired PE, subjective PE and variable PE. The phenotype of lifelong PE and therefore also the pathophysiology of lifelong PE is much more complex. A substantial number of men with lifelong PE not only have PE, but also premature erection and premature penile detumescence as part of an acute hypertonic or hypererotic state when engaged in an erotic situation or when making love. As both *erectio praecox*, *ejaculatio praecox*, *detumescentia praecox*, and the hypererotic state are part of the phenotype lifelong PE, it is argued that lifelong PE is not only a disturbance of the timing of ejaculation but also a disturbance of the timing of erection, detumescence and arousal. Since 1998, the pathophysiology of lifelong PE was thought to be mainly mediated by the central serotonergic system in line with genetic polymorphisms of specific serotonergic genes. However, by accepting that lifelong PE is characterized by the reversible hypertonic state the hypothesis of mainly serotonergic dysfunction is no longer tenable. Instead, it has been postulated that the pathophysiology of lifelong PE is mediated by a very complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and probably also epigenetic factors. Progress in research of lifelong PE can only be accomplished when a stopwatch is used to measure the IELT and the cut-off point of 1 minute for the definition of lifelong PE is maintained. Current use of validated questionnaires, neglect of stopwatch research, clinically inexperienced investigators and inclusion of anonymous men in a study performed by the Internet endanger the continuation of objective research of lifelong PE.

Keywords: Lifelong premature ejaculation (lifelong PE); *ejaculatio praecox*; *erectio praecox*; *detumescentia praecox*; hypererotic state; genetic polymorphism

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Introduction

The unique pathophysiology of lifelong premature ejaculation (PE) is best understood when this subtype of PE is compared to other forms of PE. Therefore, some basic knowledge of the history of PE classification is essential.

First PE classification of Schapiro

Despite the fact that a century ago men with lifelong PE

suffered as much as today, the specific features of lifelong PE were unknown to clinicians from the first report of PE in medical literature in 1887 (1) until the publication of Bernard Schapiro in 1943 (2). It has been the great merit of Bernard Schapiro to distinguish two subtypes of PE. Based on his long experience with men with PE, Schapiro distinguished type B or “the sexually hypertonic or hypererotic type” and type A or the “hypotonic type” (2). Both types were later called lifelong PE and acquired PE, respectively (3). Schapiro

noted that in type B (lifelong PE) “*premature ejaculation, from the very first act of coitus, was continually present*” (2). But also that “*careful questioning elicited the information that relatives of the patient (father or brother) with type B suffered from the same disorder*” (2). Therefore, Schapiro assumed that in type B (lifelong PE) “*heredity may play a part in the etiology*” (2). In addition, Schapiro noted that in type B “*libido and erection were rather overstrong, and erection was provoked by even mild sexual stimulation*”, which phenomenon he called “*erectio praecox*” (2). Moreover, Schapiro noted that in type B men, PE was associated with “*abnormally high sexual tension*”, which he called a “*hypertonus of the entire sex apparatus*” (2). Schapiro emphasized that the characteristics of men with type B or lifelong PE were “*entirely different*” than those of men with “*type A*” or “*acquired PE*”, who did not have family members with PE and in which *erectio praecox* and *hypertonus* was not part of the subtype (2).

Unfortunately, the classification of Schapiro was completely ignored by clinicians and sexologists for nearly 50 years until Godpodinoff (3) distinguished lifelong and acquired PE, which actually were type B and type A of Schapiro, respectively. But *erectio praecox* was ignored, and actually completely forgotten, until Waldinger mentioned it again in 2002 (4).

Second PE classification of Waldinger

Since the 1990s research of lifelong PE gained momentum by the introduction of the intravaginal ejaculation latency time (IELT), defined as the time between vaginal intromission and intravaginal ejaculation (5). Particularly by using a stopwatch—the most accurate tool to measure time—for IELT measurement, it became unambiguously clear that about 85% of men with lifelong PE ejaculate within 1 minute after vaginal penetration (6). In other words, lifelong PE appeared to be a matter of seconds whereas later studies showed that acquired PE was a matter of seconds to a few minutes (7).

Nevertheless, due to epidemiological stopwatch research of the IELT in the general population in five countries (8,9), it became no longer tenable to claim that there are only two types of PE. Therefore, Waldinger and Schweitzer postulated the existence of two other PE subtypes: variable PE and subjective PE (10-12). This new classification into four PE subtypes is based on differences in the duration of the IELT, the course of the IELT duration throughout life, the frequency of occurrence of short IELTs, and the cognitive and subjective experience of the IELT (10-12).

Moreover, the etiology and pathogenesis of the four PE subtypes is different (11). Men with lifelong PE suffer from IELTs that have been consistently less than 1 minute since puberty or adolescence (6). In contrast, acquired PE may be caused by erectile dysfunction, thyroid disorders, prostatitis or relationship problems (7,13-16). In Variable PE, the IELT is only sometimes very short, whereas in Subjective PE men have a normal or even long IELT duration, but still perceive themselves as having PE (12). In other words, according to Waldinger (10-12) there is a natural variation of the IELT in men with variable PE, and therefore this PE subtype is not based on (psycho)pathology, whereas subjective PE is mainly related to psychological and cultural factors (10-12). In contrast, lifelong PE is related to neurobiological and genetic factors, whereas acquired PE is related to mainly medical factors (17,18).

Prevalence of four PE subtypes

Serefoglu *et al.* (19,20) were the first to investigate and confirm the existence of the four PE subtypes in an urological clinic in Turkey (19) and in the general Turkish male population (20). Also Zhang *et al.* (21) and Gao *et al.* (22) confirmed the existence of the four PE subtypes in an andrologic clinic in China (21) and in the general Chinese male population (22). Interestingly, the prevalence rates of the PE subtypes in both countries were remarkably similar. A relatively high proportion of men—20.0% in Turkey and 25.8% in China—reported a concern with ejaculating too early (20,22), and in line with the classification of Waldinger and Schweitzer (10-12), these men could be distinguished into four PE subtypes. Both studies confirmed the prediction of Waldinger and Schweitzer (10-12) that the percentage of men with lifelong PE in the general male population is rather small, but relatively high in a clinical sample. In the general male population, it was found by Serefoglu *et al.* (20) that the prevalence of lifelong PE was 2.3% in Turkey. Gao *et al.* (22) reported a prevalence of 3% in China. In addition, the prevalence of acquired PE was 3.9% in Turkey (20) and 4.8% in China (22). Similarly, the prevalence of variable PE was 8.5% in Turkey and 11% in China, and the prevalence of subjective PE was 5.1% in Turkey and 7% in China (20,22). In other words, among men in the general male population who complain of PE or are not satisfied with their ejaculation time duration, the percentage of men with variable PE and subjective PE is twice as high as the percentage of men

with lifelong PE and acquired PE.

Mathematical formula for the prevalence of lifelong PE

The similar method and design of two prospective stopwatch studies of the IELT in the general population of five countries (8,9) and in a cohort of men with lifelong PE (6) enabled the formulation of a mathematical formula to calculate the prevalence of any IELT values in any Western Caucasian male population. This idea has recently been proposed and elaborated by Janssen *et al.* (23). Janssen *et al.* (23) introduced a new method in which the fitness of various well-known mathematical probability distributions are compared with the IELT distribution of two previous stopwatch studies of the Caucasian general male population (8,9) and a stopwatch study of Dutch Caucasian men with lifelong PE (6). It appeared that the IELT distribution of the three studies was a gamma distribution. Moreover, it was found that the Lognormal distribution of the gamma distribution most accurately fitted the IELT distribution of 965 men in the general population, with a goodness of fit (GOF) of 0.057. The Gumbel Max distribution most accurately fitted the IELT distribution of 110 men with lifelong PE with a GOF of 0.179. Notably, by the Kolmogorov-Smirnov test the accuracy of fitness is expressed by the GOF. The study of Janssen *et al.* (23) showed that there are more men with lifelong PE ejaculating within 30 and 60 seconds than can be extrapolated from the probability density curve of the Lognormal IELT distribution of men in the general population. In other words, it was shown that men with lifelong PE have a separate IELT distribution, e.g., a Gumbel Max IELT distribution, that can only be retrieved from the general male population Lognormal IELT distribution when thousands of men would participate in an IELT stopwatch study. As this will always be difficult to perform, the mathematical formula of the Lognormal IELT distribution, as calculated by Janssen *et al.* (23) appears to be useful for epidemiological research of the IELT at least when the number of men in a specific population is known. Moreover, the mathematical formula of the Gumbel Max IELT distribution of men with lifelong PE is useful for epidemiological research of the IELT among men with lifelong PE, when the number of men with lifelong PE is known. The study of Janssen *et al.* (23) provided also indications that the prevalence of lifelong PE in Western countries may be as low as about 1%.

Neurobiological and genetic hypothesis of lifelong PE

Based on *in vivo* animal research of the 1980s (24-26), Waldinger *et al.* (17) postulated in 1998 that lifelong PE in terms of an IELT of less than 1 minute is related to genetic factors and to diminished central 5-HT neurotransmission and/or a hyperfunction of 5-HT_{1A} receptors and a hypofunction of 5-HT_{2C} receptors. Notably, due to an absence of selective 5-HT_{1A} and 5-HT_{2C} receptor ligands for safe human usage, Waldinger recently noted that it has been impossible to explore and confirm his hypothesis in men with lifelong PE (27).

Notably, the hypothesis of Waldinger *et al.* (17) on genetic and central serotonin neurotransmission and receptor involvement does not mean that lifelong PE is a classical Mendelian inheritable disorder affecting all male members of a family (28). Also in 1943, Schapiro (2) did not think that lifelong PE was a genetic disorder. Instead he assumed that “*heredity may play a part in the etiology*” of lifelong PE (2). In line with this view, Waldinger *et al.* (29) reported indications of a familial, but not genetic hereditary, occurrence of lifelong PE in first degree relatives of some male patients with lifelong PE.

Genetic polymorphisms and lifelong PE

In 2009, Janssen *et al.* (30) published the first stopwatch study on the influence of 5-HTTLPR polymorphism on IELT duration in 89 Dutch men with lifelong PE. Of these men 83 men ejaculated within 1 minute after vaginal penetration, whereas 6 men ejaculated between 1 and 2 minutes. In this group of men, those with LL genotype ejaculated within 13.2 seconds, expressed in geometric mean IELT, whereas men with SL and SS genotype ejaculated within 25.3 and 26.0 seconds, respectively (P<0.05) (30). In other words, men with LL genotype ejaculated 100% faster than men with SS genotype and 90% faster than men with SL genotype (30). Notably, there were no significant differences between these men and a control group of 92 Dutch Caucasian men in 5-HTT polymorphism alleles and genotypes (30). Using the same stopwatch methodology, Janssen *et al.* (31) investigated 54 men with respect to the role of the C(1019)G polymorphism of the 5-HT_{1A} receptor gene on the IELT duration. It was shown that men with CC genotype ejaculated within 14.5 seconds, whereas men with CG and GG genotype ejaculated within 27.7 seconds, and 36.0 seconds, respectively (31). Therefore, it was concluded

that men with CC genotype ejaculated 250% earlier than men with GG genotype (31). Similarly, Janssen *et al.* (32) investigated the role of the Cys23Ser polymorphism of the 5-HT_{2c} receptor on the IELT duration. It was shown that the wildtypes (CysCys) had an IELT of 22.6 seconds, whereas the mutants (Ser/Ser) had an IELT of 40.4 seconds (32). Thus, the men with CysCys genotype ejaculated 79% faster than the homozygote mutant (Ser/Ser) men (32).

Importance of Hardy Weinberg equilibrium (HWE)

Unfortunately, up to now other researchers have not used the stopwatch methodology and exact study design of Janssen *et al.* (30-32) in the investigation of the relationship between polymorphisms of 5-HTT and 5-HT receptor genes and the duration of the IELT. However, a few clinicians have investigated the relationship between genetic polymorphisms in men with lifelong PE. For example, two questionnaire studies confirmed that there is no association in the 5-HTTLPR polymorphism between men with lifelong PE and a control group (33,34). In contrast, there have been three other studies of men with lifelong PE showing they have a higher SS genotype frequency compared with a control group (35-37). But as the latter three studies were not in HWE—most probably due to technical laboratory insufficiencies—their results are not considered to be reliable (38). Interestingly, an association of the 5-HT_{1A} receptor gene polymorphism had been previously also found by a questionnaire study of the IELT (and not IELT) in a Finnish cohort of twins (39). The relatively few aforementioned studies might indicate—at least in men with lifelong PE who ejaculate within 1 minute—that the duration of the IELT is associated with polymorphism of the 5-HTTLPR gene, the C(1019)G polymorphism of the 5-HT_{1A} receptor, and the (HTR2C)- CysSer polymorphism of the 5-HT_{2C} receptor. However, more studies are needed in a large cohort of men with lifelong PE and a control group with well controlled polymerase chain reaction analysis and which are in HWE in order to confirm the robustness of these indications of a possible link between the aforementioned gene polymorphism and the duration of the IELT in men with lifelong PE. Indeed, Genome Wide Association Studies (GWAS) may represent the best available approach to finding candidate genes related to the IELT and lifelong PE. Nevertheless, it is interesting to note that both the studies of Janssen *et al.* (30-32) and the animal studies (24-26) that formed the basis for the neurobiological-genetic hypothesis of Waldinger *et al.* (17)

provide indications that the short IELT of men with lifelong PE may be associated with central 5-HT neurotransmission, 5-HT_{1A} and 5-HT_{2C} receptor functioning. Although speculative, Waldinger does not exclude the possibility that environmental (maternal and non-maternal) factors that affect gene expression prenatally, shortly after birth or later in life may be associated with the persistent short IELTs in men with lifelong PE (28). Such epigenetic studies should also be conducted in men with lifelong PE (28).

Characteristics of lifelong PE

IELT and lifelong PE

Lifelong PE is characterized by the following symptoms (12): (I) early ejaculation exists from the first or nearly first sexual intercourse; (II) it is present with (nearly) every female partner in more than 80–90% of events of intercourse; (III) there is little change in the IELT as men age, or the IELT aggravates in 25–30% of the patients at around the age of 30–35 years; (IV) it occurs within 30–60 seconds after vaginal penetration with nearly every coitus in the majority, i.e., >85% of men affected by the dysfunction, whereas about 10–20% of men complaining of lifelong PE ejaculate within 1–2 minutes; and (V) these symptoms lead to irritability, annoyance and other mental symptoms of embarrassment (4,40). The aforementioned features are characteristic of lifelong PE, but there is no such detailed description in the ISSM definition of lifelong PE (7,41) nor in the DSM-5 definition of PE (42) as in general a definition of a disorder cannot encompass all the detailed features of the disorder. According to the ISSM definition, lifelong PE is defined as “*a male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration and the inability to delay ejaculation on all or nearly all vaginal penetrations, which results in negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy*” (7,41). In contrast, in DSM 5 lifelong PE is not separately defined but PE is defined as “*a persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within approximately 1 minute following vaginal penetration and before the individual wishes it*” (42).

Erectio praecox (premature erection) and lifelong PE

Erectio praecox or premature erection is a clinically important and specific clinical feature of lifelong PE (2). Men with erectio praecox get an erection “too early”. This

subtle symptom of lifelong PE has never been quoted in sexological literature until 2002, when Waldinger (4) re-introduced the term, thereby noting that many men with lifelong PE report this phenomenon either spontaneously or when asked for it. The phenomenon is so subtle, that men with lifelong PE may not be aware of it. It is not strange that it is noted by their female partner when she has had previous sexual experiences with men who did not have lifelong PE. However, until now there has not been any evidence based research into this remarkable and completely underreported clinical phenomenon, although we are currently investigating its occurrence in men with lifelong PE.

The hypertonic type versus the hypertonic state and lifelong PE

Schapiro denoted type B with *erectio praecox* as “*the sexually hypertonic or hypererotic type*” (2). In contrast, he reported that type A or “*the hypotonic type*” was often accompanied by erectile dysfunction (2).

Recently, Waldinger (28) noted that many men with lifelong PE report a very sudden increased arousal, facilitated erection and facilitated ejaculation as soon as they are engaged in erotic or intimate circumstances. Therefore, Waldinger preferred the word hypertonic “state” for this phenomenon, which is characteristic for the inner mental state of men with lifelong PE (28). As soon as these men get involved in an erotic intimate situation, they are overwhelmed by an acute hypertonic state that starts with a facilitated erection (*erectio praecox*) and leads to an early ejaculation (*ejaculatio praecox*). The hypertonic or hypererotic state should not be confused with hypersexuality (28). Hypersexuality is not a symptom of lifelong PE. The hypertonic or hypererotic state is a rather acute occurring physical sexual state that only occurs in situations of eroticism or making love.

Detumescencia praecox (premature detumescence) and lifelong PE

Recently, Waldinger (28) also noted a sofar unknown clinical symptom in men with lifelong PE. He reported that a substantial number of men with lifelong PE experience a rather immediate and/or complete detumescence of the penis after an ejaculation (28). Analogous to “*ejaculatio praecox*” and “*erectio praecox*”, Waldinger denoted this as “*detumescencia praecox*” or “*premature detumescence*” (28). Notably, he also reported that a substantial number of men with lifelong

PE report difficulties in attaining a second erection after a PE preventing them from a second intercourse (28). It is as if they have difficulties becoming sexually aroused for the second time. This may be related to the psychological impact of disappointment and irritation from their early ejaculation, but Waldinger suggested that this impairment is probably more related to a sofar unknown underlying neurobiological mechanism that is related to the underlying neurobiological cause of the acute hypertonic state (28). Interestingly, Waldinger also noted that daily use of 20 mg paroxetine in some men delayed the penile detumescence in such a way that they were still able to thrust with a gradual diminishing erection (28). In other words, in these men with lifelong PE 20 mg paroxetine did not lead to erectile dysfunction but prolonged erection for a short time.

Classification into four PE subtypes according to genital tonus

By including the hypertonic state, *erectio praecox* and *detumescencia praecox* into the Four PE subtype classification, the separate characteristics of the four PE subtypes become more delineated. Lifelong PE is characterized by a hypertonic state. Acquired PE is characterized by a hypotonic state and variable PE and subjective PE are characterized by a normotonic state (43). *Figure 1* shows the historical development of the classification of PE into four PE subtypes.

Neurobiological hypothesis of lifelong PE

Adaptation of the neurobiological hypothesis

In 2014, Waldinger (28) noted that the new triad of “*ejaculatio praecox*”, “*erectio praecox*” and “*detumescencia praecox*” as part of the acute “hypertonic or hypererotic” state of lifelong PE necessitates an adaptation of his neurobiological hypothesis of 1998 (17). The hypertonic state indicates that lifelong PE is not only characterized by a diminished serotonergic neurotransmission and a disturbance of 5-HT_{1A} and 5-HT_{2C} receptor functioning causing a disturbed serotonergic modulation of the IELT (28). Based on currently available neurobiological knowledge on ejaculation, erectile functioning, and sexual arousal, Waldinger speculated that lifelong PE—when characterized by an acute hypertonic phenotype—is mediated by a more complex interaction of the central nervous system, the peripheral nervous system and the endocrinological system (28). Therefore, it would have to include serotonergic and other

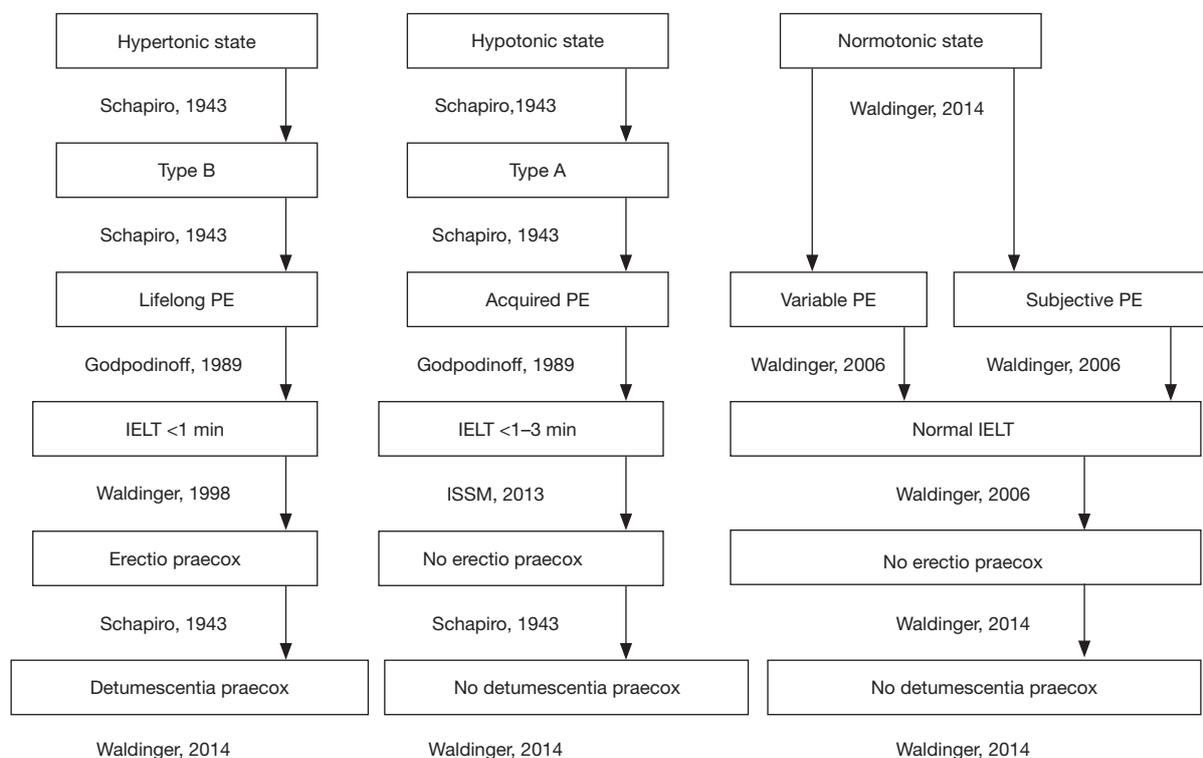


Figure 1 Classification of four PE subtypes. The classification by Waldinger (28) is an extension of the original classification of Schapiro (2) and includes erectio praecox, that was originally reported by Schapiro but has been ignored for many decades. In this classification the hypertonic and hypotonic types of Schapiro have been renamed hypertonic state and hypotonic state. The two new subtypes variable PE and subjective PE are examples of a normotonic state with normal IELT values.

neurotransmitter and endocrinological processes—e.g., increased oxytocinergic, and/or increased dopaminergic neurotransmission, decreased prolactinergic functioning and increased activity of gonadotrophic factors (28). Also involved is the peripheral nervous system, e.g., the sympathetic and parasympathetic nervous system (28). What needs to be investigated is any interaction between all these factors which may give rise to a very rapidly occurring “overactivated” or “hypertonic” state of the genital area in relation to the sense organs (28). New neurobiological and pharmacological research is required to unravel the factors mediating this hypertonic state of lifelong PE. The remarkable phenomenon that SSRIs induce much less erectile dysfunction and decreased libido in men with lifelong PE compared to depressed patients without lifelong PE, may well be related to the fact that these drugs diminish the hypertonus state of erection, ejaculation and arousal toward a more “normal” state represented by “normal” sexual functioning (28).

In recent years, research into oxytocinergic, dopaminergic

and endocrinological factors related to PE has been conducted by a number of research groups (16,44-48). However, their attention has not been directed to the hypertonic state of lifelong PE. But hopefully, the integration of neurobiological and endocrinological knowledge to elucidate the acute co-occurrence of PE, premature erection, premature detumescence, and the acute hypererotic state, will become a new focus of research in the current decade (28).

Oxytocin, erection, ejaculation and penile detumescence

Although other factors may be involved, there are preliminary indications that the rather unknown phenomena of facilitated erection, PE and rapid penile detumescence are associated with an increased release of and/or increased receptor sensitivity to oxytocine (28).

Erection

The release of oxytocin from centrally projecting

parvocellular neurons is well known to influence erection and, less clearly, ejaculation [for review see (44)]. Increased oxytocinergic neurotransmission in the paraventricular hypothalamic nucleus (PVH) or hippocampus induces either an increase in the number of penile erections or an increase in intracavernous pressure, which is an indication of erection (45,46).

Detumescence

On the other hand, some evidence indicates that peripherally injected oxytocin might have an inhibiting rather than stimulating effect on erection (44). For example, systemic oxytocin treatment inhibited the increase in intracavernous pressure elicited by electrical stimulation of the cavernous nerve in rats, which could be prevented by an oxytocin antagonist (46). It therefore appears that peripheral oxytocin receptors in the corpus cavernosum are involved in penile detumescence (44).

Ejaculation

After ejaculation, oxytocin levels are raised in the blood plasma in rabbits (49) and in the cerebrospinal fluid in rats (50).

Preliminary pathophysiology of premature erection, ejaculation and penile detumescence

In men, plasma oxytocin levels are elevated during sexual arousal, erection, and at the time of orgasm, although the degree of the elevation varies between different studies (51-54). Taking together animal and human studies, oxytocin appears to play at least a modulating role in erection and ejaculation (43), and in male sexual behavior both peripheral and central oxytocin release seem to be involved (43). In 2002, Waldinger *et al.* (4) hypothesized that *erectio praecox* in the context of lifelong PE may be associated with increased central oxytocin release during coitus as oxytocin facilitates erection and ejaculation. It may further be postulated that an increased peripheral release of oxytocin during ejaculation in men with lifelong PE may be associated with a quick penile detumescence (28).

Dangers that threaten scientific research of lifelong PE

Ignoring the PE classification of Bernard Schapiro in lifelong and acquired PE is not solely a tragic phenomenon of the past. Even today the danger exists that long standing

hard characteristics of lifelong PE are ignored or become distorted. For example, recently Ventus *et al.* (55) argued on the basis of a retrospective questionnaire study among a very small sample of Finnish twins and patients that the term lifelong PE is probably inappropriate. The consequences of such attempts to ignore or distort the existence of lifelong PE extremely threatens the scientific research of PE in general and will enormously harm the patient with lifelong PE (56).

Recently, Waldinger (56) has expressed his concern on current research of lifelong PE, noting that PE research seems more and more to become performed by clinically inexperienced individuals who do not talk to or see patients with PE, do not have clinical experience with PE patients, but who sit behind their PCs, play with statistical programs, try to intimidate clinicians and reviewers with validated questionnaires, selectively choose references, and omit or ignore important information that does not support their view. Particularly, ignoring the necessity of using a stopwatch for accurate IELT research, ignoring the IELT cutoff point of 1 minute for inclusion of men with lifelong PE in a study, and with regard to genetic research ignoring the importance of HWE endangers the evidence based clinical, pharmacological and genetic research of lifelong PE.

But not only that. Research of lifelong PE that is solely performed by validated questionnaires without face to face contact with a patient with lifelong PE ought to be discouraged. Particularly, studies in which anonymous men are recruited by Internet and are solely investigated by validated questionnaires and become diagnosed as lifelong PE endanger objective research of lifelong PE.

The study of Ventus *et al.* (55) and the study of Zhu *et al.* (57) are good examples to which erroneous but catastrophic conclusions such studies can lead. For example, according to the study of Ventus *et al.* (55) the authors suggest that lifelong PE is an inappropriate diagnosis. And according to Zhu *et al.* (57) 5-HTTLPR is associated with lifelong PE and L alleles might protect the male against lifelong PE.

Fortunately, the serious limitations and erroneous conclusions of these studies have been reported by other authors (38,56). But nevertheless, research of lifelong PE remains endangered by studies that only use validated questionnaires, include anonymous patients, ignore the stopwatch and objective realtime measurement of the IELT.

In order to avoid publication of such potentially harmful articles, Waldinger strongly advised clinicians, reviewers

and editors not to succumb under pressure of technocrats using statistics and questionnaires to understand patients.

Conclusions

For many years it has been thought that lifelong PE is only characterized by complaints of persistent early ejaculations. Both *in vivo* animal research, and neurobiological, genetic and pharmacological research in men with lifelong PE have much contributed to a better understanding of how the central and peripheral nervous system mediate ejaculation and contribute to persistent early ejaculations. However, our current understanding of the mechanisms behind early ejaculations is far from complete. The new classification of PE into four PE subtypes has much contributed to a better delineation of lifelong PE against acquired PE, subjective PE and variable PE. It has been shown that the symptomatology of lifelong PE strongly differs from the three other PE subtypes. The phenotype of lifelong PE and therefore also the pathophysiology of lifelong PE is much more complex than the phenotype of the three other PE subtypes. A substantial number of men with lifelong PE not only has PE, but also premature erection and premature penile detumescence as part of an acute hypertonic or hypererotic state when engaged in an erotic situation or when making love. As both *erectio praecox*, *ejaculatio praecox*, *detumescencia praecox*, and the hypererotic state are part of the phenotype lifelong PE, it is argued that lifelong PE is not only a disturbance of the timing of ejaculation but also a disturbance of the timing of erection, penile detumescence and arousal. Since 1998, the pathophysiology of lifelong PE was thought to be mainly mediated by the central serotonergic system in line with genetic polymorphisms of certain serotonergic genes. However, by accepting that lifelong PE is not only a matter of a short IELT, but also characterized by a facilitated erection and facilitated penile detumescence as part of an acute but reversible hypertonic state, the hypothesis of mainly serotonergic dysfunction is no longer tenable. Instead, it has been postulated that the pathophysiology of lifelong PE is mediated by a very complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and probably also epigenetic factors. Progress in research of lifelong PE can only be accomplished when a stopwatch is used to measure the IELT and the cut-off point of 1 minute for the definition of lifelong PE is maintained. Current use of validated questionnaires, neglect of stopwatch research,

clinically inexperienced investigators and inclusion of anonymous men in a study performed by the Internet endanger the continuation of objective research of lifelong PE and ought to be discouraged.

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Footnote

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